



The LEWIN GROUP

The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care

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Table of Contents

Executive Summary	1
A. Key Findings	2
B. Recommendations	7
Introduction	12
I. Description of Diagnostic Products	14
A. What are In Vitro Diagnostics?	14
B. Essential Components or Attributes of Diagnostics	16
C. History of Diagnostic Products and Other Sentinel Events	17
D. Main Categories of Diagnostics	23
E. Settings of Use	26
F. Value of Diagnostics to Health Care and Health Status	28
II. Current and Future Use of Diagnostic Products	30
A. Primary Uses of Diagnostics	30
B. In Vitro Diagnostics: Overview of Future Trends and Directions	32
III. Profile of the Diagnostics Industry	44
A. Scope and Magnitude of the US and International Diagnostics Industry	44
B. Financing Opportunities in the US Diagnostics Industry	54
C. Research and Development	56
D. Main Customers of the Diagnostics Industry	57
E. Main Factors Affecting Diagnostic Product Development	59
F. Market Drivers that Affect the Diagnostics Industry	64
G. Expectations for Diagnostics	67
H. Diagnostic Technology Trends and Pipeline	70
IV. US Regulation of Diagnostics	72
A. FDA Regulation of Diagnostics	72
B. Primary Regulatory Paradigms for In Vitro Diagnostics	73
C. Trends, Challenges and Future Considerations for Diagnostics	79
D. Implications for Diagnostics Industry Innovation	89
E. Diagnostics Regulation: Findings and Recommendations	90

V.	US Reimbursement of Diagnostics	92
	A. Overview of US Reimbursement Systems	93
	B. Medicare	94
	C. Medicaid	118
	D. Private Payers	120
	E. Medicare Prescription Drug Improvement and Modernization Act of 2003	124
	F. Diagnostics Reimbursement: Findings and Recommendations	125
VI.	Additional Factors Affecting Viability and Value of Diagnostics	131
	A. International Regulatory and Payment Requirements	131
	B. Regulation and Reimbursement in Europe	132
	C. Regulation and Reimbursement in Japan	135
	D. Implications for International Access to In Vitro Diagnostics	136
	E. Societal, Ethical and Legal Considerations for Diagnostics	137
	F. Other Market Factors: Work Force Considerations	144
VII.	The Value Chain of Diagnostics: Direct and Cumulative Impacts on Health Care, Outcomes and Costs	147
	A. Overview of the Value of Diagnostics	148
	B. The Clinical Analytic Framework as a Model for Assessing Value	150
	C. Understanding the Value of Diagnostics in Patient Care	152
	D. Understanding the Value of Diagnostics to the Health Care System	175
	E. Emerging and Future Diagnostics: Implications for the Health System	184
	F. Comparing Costs of Diagnostic Testing and Care per Patient Episode: Four Case Studies	187
	G. Impact of Diagnostic Use on the Health Value Chain	208
	H. Optimizing the Impact and Value of Diagnostics	213
Appendix A: Glossary		
Appendix B: Coverage During Clinical Trials		
Appendix C: Important Aspects of the CPT Application Process		
Appendix D: Key Provisions of MMA for Diagnostics		

Executive Summary

Health care increasingly is subject to demands for improved health and quality of life and constraints on the spending required to deliver these improvements. *In vitro* diagnostics, henceforth in this report referred to as diagnostics,¹ aid in responding to such demands by enabling accurate detection of health risks and disease at earlier stages and improving treatment and disease management, while diminishing subsequent health problems and their associated costs. Diagnostics serve a key role in the health value chain by influencing the quality of patient care, health outcomes and downstream resource requirements.

From consumer-friendly at-home pregnancy and glucose monitoring tests to more complex automated laboratory-based systems, these tests are often first-line health decision tools. While diagnostics comprise less than 5% of hospital costs and about 1.6% of all Medicare costs, their findings influence as much as 60-70% of health care decision-making. The value of diagnostics accrues not only to clinicians and patients, but to health care managers, third-party payers and quality assurance organizations that use diagnostic performance to measure and improve health care quality.

Diagnostics have evolved with our understanding of biological systems and disease, along with advances in science and technology. Emerging today are entirely new categories of diagnostics, based on full continuum of care and personalized medicine approaches. With the potential to fundamentally alter clinical practice, these technologies are intended to match the “right patient with the right treatment at the right time.” As such products mature, clinicians and patients will be better able to assess the risks and benefits of care options and customized health management strategies to optimize individual health and quality of life.

Considering the increasing reliance on diagnostics in all phases of patient care, they afford substantial opportunity to improve quality and efficiency. Despite the value and potential of diagnostics, certain internal and external constraints, including regulatory, reimbursement, market, scientific/technical and societal issues, can inhibit the development, adoption and appropriate use of diagnostic products.

The Lewin Group was commissioned by AdvaMed to assess key aspects of the US diagnostics industry. The objectives of this study are to:

- Characterize diagnostic products
- Describe the state of the diagnostics industry
- Examine the clinical and economic value of diagnostics

¹ Though the term “*in vitro* diagnostics” (IVDs) is not commonly recognized, almost all Americans have undergone such testing. In general, IVDs are conducted on samples taken from the body (e.g., blood, urine, spinal fluid, DNA). IVDs are distinct from other diagnostic procedures such as magnetic resonance imaging, ultrasounds, or other types of imaging. Technologies that image or otherwise assess health status inside of the body or measure body functions as they occur (such as heart rate monitoring) are referred to as “*in vivo* diagnostics.” In this report, “diagnostics” refers only to IVDs, unless additional clarification is appropriate. “IVDs” or “*in vitro* diagnostics” are also retained where specifically referenced as such in regulatory language and other documentation.

- Evaluate the diverse factors that enhance or inhibit innovation, adoption and diffusion of diagnostic products
- Provide recommendations for improving appropriate patient access and fostering innovation.

The key findings and recommendations of this study are summarized as follows.

A. Key Findings

- 1) Appropriate use of diagnostics is integral to high quality health care, including informing earlier, more targeted health care interventions and averting adverse health outcomes and unnecessary costs.
 - Of the 26 Health Plan Employer Data and Information Set (HEDIS) effectiveness of care quality measures, which are used in 90% of US managed care organizations and thousands of individual provider sites, 16 (62%) are informed by diagnostic tests, including 6 (23%) that are direct measures of diagnostic test use, such as cervical cancer screening, LDL cholesterol screening following a heart attack and chlamydia screening.
 - Of the 660 disease-related quality measures in the National Quality Measures Clearinghouse, 92 (14%) are for diagnostics, such as hemoglobin A1c testing to assess glycemic control and hepatitis C testing for high risk patients.
- 2) The expanding body of evidence-based clinical practice guidelines substantiates the critical role of diagnostics in health care decision-making.
 - Specific diagnostic tests are recommended in more than one-third of 1,230 evidence-based clinical practice guidelines identified and examined for this report.
 - Evidence-based guidelines specify using diagnostics in the standard of care for 12 of the 15 most clinically and economically burdensome disease/condition categories in the US.
- 3) While some diagnostics are overused, many diagnostics that are recommended as standards of care and supported by clinical evidence are grossly underused in practice. Diagnostic underuse has significant implications for quality and cost of care in the US.
 - A sentinel study conducted by the RAND Corporation reported that standard of care diagnostics were underused 51% of the time (ranging from 10% to 100% underuse depending on the test), based on analysis of 102 diagnostics-based quality indicators in 30 preventive, acute and chronic condition areas.
 - Low compliance with diagnostics-based quality measures for diabetes, cardiovascular disease, colorectal cancer and breast cancer alone was linked to 56,200 avoidable adverse health events, up to 34,000 avoidable deaths and \$899 million in avoidable health care costs in 2004, according to the National Committee for Quality Assurance (NCQA).
- 4) Although diagnostics comprise only a small fraction of total hospital (under 5%) and Medicare (1.6%) costs, diagnostic information influences a much larger proportion of

downstream health care decision-making that contributes to improved health outcomes and results in cost savings in many instances. For example:

- Combined creatinine kinase, myoglobin and troponin testing for rapid detection of heart attack in patients presenting with chest pain in the emergency room is reported to yield up to a 30% savings in hospital costs for patients experiencing heart attack and for those found to have chest pain due to other reasons.
- 5) New testing platforms continue to improve the efficiency, integration and sophistication of existing diagnostic modalities. These advances hold the potential to change paradigms for delivery of health services.
 - High-throughput tests can yield large numbers of bundled diagnostic test results with enhanced efficiency and lower costs. Emerging targeted tests, such as pharmacogenomic assays and therapeutic drug monitoring, enable more patient-specific results and disease management capacity.
 - 6) The worldwide market for diagnostics is projected to be \$28.6 billion in 2005, of which the US market share is projected to exceed \$11.2 billion. In 2003, the US accounted for 43% of the total international market share for diagnostics.
 - 7) The majority of US diagnostic testing is conducted within hospitals, accounting for 60% of the industry's revenue. Labs in physician practices make up 55.4% of all sites of service. Though reference labs comprise only 2.8% of US clinical labs, they account for 32% of the diagnostics industry's revenue, because of high-volume testing.
 - 8) Nearly half of all diagnostics firms are small businesses (i.e., fewer than 50 employees), but co-marketing, licensing and merger and acquisition activity within the industry is reducing their number. The number of diagnostics industry IPOs was modest during 1997-2003, but 2004 suggested a recovery, with 9 IPOs raising a total of \$442 million.
 - 9) Publicly traded diagnostics companies with marketed products invest about 35% of their revenue into R&D, a level higher than that of the pharmaceutical and broader medical device industries. Among these, companies with annual sales under \$5 million may invest 200% or more of their revenue into R&D. These smaller companies are highly sensitive to regulatory and reimbursement hurdles.
 - 10) At the core of the diagnostics manufacturing industry is a cohort of highly skilled scientists, laboratory technicians/technologists and managers. The diagnostics, clinical laboratory and other health industries face significant challenges to retaining an adequate and qualified workforce to support expected growth.
 - The US diagnostics manufacturing industry employs more than 40,000 individuals in nearly 180 separate firms. In 2001, the average salary in the diagnostics manufacturing

industry was \$63,000, 80% higher than the average salary of \$35,000 of all working Americans that year.²

- Vacancies for clinical laboratory workers in 2002 were about 16% higher than the average unemployment rate, at about 7%. A 60-69% deficit in specialized/certified clinical laboratory personnel has been projected through 2012.³

11) Important changes have occurred in regulation of diagnostics in recent years. These are intended to improve coordination of the regulatory process within FDA, communication between manufacturers and FDA and access to new diagnostics.

- FDA has developed more efficient means of regulating diagnostics and other devices, including coordinating diagnostics regulation using a total product life cycle approach and a pilot “turbo 510(k)” process for streamlining 510(k) submissions.
- For diagnostics, average PMA and PMA supplement review times fluctuated between 1999 and 2004, with a large increase in average non-FDA review time for both categories in 2004. Average review times for 510(k)s, the most frequent type of submission, were largely consistent during this period. Review times are influenced by many factors, confounding assessments of year-to-year changes. Iterative communications between FDA and the diagnostics industry throughout all phases of development may contribute to achieving and maintaining efficient reviews, even for particularly complex products.

12) Despite recent gains, many barriers to efficient product development and timely diffusion remain. Certain regulatory requirements, capacity and guidance for development of diagnostics are outdated or insufficient for addressing complex and unique considerations of emerging diagnostics. Among these are the following:

- Laboratory-developed tests (sometimes known as “home brews”) are not subject to the same FDA regulation required of functionally similar tests developed by diagnostic manufacturers, but are subject to performance standards of CLIA, overseen by CMS.⁴ This difference in regulation for functionally similar tests can create disincentives for developing tests that would be subject to FDA’s more time- and resource-intensive regulatory pathways.
- Ambiguity regarding regulation of analyte specific reagents (ASRs) poses uncertainty to industry and FDA. There is a lack of explicit policy over the regulation of new and emerging technologies in this area, such as gene- or immunohistochemistry-based ASRs.

² Comparable to an average salary of \$62,000 in the pharmaceutical manufacturing industry.

³ Estimates based on data from the Bureau of Labor Statistics.

⁴ Under CLIA, FDA classifies new commercially marketed laboratory-developed tests into one of three categories: waived complexity, moderate complexity, or high complexity. CMS is responsible for oversight of CLIA test performance standards, including inspections of laboratories. Marketing claims for these tests are regulated by the Federal Trade Commission. Manufacturers of ASRs (which are biological or chemical reagents used in some laboratory-developed tests) must restrict their sale to high-complexity, CLIA-certified laboratories.

- Patient informed consent is protected by Department of Health and Human Services (DHHS) regulations applying to all clinical research conducted or sponsored by the federal government and by specific FDA regulations for studies conducted in support of new product submissions. Investigations of diagnostics conducted for FDA submissions rarely require direct patient involvement, as these studies may use “leftover” or “banked” samples from earlier tests. However, even when these samples have been stripped of individual identifying information, the more conservative FDA regulations requiring informed consent for testing these samples can be an unnecessary barrier to beneficial research.
- 13) Current coding, coverage and payment processes pose disincentives to manufacturers to develop new tests and can inappropriately influence test ordering by providers. Although the Institute of Medicine’s 2000 report on Medicare laboratory payment policy provided recommendations for correcting existing flaws in the system, the reimbursement process for diagnostics remains largely unchanged.
- The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) calls for significant advances in establishing open, rational and iterative processes in the reimbursement of diagnostics and other technologies. However, these remain to be fully implemented.
- 14) The successful adoption and use of new diagnostic tests can depend directly on CPT coding, because assignment of a particular code determines the payment level for a test. Despite recent improvements, current mechanisms for securing proper codes can be complex and time-consuming and would benefit from more direct involvement of physicians, laboratories, diagnostics manufacturers and other sponsors.
- The timelines for updating codes applicable to the Medicare Clinical Laboratory Fee Schedule (CLFS) remain lengthy. Depending on the date of submission for new or revised coding, it can take 14-26 months for a CPT Category I code to become effective and 10-16 months for a Category II or III code to become effective. Further delays can occur if the participating medical specialty societies and reviewers do not arrive at consensus regarding coding decisions or if reviewers conclude that a technology has not met CPT requirements for widespread use or for efficacy and clinical utility.
 - Recently, the American Medical Association (AMA), which governs the coding processes, began considering certain coding recommendations of the Pathology Coding Caucus, which was established by the College of American Pathologists.
- 15) Coverage establishes the clinical indications for which a new diagnostic can be paid and describes circumstances of use. There is no uniformly applied method for making coverage decisions for diagnostics, and decisions often seem to be ambiguous, arbitrary or redundant.
- Payers increasingly require evidence linking diagnostic test use to health and economic outcomes. It is appropriate to require evidence of the health, economic and/or other valued impacts of diagnostics. However, establishing causal effects of diagnostics, particularly on health outcomes, can be challenging and sometimes impractical, as

various factors (e.g., use of multiple diagnostics, physicians' desire to rule out conditions and multiple treatment options) can confound these downstream effects.

- Coverage of emerging diagnostics that test for multiple biomarkers or provide predictive data is inhibited by current interpretations of medical necessity. While such tests may offer new paradigms for patient care, the current medical necessity hurdles may limit rapid development and diffusion of diagnostics.

16) Methods of setting Medicare payment levels for new diagnostics are archaic, inconsistent and severely flawed. They fail to reflect the relative value of diagnostics to health care, sending inefficient market signals to innovators, clinicians and payers.

- Payment levels often do not reflect the value of diagnostics to patient health or the health care system. A new test that confers greater benefits often is paid the same as or less than an existing one sharing the same code. As such, both incremental and breakthrough advances in diagnostics frequently are underpaid, precipitating suboptimal resource allocation and disincentives for innovation.
- The CLFS has not been updated for inflation in 11 of the past 15 years and will not be updated again until after 2008. As a result, each dollar paid in 2004 under the CLFS is equivalent to \$0.75 in 1984 dollars, after adjusting for inflation and mandated payment reductions below the National Limitation Amount (NLA).⁵
- The “crosswalk” and “gap-fill” methods used for setting initial payment levels for diagnostic tests and updating existing ones in the CLFS used by Medicare are non-standardized and inconsistently applied.
- The flaws of the CLFS used by Medicare extend beyond that program to payment for care for many millions of other patients, whose payers use or are guided in their payment of diagnostics by Medicare payment policies.
- There are great discrepancies in payment for diagnostic laboratory tests among state Medicaid programs, which are bound by the NLAs set by Medicare. While some diagnostics are overpaid in these fee schedules,⁶ decisions resulting in underpayment are more likely, including many that are significantly below the NLA, compounded by national decisions to withhold CLFS updates for inflation.

17) Use of emerging diagnostics may be inhibited by variations in regulatory and reimbursement environments across countries, including the EU and Japan.

- Continued harmonization of global standards may improve adoption of diagnostics across international markets. Classification in non-US payment systems also aids in placing new diagnostics into clinical practice quickly, which is one reason why many diagnostics initially are launched outside of the US.

⁵ The NLA currently caps Medicare payments at 74% of the median contractor fee schedule amounts.

⁶ In cases where a Medicare fee is not available for a test being provided under a Medicaid plan, the payment is not bound by these limitations.

18) Clinical utility and acceptance by consumers and patients of tests for genetic or other risk factors could be diminished by their actual or perceived potential use (e.g., by employers or health insurers) for employment actions or access to health care.

- While they have great potential to improve care, emerging diagnostics must be subject to appropriate confidentiality safeguards and accompanied by counseling and other services to support informed decisions by clinicians and patients.
- As the volume of diagnostic data continues to increase, clinicians will require adequate health information technology and related support systems for accurate reporting and informative presentation of test results, to ensure better patient management and accurate and timely coding and payment.

B. Recommendations

1) CMS should promptly modernize the Medicare CLFS into a single national payment schedule with an open, systematic and accountable process that would reduce wide pricing variations among carriers. While implementing this modernized process, CMS also should correct historic pricing and coding errors, clarify processes and criteria for incorporating new tests into the CLFS and provide for regular stakeholder input on CLFS modifications.

- CMS should publish and implement clear administrative procedures for responding to contractor and other stakeholder requests to correct historical pricing errors and inappropriate cross-walks of new test codes to “clinically similar” test codes in the CLFS. To minimize the burden on CMS of responding to these requests, clear criteria for considering requests should be established, including, e.g., substantive patient access concerns, evidence of incorrect cross-walk assignment or pricing of predicate tests and limits on the number of updates considered annually.
- CMS should develop a clear, value-based process and criteria for incorporating new tests into the CLFS that overcomes limitations of the current cross-walk and gap-fill processes. CMS should establish a predictable, transparent gap-fill process for new tests, with effective oversight of fees set by Medicare carriers.
- CMS should use interim pricing strategies (e.g., that are subject to annual revision) for such new tests to enable later adjustments for technological change, potential initial pricing errors and impact on providers and patient access. For any approach to incorporating new tests into the CLFS, CMS should provide clear rationale and evidentiary basis for price setting.
- CMS should provide a clear and accountable process for stakeholders to appeal cross-walk and pricing decisions, with the ability to incorporate new information about a technology, how it is used or its impact on practice or access.
- The CLFS should be adjusted annually for inflation, based on the Consumer Price Index or similar means and for reasonable costs of providing clinical laboratory services.

- The open and ongoing process for maintaining the currency of the CLFS should reflect technological advances and market conditions and assess the impact of pricing decisions on providers, patients, manufacturers and other stakeholders. It should include development of guidance, and regulations as necessary, that address and clearly explain standard criteria for updating decisions.
- 2) In parallel to the modernization into a single national payment schedule, CMS should develop and implement value-based payment for clinical laboratory tests that overcomes inherent limitations of the current cross-walk and gap-fill processes. This process should shift over a period of years from existing payment practices to a value-based resource payment approach that better recognizes the clinical, economic and other benefits of improved diagnostic testing.
- The system should be applied initially to new tests and gradually extended to existing tests on the CLFS.
 - This value-based payment process should be open, transparent and deliberative. At a minimum, it would involve open planning meetings with stakeholders, but also may be supported by a FACA-compliant⁷ clinical laboratory test payment advisory committee. This committee would be responsible for review of fee schedule submissions and development of recommendations to CMS regarding payment level updates/changes and other payment system refinements. Represented stakeholders should include experts from industry, laboratories, and clinical care.
 - Negotiated rulemaking should be employed as a means of establishing payment for high national priority or controversial clinical laboratory tests.
- 3) Access to new diagnostics depends on timely, appropriate coding assignments, as well as designation of adequate payment levels. Therefore, while recognizing the practical time requirements of gaining and processing expert input, the AMA and CMS should continue to strive for greater efficiency and shorter timelines for establishing these codes.
- Of particular value would be reductions in the 14-26 month period and any associated delays entailed in establishing and making effective a new or revised Category I CPT code.
 - The AMA should allow for increased transparency and stakeholder input, including from diagnostics manufacturers and clinical laboratories, to processes for assigning new and revised CPT codes. Greater transparency would entail, e.g., more sharing of relevant documentation and information about disposition of coding decisions on designated web sites.

⁷ The Federal Advisory Committee Act (FACA) of 1972 sets requirements for any group established by the government for the purpose of advising the government and that includes any members that are not government employees.

- 4) For purposes of making Medicare coverage decisions, CMS should carefully consider evidence requirements for diagnostics, given the challenges of establishing direct evidence of the causal effects of using diagnostics on improvements in health and economic outcomes.
 - Evidence requirements for diagnostics, including applicable methods and data sources, should be developed with input from various appropriate methodological experts and stakeholders, including health care providers and representatives of diagnostics manufacturers and the clinical laboratory industry.
 - Implementation of standardized, evidence-based coverage decision criteria for diagnostics across local Medicare coverage processes, though retaining local coverage decisions, would reduce inefficiencies and improve health care access and quality.
- 5) Public and private payers should establish a transparent basis for determining medical necessity of clinical laboratory tests reflecting opportunities of evolving diagnostic technologies.
 - Stakeholders should move to adopt the ICD-10-CM coding system for clinical laboratory services. While initially burdensome, this will offer the capacity to accommodate the increasing volume and complexity of tests entering the market. CMS should develop and implement reasonable incentives to facilitate this transition consistent with MMA reform requirements.
 - Along with other payers and with input from informed stakeholders, CMS should anticipate the potential benefits of broadening interpretations of medical necessity as it applies to many emerging diagnostics, such as those involving multiple biomarkers or gene-based predictive tests, that hold significant potential for early and effective preventive care in specific populations.
- 6) In consultation with DHHS, health professional groups and other stakeholders, Congress should consider transferring responsibility for coverage determinations for preventive services under Medicare to DHHS. This would enable more timely, evidence-based coverage for diagnostics that are demonstrated to be useful in screening and prevention.
 - While most diagnostics currently are not used for screening purposes, many (including some emerging diagnostics) hold great promise as screening tests for certain high-risk populations. The Medicare statute does not provide for coverage of screening tests, except as mandated by Congress. Transfer of this responsibility likely would require a change in the Medicare statute, as has been proposed under S. 2535, the Medicare Preventive Services Act of 2004, introduced in the 108th Congress.
 - Coverage determinations for diagnostics should continue to be informed by the US Preventive Services Task Force, with input from the Medicare Coverage and Advisory Committee, as appropriate. This may include expanded technical support from the Agency for Healthcare Research and Quality (AHRQ) and its Evidence-based Practice Centers program, health professions groups and others with objective and well-documented evidence review processes.

- 7) The FDA, in conjunction with CMS, the Federal Trade Commission (FTC) and others as appropriate, should establish a unifying set of regulations for diagnostics and diagnostic components, regardless of their site of production or use.
- These agencies should clarify regulations and oversight pertaining to laboratory-developed tests and manufacturer-produced ASRs, including apparently finished devices marketed as ASRs, to minimize potential risks to safety and public health.
 - The FDA, CMS and other stakeholders should develop an equitable process for regulation of tests/test kits and laboratory-developed tests that does not substantively inhibit or preclude development or availability of these tests.
- 8) For emerging diagnostics with high potential to affect health care delivery, FDA should develop a more timely and structured process to update existing agency guidance documents that may be outdated and generate new guidance as needed, including pertaining to practical and informative evidence requirements for these diagnostics.
- Applicable federal agencies should expand collaboration with industry and other stakeholders via such means as the IVD Roundtable to identify high priority areas (e.g., for ASRs, banked samples, and pharmacogenomics) for guidance development and clarification of regulatory requirements.
 - FDA and CMS should maintain communication regarding their respective evidence requirements and timelines for market clearance and reimbursement of diagnostics, respectively, particularly to improve the relevance and efficiency of necessary data collection, as well as the timeliness of patient access to proven technologies.
- 9) In collaboration with CMS, the DHHS Office for Civil Rights and other relevant stakeholders, FDA should determine whether there are circumstances under which the informed consent requirements currently applicable to diagnostics studies are unnecessary.
- Providing that patient information safeguards are upheld consistent with The Health Insurance Portability and Accountability Act (HIPAA) and other relevant legislation, these agencies and other stakeholders should develop an informed consent waiver process for previously collected, de-identified patient clinical samples.⁸ A viable informed consent waiver process would eliminate unnecessary hurdles and costs required to bring diagnostics to market.

⁸ HIPAA covers communication and use of individual and other health information, including requirements for informed consent. HIPAA's main provisions include: standards for electronic health information transactions; mandate on health plans and providers, and timetable; privacy; pre-emption of state law; and penalties. Pursuant to HIPAA, DHHS published a Privacy Rule that became effective in April 2001. The DHHS Office for Civil Rights has authority for administering and enforcing compliance with the Privacy Rule. CMS has authority for administering and enforcing compliance with the non-privacy HIPAA rules.

- These stakeholders should consider harmonizing the multiple prevailing sets of regulations pertaining to informed consent. Particular attention should be given to unnecessary or inappropriate distinctions between the “Common Rule” regulations for research conducted or sponsored by DHHS and the regulations applying to clinical investigations involving products regulated by the FDA.⁹
- 10) DHHS and other stakeholders should address the staffing shortage of trained clinical laboratory personnel to avert significant workforce gaps related to provision of clinical laboratory services.
- Solutions may include scholarships in medical technology and related disciplines, expanded internship opportunities and tuition reimbursement for eligible priority students that work a fixed number of years in a laboratory sciences-related position following graduation. H.R. 1175, The Medical Laboratory Personnel Shortage Act of 2005, introduced in the 109th Congress, offers one vehicle for addressing this need.
- 11) DHHS agencies, quality assurance organizations and other stakeholders should assess the feasibility and potential impacts of standardizing diagnostic data collection for priority health outcomes and quality tracking.
- An iterative effort, with well-defined and realistic milestones, would enable generation of standard approaches for data collection and pilot initiatives, including linking selected diagnostic data to patient outcomes across the continuum of care. The DHHS National Committee on Vital and Health Statistics suggestion to use all or a subset of the priority health conditions identified by the IOM report, *Priority Areas for National Action: Transforming Health Care Quality* (2003), is a reasonable starting point for a demonstration project with this focus.
 - Diagnostic data may help to expedite development of health quality measures and compliance with evidence-based health care recommendations through pay-for-performance or other quality improvement initiatives. Potential lead organizations for these functions would include AHRQ and NCQA.

⁹ The general regulations for protecting the rights and welfare of human subjects involved in research conducted or supported by DHHS are contained in Title 45 CFR Part 46, known as the “Common Rule.” Clinical investigations involving products regulated by the FDA are subject to the more conservative regulations for protection of human subjects, i.e., Title 21 CFR Parts 50 and 56.

Introduction

Health care increasingly is subject to demands for improved health and quality of life and constraints on the spending required to deliver on these improvements. *In vitro* diagnostics aid in responding to such demands by enabling accurate detection of health risks and disease at earlier stages, improved treatment and disease management and diminishing subsequent health problems and their associated costs. Diagnostics serve a key role in the health value chain by directly influencing the quality of patient care, health outcomes and downstream resource requirements.

While diagnostics comprise less than 5% of hospital costs and about 1.6% of all Medicare costs, their findings influence as much as 60-70% of health care decision-making. The value of diagnostics accrues not only to clinicians and patients, but to health care managers, third-party payers and quality assurance organizations that use diagnostic performance to measure and improve health care quality.

Diagnostics have evolved with our understanding of biological systems and disease, along with advances in science and technology. Although manual in-house diagnostics are still developed, primarily for biomedical research purposes or early-phase product development (e.g., certain genetic assays), most emerging diagnostic technologies are designed for broader markets and are standardized, accurate, reliable and affordable. From consumer-friendly at-home pregnancy and glucose monitoring tests to more complex automated laboratory-based systems, these tests are often first-line tools for health care decision-making.

Entirely new categories of diagnostics, based on full continuum of care and personalized medicine approaches, also are emerging. With the potential to fundamentally alter clinical practice, these technologies are intended to match the “right patient with the right treatment at the right time.” As such products mature, clinicians and patients will be better able to assess the risks and benefits of care options and develop custom health management strategies toward optimizing individual health and quality of life.

As is the case in other sectors of health technology, the pace of advancement appears to be exceeding the ability of the health care system and certain of its regulatory, payment and other governing mechanisms to adapt. Efforts to sequence the human genome initiated complex intellectual property protection and social/ethical debates (e.g., patient privacy rights, genetic discrimination). Some US and international regulatory agencies and payers have developed new standards, strategies and, in some cases, organizational structures to accommodate changing concepts and technologies. However, bureaucratic inertia inherent in these processes remains, and is complicated by, the interdependence of intellectual property; regulation of market access; third-party payment; social, ethical and legal considerations; and international markets.

Given relentlessly escalating health care costs, stakeholders in the health care value chain are increasingly pressured to restrain costs while maintaining or improving quality of patient care. Considering the increasing reliance on them in all phases of patient care, diagnostics afford substantial opportunity to respond to these demands. Despite the value and potential of diagnostics to contribute to needed improvements in the provision and delivery of health services, certain internal and external constraints, including regulatory, reimbursement,

scientific/technical challenges, societal issues and other market factors, can inhibit the development and adoption of diagnostics products.

The Lewin Group was commissioned by The Advanced Medical Technology Association (AdvaMed) to examine certain key aspects of the US diagnostics industry. This document is intended to: a) educate and inform various audiences about diagnostics and the industry that develops them; b) describe the value of diagnostics through the health care continuum and the broader health system; c) describe the technology evolution in diagnostics and potential of these technologies to alter clinical practice; d) identify and describe the hurdles to product development and dissemination; e) identify changes necessary to overcome these challenges; and f) define actionable recommendations for enabling clinicians, patients, provider institutions, payers and other stakeholders to better realize the value and potential of diagnostics to improve health care delivery, individual health and the public's health.

I. Description of Diagnostic Products

A. What are In Vitro Diagnostics?

Though the term “*in vitro* diagnostics” is not commonly recognized, almost every American has undergone such testing in his or her lifetime, with the first experience usually occurring during the first few hours of life. All newborns undergo *in vitro* diagnostic testing, from a small sample of blood typically taken from the heel of the foot, for certain metabolic disorders. Periodic health examinations for adults frequently involve a panel of routine tests of blood and urine samples. Even when we donate blood, the collection center uses *in vitro* diagnostics to test the donation for infectious diseases such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) to ensure the safety of the blood supply.

In vitro diagnostic tests (IVDs) should not be confused with other commonly used diagnostic procedures, such as magnetic resonance imaging (MRI), X-rays, ultrasounds or other types of imaging. Technologies that image or otherwise assess health status inside of the body or measure body functions as they occur (such as heart rate monitoring) are referred to as *in vivo* diagnostics. In general, IVDs are conducted on samples taken *from* the body (e.g., blood, urine, spinal fluid, DNA). The Latin phrase *in vitro* means “in glass,” referring to the test tubes in which many IVDs were originally conducted.¹⁰ **Figure 1.1** below provides examples of commonly used *in vivo* and *in vitro* diagnostics.

The Food and Drug Administration (FDA) defines *in vitro* diagnostic products as:

“[T]hose reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.”

[21 CFR 809.3]

While this broad definition is sufficient for identifying IVDs for regulatory purposes, the FDA’s definition does not capture the true scope, nature and utility of IVDs. More specifically, IVDs are reagents, instruments and systems for testing specimens taken from the body and intended for use in a broad spectrum of health care applications, including:

- evaluation of an individual’s risk(s) for developing specific diseases or conditions
- early detection of diseases and conditions
- generation of risk-related medical information that informs clinical action (e.g., helping clinicians to rule in/rule out disease)
- diagnosis of diseases and conditions
- identification or quantification of medication or other treatment risks and/or targeted treatment selection
- estimation of patient prognosis (e.g., risk for recurrent stroke, heart attack, or infection)

¹⁰ Diagnostic tests. Brussels, Belgium: European Diagnostic Manufacturers Association (EDMA), 2004. Accessed October 26, 2004. <http://www.edma-ivd.be/labofr01.htm>.

- monitoring of treatment effectiveness
- informing the development of targeted, patient-specific disease management strategies
- identification of environmental risks to patients' or the public's health

IVDs are used alone or in combination with other disease state indicators as first-line clinical decision-making tools and at various stages of disease progression. These tests inform selection and timing of health interventions to prevent, mitigate, treat and cure diseases or conditions. For the remainder of this report, the term *diagnostics* will be used to refer only to *in vitro* diagnostics (IVDs), unless additional clarification is appropriate.

Figure 1.1
Examples of Commonly Used Diagnostics and *in vivo* Diagnostics

Diagnostics (IVDs)
• cholesterol test • Papanicolaou (Pap) smear to detect cervical cancer • conventional glucose monitoring tests • pregnancy test • prostate specific antigen (PSA) test to detect prostate cancer • blood chemistry tests (e.g., sodium, potassium, iron)
<i>In Vivo</i> Diagnostics (non-IVDs)
• blood pressure screening • MRI • thermometer • ultrasound • x-ray • computed tomography (CT) scan

Medical professionals, patients, at-risk individuals, caregivers and others use diagnostics to obtain the information needed to make health care decisions and lifestyle choices. Millions of Americans depend on diagnostics to measure cholesterol and other blood lipid levels, the results of which may indicate the need for diet modification, increased physical activity and/or pharmaceutical intervention to reduce the risk of heart disease. In order to avoid serious, even fatal, complications of their disease, millions of diabetics must monitor their blood glucose levels several times per day using diagnostics such as glucose monitors. The information provided by these monitors enables diabetics to make instantaneous and informed decisions about which foods to eat or how much insulin to take, thereby helping them to live more satisfactory, longer and healthier lives.¹¹

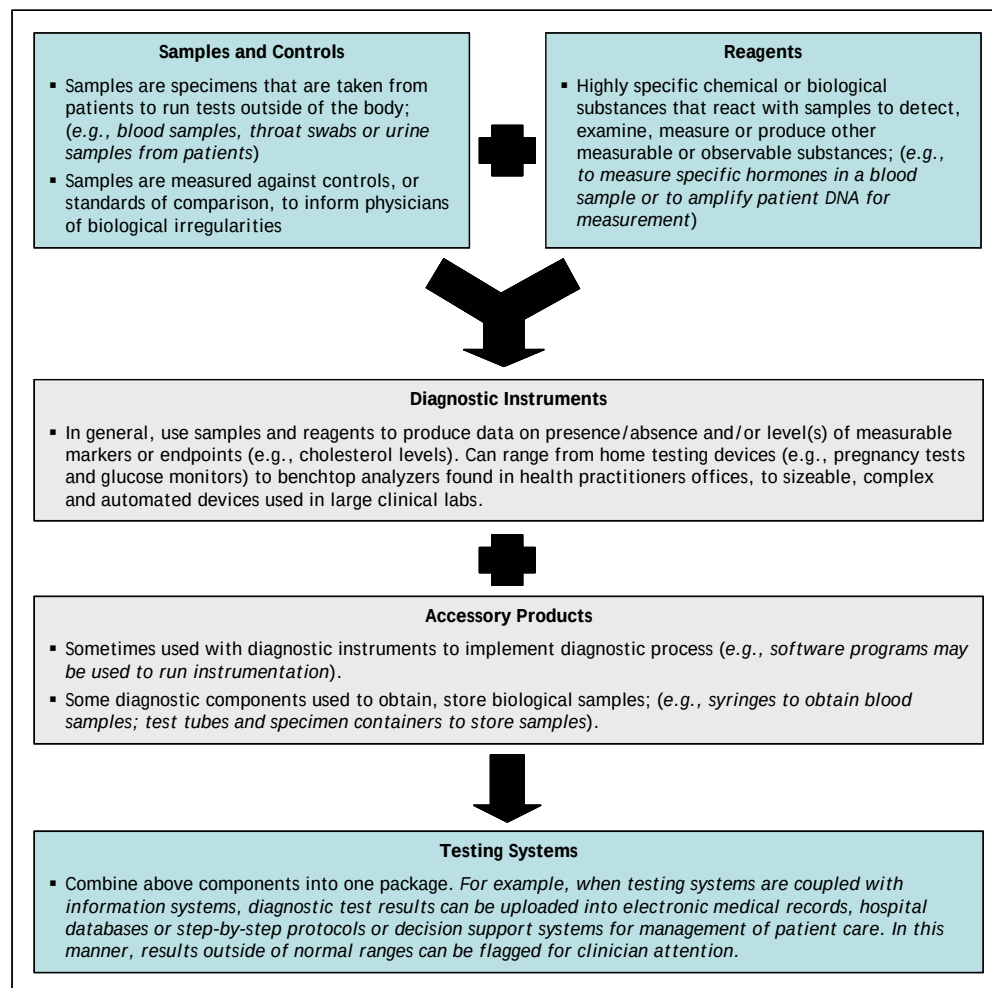
¹¹ American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care. 2000;23 Suppl 1:S43-6.

B. Essential Components or Attributes of Diagnostics

Valuable information about patient health status is obtained through specimen collection and subsequent diagnostic testing involving, for example, cellular analysis, measuring the concentrations of various biochemicals or metabolites and identifying differences in patient DNA. As a supplement to patient history and clinician observation and experience, diagnostic tests provide the objective information that is essential for safe and effective health care decision-making.^{12,13} The types of tests used for collecting diagnostic information can range broadly from basic chemical tests to hand-held glucose monitors to complex, automated instrument systems used in large clinical laboratories.

Despite their variety, almost all diagnostics have certain common functional elements that are used in a variety of combinations to detect disease and allow health status assessment. These primary components of diagnostic processes include *samples, controls, instruments and accessories*, as shown in **Figure 1.2**.

Figure 1.2
Primary Components of IVD Processes



¹² The diagnostics outlook to 2005. Healthcare Reports. London, England: Reuters Business Insights, 1999.

¹³ The outlook for the biotech sector in the post-genomic era: strategies for drug discovery, diagnostics and personalized medicine. Healthcare Reports. London, England: Reuters Business Insights, 2003.

Some of these components, such as reagents, test tubes and other accessory items, may be manufactured by entities contributing to the broader medical device and life science industries. These components then are incorporated into the diagnostic product, kit or device. The following examples illustrate how certain combinations of components can constitute a diagnostic test.

- **Bacterial culture test** can involve: a) collecting a sample via swab, blood draw or other method; b) growing bacteria from the sample on culture plates using appropriate cell culture media; c) gram staining with appropriate reagents to identify the type/class of bacteria involved; d) growth of the bacteria in the presence of antibiotics to identify treatment resistant strains; and e) processing of results in an interpretable format.
- **Blood glucose test** can involve: a) a lancet to puncture the finger for a small blood sample; b) blood collection strips to capture this sample; and c) a detection instrument to quantify the amount of blood glucose from a patient sample.
- **Genetic test** can involve: a) materials involved in blood collection (e.g., test tubes or vials); b) materials and reagents involved in separating and purifying DNA from other blood components (e.g., reagents that precipitate certain blood components and lyse cells that contain DNA); c) adjustment of DNA concentration to levels required to conduct the test; d) amplification of the amount of DNA (e.g., using biochemical methods such as the polymerase chain reaction); e) measurement of test results using certain instruments (e.g., agarose gel electrophoresis or quantitative real-time PCR); and f) processing of results into an interpretable format.

Depending on the relative complexity and level of demand for a particular test, diagnostics can be referred to as either “routine” or “esoteric” (i.e., specialized). Standard of care/routine diagnostics can measure various health indicators, such as functions of the liver, heart, kidney or other organs. Examples of these tests include cholesterol tests, urinalysis and complete blood cell counts. Esoteric tests, such as some gene-based testing (e.g., gene sequencing or real-time PCR), cardiac enzyme testing for detection of heart attack or multiplexed (i.e., conducting multiple reactions in the same tube) molecular tests, generally require more sophisticated technology, supplies and equipment, as well as highly skilled professionals/technical personnel to conduct these tests in a replicable manner.¹⁴

C. History of Diagnostic Products and Other Sentinel Events

The first recorded diagnostic tests took place in 400 BC, when physicians in ancient Mesopotamia and Egypt poured patients’ urine on the ground and observed for the attraction of certain insects to confirm suspected boils. In the 17th century, clinicians rendered a diagnosis of diabetes based on the level of sweetness of urine samples. Following establishment of the first hospital laboratory in Britain at the end of the 18th century, diagnostics started to become increasingly recognized as a standard and indispensable part of health care. The 19th century marked an increasing reliance on diagnostic information by medical professionals, as complex causal pathways linking diagnostic information to the physical symptoms of disease were identified. The value of diagnostics was expanded throughout the 20th century and into the 21st

¹⁴ Earning your trust: 2003 annual report. Teterboro, NJ: Quest Diagnostics, 2003. Accessed October 1, 2004. http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=DGX&script=700.

century by breakthroughs in scientific and medical technologies, computer and information sciences and engineering/automation.¹⁵ As such, diagnostics of the 21st century are increasingly advanced, reliable and objective, providing information essential to making informed health decisions and improving health status.

1. Diagnostics in the Twentieth Century

In the 20th century, clinical laboratories became permanent components of US hospitals, and various types of specialized and reference laboratories rapidly emerged (see **Figure 1.3**).¹⁶ The role of diagnostics increased with the steep expansion of health care. Blood transfusion was introduced in the **1940s**, prompting the need for tests that could identify blood types to ensure that patients received compatible serum, as well as identify blood-borne pathogens (bacteria, viruses or fungi) so that contaminated samples could be removed from the supply. As new pathogens such as HIV and West Nile virus have been identified, new diagnostics have been developed and refined to continually ensure the safety of the blood supply.

In the **1950s, 1960s and 1970s**, increasing understanding of genetic and molecular structures laid the foundation for later development of diagnostic tests of importance to significant clinical conditions such as diabetes, heart disease and chronic kidney disease.¹⁷ It was during this time frame that the structure of DNA was discovered, as well as oncogenes (genes directly involved in cancer development) and the enzyme known as reverse transcriptase (essential for evaluating the structure and function of human genes). A host of various diagnostic markers (e.g., substances or chemicals that are linked with disease state) discovered during this period paved the way for new diagnostics to improve the capabilities of health care. Advances in technology during this time led to the automation of many tests that previously were conducted manually. Automation has enhanced the value of diagnostics, as test results can be produced faster (informing patient care in a more timely manner) and laboratories can perform many tests concurrently, increasing their capacity to serve large numbers of patients.

Business opportunities and regulatory changes have accompanied the scientific advances and technical achievements in diagnostics. In 1978, the first medical technology company with a concentration in diagnostics was listed on the New York Stock Exchange (NYSE). The 1967 Clinical Laboratory Improvement Act regulated laboratories involved in interstate commerce, but did not extend regulation to physician office laboratories. The 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act included IVD reagents under the definition of a device, officially bringing the regulation of diagnostics under the authority of the FDA.¹⁸

The **1980s** saw substantial shifts toward privatization and changes in health care payment, in response to rising health care costs and cost-containment pressures. The discovery of the polymerase chain reaction (PCR) in 1985 dramatically expanded understanding of how genes influence disease state. One year after the discovery of PCR, the first commercial automated

¹⁵ Buttner J. Impacts of laboratory methodology on medical thinking in the 19th century. Clin Chem Lab Med 2000 Jan;38(1):57-63.

¹⁶ Ibid.

¹⁷ Closing in on cancer. Bethesda, MD: National Cancer Institute. Accessed October 27, 2004. <http://press2.nci.nih.gov/sciencebehind/cioc/ciocframe.htm>.

¹⁸ Milestones in US food and drug law history. Washington, DC: US Food and Drug Administration, 1999. Accessed October 26, 2004. <http://www.fda.gov/opacom/backgrounders/miles.html>.

DNA sequencer was marketed by a diagnostics firm, improving the capacity for rapid and high throughput DNA analysis and dramatically increasing the pace of molecular research.¹⁹

The Clinical Laboratory Fee Schedule, implemented by Congress as part of The Deficit Reduction Act of 1984, established the determination of Medicare fees for existing laboratory tests as: a) the lowest submitted charge; b) the National Limitation Amount (NLA); or c) the local fee schedule amount developed by the carrier.²⁰ New tests added to the Clinical Laboratory Fee Schedule then were reimbursed, based upon existing codes and payment levels already in the fee schedule or based upon carriers' determination of payment in the first year for cases in which there were no comparable existing tests.²¹ The Clinical Laboratory Improvement Amendments (CLIA) of 1988 (discussed in **Section IV** and elsewhere) consolidated regulation of all types of clinical laboratories (including physician office laboratories) under one statute and established standards for quality assurance, record maintenance and proficiency testing of personnel for all laboratories in the nation.^{22,23}

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) mandated a five-year freeze on the Consumer Price Index (CPI) adjustment to the Medicare clinical laboratory fee schedule. Effective through 2008, this freeze prevents annual adjustment for inflation, implemented as an alternative to requiring a 20% co-pay for laboratory services for Medicare beneficiaries (which would have been unnecessarily burdensome to collect for the clinical laboratory industry). Implications of this freeze include flat payments for lab services during a time when costs of health care services and products are anticipated to continue to rise faster than those of other goods and services, along with a potential reduction in available test menus by the clinical laboratory industry as a cost-control measure and decreased investment in new diagnostics.^{24,25}

¹⁹ Perkel JM. How it works: an automated DNA sequencer. *Scientist* 2004;18(18):40.

²⁰ Medicare program; procedures for coding and payment determinations for clinical laboratory tests and for durable medical equipment. Baltimore, MD: Center for Medicare & Medicaid Services, 2004. Accessed November 8, 2004.
<http://64.233.161.104/search?q=cache:FYrtBUxyTasJ:www.cms.hhs.gov/medicare/hcpcs/codpayproc.asp+%22cross-walk%22+definition+%22gap-fill%22&hl=en&start=3>.

²¹ Ibid.

²² CLIA program. Washington, DC: Centers for Medicare & Medicaid Services, 2004. Accessed October 12, 2004.
<http://www.cms.hhs.gov/clia/>.

²³ As described in the February 28, 1992 *Federal Register* (57 FR 7139), certain types of clinical laboratories are exempt from regulation under CLIA (1988). These types of laboratories include: a) laboratories solely conducting forensic testing; b) research laboratories that use human specimens but do not provide results intended for patient care; c) Substance Abuse and Mental Health Services Administration-certified laboratories conducting drug testing; and d) certain federal laboratories exempted from CLIA requirements. Examples of exempted federal laboratories include Department of Defense and Veterans Affairs clinical laboratories, which operate under separate regulatory guidelines.

²⁴ Ivor L. The Medicare Modernization Act: What's in it for IVDs? *IVDT* 2004;4(1):18.

²⁵ Reardon SZ. The importance of access to congress: how IVD manufacturers can make a difference. *IVDT* 2004;7(1):22.

Figure 1.3
Sentinel Events in Diagnostics and Health Care, 1953-2005

Scientific Advancements	Policy Milestones
1953: DNA structure defined by Watson & Crick 1964: Cancer marker alpha-1-fetoprotein (AFP) was first described as a tumor-associated marker 1968: First fully automated discrete chemistry analyzer for whole blood or serum 1973: First system to measure blood gas, metabolites, electrolytes and CO-oximetry from a single sample 1976: Discovery of hemoglobin glycosylation 1977: Sanger develops method of DNA sequencing 1979: First point-of-care device developed 1985: HER-2/neu gene is cloned 1985: Mullis develops polymerase chain reaction (PCR) for copying DNA 1985: First diagnostic test to screen blood and blood products for HIV 1986: First automated DNA sequencer is produced 1988: First-generation test kits for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoea</i> infections 1990: Human Genome Project launches 1993: Relationship between severity of Type 1 diabetes and degree of glycemic control demonstrated 1994: BRCA-1, the first breast cancer susceptibility gene, is discovered 1995: First fully automated system for high-volume blood screening laboratories 1998: First targeted treatment (Herceptin) for HER-2/neu positive metastatic breast cancer patients 2001: Launch of a rapid anthrax test 2001: First non-invasive glucose monitor using a low electrical current to take glucose readings without puncturing the skin 2001: Publication of initial Human Genome Program working draft sequence - Collins & Venter 2002: First fully-automated congestive heart failure test for diagnosis and monitoring treatment response 2003: West Nile virus blood screening assay available for use by U.S. manufacturers 2003: First fully automated, high-throughput diagnostic instrument for detecting <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoea</i> 2004: First pharmacogenomic array to identify variations in drug metabolism 2004: First oral specimen rapid HIV test	1965: Social Security Amendments authorizing Medicare and Medicaid 1966: AMA establishes and publishes first CPT coding system 1967: <i>Clinical Laboratory Improvement Act (CLIA)</i> - Federal government enacts licensing, regulatory authority over clinical laboratories 1973: Federal Register published new FDA regulations on labeling requirements & procedures for standards for diagnostics 1976: Medical Devices Amendments to Food, Drug, & Cosmetic Act 1983: Social Security Amendments enacted, including Medicare prospective payment system based on DRGs 1984: Deficit Reduction Act requires labs to bill Medicare directly; creates Clinical Laboratory Fee Schedule to cap payments for lab services 1988: Clinical Laboratory Improvement Amendments consolidate regulation of all clinical laboratories under one statute* 1990: Safe Medical Devices Act 1990: Negotiated Rulemaking Act enacted 1992: Safe Medical Device Amendments establish single reporting standard for user facilities, manufacturers, distributors 1993: ICD-10 codes first released by World Health Organization as an option to replace ICD-9 codes 1996: Health Insurance Portability and Accountability Act (HIPAA) enacted 1997: FDA Modernization Act 1998: EU In Vitro Diagnostics Directive 1999: FDA Draft Guidance on Labeling for Laboratory Tests 1999: Balanced Budget Refinement Act of 1999 pays outpatient clinical laboratory tests at Critical Access Hospitals (CAHs) on a reasonable cost basis versus a fee schedule 2000: Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000 (BIPA) 2001: Final rule in <i>Federal Register</i> establishes NCDs for 23 diagnostic tests as a result of negotiated rulemaking with industry stakeholders 2002: Medical Device User Fee & Modernization Act 2002: FDA Office of IVD Device Evaluation and Safety (OIVD) formed to consolidate regulatory oversight of diagnostics 2002: CMS publishes interim final rule regarding inherent reasonableness (IR) authority 2003: Compliance required for IVDs: all IVD products must be "CE marked" or be prohibited from sale in EU 2003: FDA draft guidance for pharmacogenomic data submissions released 2003: Medicare Prescription Drug, Improvement and Modernization Act (MMA) enacted 2004: Freeze on clinical laboratory fee schedule becomes effective through 2008 2005: Genetic Information Nondiscrimination Act of 2005

* As discussed previously, certain types of clinical laboratories are not covered under CLIA (1988) as specified in the February 28, 1992 Federal Register (57 FR7139).

Launched in 1990, the Human Genome Project (HGP) is an initiative to characterize the full complement of human genes and serve as a roadmap for better understanding of how genes influence disease development. This understanding is leading to new avenues for diagnostic and treatment development.²⁶ The initial working draft of the HGP was published in 2001, comprising approximately 30,000 genes in the human genome and over three billion DNA base pairs of genetic information. As information resulting from this and related efforts emerged, other technological and diagnostic innovations occurred, including proliferation of entirely new testing modalities. These have included array-based and biosensor technologies that enable high throughput and rapid analysis of DNA, proteins, metabolites and other biochemicals.²⁷ Such advances have enabled development of integrated and highly sophisticated diagnostics that process multiple samples rapidly and more cost effectively than was previously possible.

2. Diagnostics Today

New domestic policies, including those stemming from negotiated rulemaking for Medicare coverage of clinical laboratory testing and the Medical Device User Fee and Modernization Act in 2002 and MMA 2003, have expanded the regulatory requirements for diagnostics. The Negotiated Rulemaking Act of 1990 established a voluntary process in which all stakeholders are brought together in public negotiation sessions to develop a consensus on some or all aspects of a rule.²⁸ This process has since been utilized with regard to issues surrounding clinical laboratory testing. For example, in the Balanced Budget Act of 1997, Congress stipulated that policies concerning the administration of claims for laboratory tests payable under Part B of Medicare be developed through the process of negotiated rulemaking.²⁹ In multi-year collaborations, a broad spectrum of stakeholders involved in clinical laboratory testing (e.g., physicians, laboratories, government agencies and representatives from the diagnostics industry) convened for negotiated rulemaking for Medicare coverage of clinical laboratory testing. This process led to new requirements for clinical laboratory documentation and billing under Medicare.³⁰

The Medicare, Medicaid and SCHIP Benefits Improvement and Protection Act of 2000 (BIPA) required Medicare to establish procedures for determining payment and coding for new clinical diagnostic lab tests and addressed the need to speed the coverage and appeals process. Among other requirements, BIPA set NLAs capping payments for new tests (i.e., tests with NLAs established on or after January 1, 2001) based upon 100% of the median of local fee schedule amounts. Payment for tests with NLAs established before January 1, 2001, was capped at 74%

²⁶ Human genome project information. Washington, DC: Human Genome Program of the US Department of Energy Office of Science, 2004. Accessed October 1, 2004.

http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml.

²⁷ Collins FS. Testimony on advances in genetic research and technologies: challenges for public policy. Washington, DC: Senate Committee on Labor and Human Resources, July 25, 1996. Accessed October 21, 2004. <http://216.239.41.104/search?q=cache:BMFUdxN6dOgJ:www.hhs.gov/asl/testify/t960725a.html+Human+Genome+Project+diagnostic+advances&hl=en>.

²⁸ Breger MJ. Negotiated rulemaking. Washington DC: US Department of Labor, 2004. Accessed November 5, 2004. <http://www.dol.gov/asp/programs/negreg/nrbintro.htm>.

²⁹ Mannen T. Negotiated rulemaking for Medicare coverage: what have we learned? IVDT 1999;9:22.

³⁰ Statement of the American Clinical Laboratory Association to the workgroup for electronic data interchange on the HIPAA standards for electronic transactions. Washington DC: American Clinical Laboratory Association. Accessed November 8, 2004.

<http://www.wedi.org/cmsUploads/pdfUpload/eventsPresentationInformation/pub/ACF2155.pdf>.

of the median local fee schedule amounts.³¹ This legislation also mandated that Medicare beneficiaries are not liable for any copayment, deductible, coinsurance or other cost sharing vehicle for diagnostic lab services provided in outpatient critical access hospitals and that these facilities be reimbursed on the basis of reasonable cost rather than according to the clinical lab fee schedule.³² BIPA is regarded as a positive policy step for the diagnostics industry, as it brought together multiple stakeholders (including the diagnostics industry) to discuss reimbursement levels for diagnostic services.

The US diagnostics industry has been affected as well by increasing international regulations for health-related technologies. One of the most significant regulatory changes of the late 1990s was the introduction of the In Vitro Diagnostics Directive (IVDD) by European Union member countries. As of December 2003, the IVDD requires that all IVDs produced within and imported by the EU must meet specific regulatory requirements and obtain a CE mark (a declaration by the manufacturer that a product meets the requirements of the IVDD) in order to be sold in the EU.³³ As a result, diagnostics manufacturers within the US must meet labeling and language requirements to sell products in Europe. For example, the IVDD requires translation of labeling into appropriate national languages and encourages the use of harmonized symbols, which typically are not used without accompanying text within the US.³⁴ As the IVDD has posed significant challenges to the labeling, packaging and distribution systems of diagnostic manufacturers, the industry has worked to develop best practices for label translation and design.³⁵

Substantial scientific advances also have occurred during just the last few years. In addition to the completion of the human genome draft sequence in 2001, advances in other scientific and technology sectors, such as informatics and microprocessing, have led to the development of diagnostics that can be incorporated into electronic medical records, smaller diagnostics that can be used at the bedside and more advanced diagnostics such as those that generate genetic, proteomic (study of the proteins produced by genes) and metabolomic (study of the body's metabolic reactions to stress and/or disease) information.

Scientific advancement and substantial parallel regulatory changes in recent years have significantly expanded and altered the diagnostics industry. Evolving regulatory initiatives, such as the final Guidance for Industry Pharmacogenomic Data Submissions (2005) and drug-diagnostic co-development draft concept paper (2005), will expedite the development of drugs and associated companion diagnostics as we learn more about the relationships between genetics and drug response.^{36,37} Recent legislation, such as the Genetic Information

³¹ CMS manual system. Pub. 100-04 Medicare claims processing. 2005 annual update for clinical laboratory fee schedule and laboratory services subject to reasonable charge payment. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed April 12, 2005. http://www.cms.hhs.gov/manuals/pm_trans/r363cp.pdf.

³² Federal legislation and regulation: the Medicare, Medicaid, and SCHIP benefits improvement and protection act of 2000. Washington, DC: American Hospital Association. Accessed November 10, 2004. http://www.hospitalconnect.com/aha/member_relations/cah/regulation.html.

³³ Dati F. The new European directive on in vitro diagnostics. Clin Chem Lab Med 2003;41(10):1289-98.

³⁴ Heuberger A. Labeling and language requirements under the IVD directive. IVDT;6(1):22.

³⁵ Ibid.

³⁶ Guidance for industry. Pharmacogenomic data submissions. Rockville, MD: US Food and Drug Administration, 2005. Accessed April 12, 2005. <http://www.fda.gov/cder/guidance/6400fnl.pdf>.

³⁷ Drug-diagnostic co-development concept paper. Draft. Rockville, MD: US Food and Drug Administration, 2005. Accessed April 12, 2005. <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf>.

Nondiscrimination Act of 2005, will enhance opportunities for diagnostic development by providing essential protections affecting use of patient diagnostic information.³⁸ While there appears to be no ceiling for expansion and advancement within the diagnostics industry, current and potential regulatory developments will affect the direction and magnitude of these advances, as well as patient access and payment for these.

D. Main Categories of Diagnostics

While all diagnostics analyze samples collected from the body, the specific technology employed varies considerably depending on the type of information needed. For example, a blood sample may be obtained for a number of reasons: a) detection of cancerous cells; b) monitoring of the levels of biochemicals (such as insulin, glucose and cholesterol) or compounds (such as iron); or c) detection of infectious disease. While delineations between categories are not always distinct, the range of diagnostic test applications can be divided into five broad industry segments: a) general or clinical chemistry; b) immunochemistry; c) hematology/cytology; d) microbiology; and e) molecular testing (see **Figure 1.4**). Certain types of tests, such as fecal occult blood testing (FOBT), may be offered in various formats across these segments, reflecting different detection strategies and the rapid evolution of many diagnostics.

Figure 1.4
Categories and Examples of Diagnostic Products

Clinical Segment	Purpose	Examples
Immunochemistry	Match antibody-antigen response to indicate the presence or level of a protein, frequently used in point-of-care testing (POCT) and blood banking	• Immunoassay tests for troponin • Antibiotic susceptibility testing • anti-Tg (for thyroid disease) • Alpha-fetoprotein (AFP) tests • Enzyme immunoassays (EIAs) for specific antigens • Direct fluorescent antibody tests (DFA) • HIV antibody testing • Testing for allergic reactions • Prostate specific antigen (PSA) testing • Fecal occult blood testing (FOBT) • Substance abuse tests • Tumor markers
General (Clinical) Chemistry	Measurements of base compounds in the body (often performed on patient entry into a hospital)	• “Chem 7” chemistry panel performed on blood serum • Urinalysis strips • Calcium level testing • Phosphorus level testing • Serum iron studies • Cholesterol tests • Fasting plasma glucose tests • Hemoglobin A1c (HbA1c) testing • Fecal occult blood testing (FOBT) • Vaginal pH levels • Carbohydrate deficient transferrin (CDT)

³⁸ Genetic Information Nondiscrimination Act of 2003. US Senate 2003. Accessed November 12, 2004.
<http://thomas.loc.gov/cgi-bin/query/D?c108:1:/temp/~c108X5FdtE>.

Clinical Segment	Purpose	Examples
Hematology/ Cytology	Study of the blood, blood-producing organs and cells of the body. Currently the most frequently ordered tests in clinical labs	• Complete blood count • Partial thromboplastin time (PTT) testing • CD4 cell counts • Preoperative coagulation tests • Estradiol tests • Papanicolaou (Pap) smear
Microbiology/ Infectious Disease	Detection of disease-causing agents	• Streptococcal testing • Bacterial urine testing/urine culture • Antibiotic susceptibility testing • West Nile virus (WNV) blood screening • SARS blood screening
Molecular: Genomic, Proteomic, Metabolomic	Study of DNA and RNA to detect genetic sequences that may indicate presence or susceptibility to disease	• HER2/neu overexpression testing • Epidermal growth factor receptor gene (EGFR) testing • Antibiotic susceptibility testing • Pharmacogenetic testing using microassays • BRCA-1 and BRCA-2 testing • Nucleic acid hybridization tests and nucleic acid amplification tests • Fluorescence in situ hybridization (FISH) for prenatal abnormality detection • SARS PCR assay • Pharmacogenomic profiling • Cytochrome p450 (CYP450) diagnostics • Polymerase chain reaction (PCR) and real-time PCR • HIV viral load testing and other HIV assays • Genomic disease management tests to monitor disease progression and recurrence

Source: Adapted from RBC Capital Markets (*The In-Vitro Diagnostics Industry*) classifications.

- 1) **Clinical chemistry**, which involves the measurement of compounds and chemical reactions in the body, and immunochemistry (i.e., testing for the presence or level of substances involved in immune response) represents the largest revenue segment of diagnostic testing. The clinical chemistry sector is very broad and involves detection and measurement of certain chemicals indicative of changes in organ function or status of various biological systems (e.g., circulatory system, metabolic systems, digestive system). Since multiple compounds often must be measured in order to make an accurate assessment of the level of functioning, many clinical chemistry tests are combined and organized into “chemistry panels.” Some battery of clinical chemistry tests usually are performed on all patients upon entry into the hospital, because they provide a broad information base regarding patients’ overall health.³⁹
- 2) **Immunochemistry** is a branch of immunology that focuses on the chemical and biochemical detection of immune reactions. Tests in this category measure the body’s antigen/antibody reaction (i.e., the body’s natural immune response) to foreign agents (e.g., external environmental agents, internal autoimmune response). Immunochemistry tests can be used

³⁹ Smith RE. *The Diagnostics Outlook to 2005*. London: Datamonitor PLC, 1998.

in testing for cancer, allergies, fertility and infectious disease, among other conditions, and are primarily performed by hospital and commercial laboratories as well as blood banks.⁴⁰

- 3) **Hematology** involves the science of the components of the blood (e.g., hemoglobin, white blood cells, platelets) and blood-producing organs with hematology tests designed to count and characterize these blood components. These tests help to detect blood abnormalities, including an inability to clot, which can indicate an adverse drug reaction or serious medical condition such as hemophilia, or abnormal proliferation of white blood cells, a warning sign of leukemia. While not specifically confined to the study of blood, the field of cytology examines cells within the body, including cellular samples obtained to diagnose diseases such as cervical cancer. Cytology tests are applicable to a wide range of health conditions, including sickle cell anemia, thrombocytopenia and blood-borne cancers.
- 4) **Microbiology** is the science of investigating microorganisms (e.g., viruses, bacteria, fungi, algae). Tests in this category are designed to directly detect the presence of disease-causing agents and to determine microorganism resistance to specific treatments such as antibiotics. Microbiology tests range from simple streptococcus testing of an individual with a sore throat to screening of the blood supply for West Nile virus. These tests are increasingly important in the identification and control of emerging contagious infections such as severe acute respiratory syndrome (SARS) and West Nile virus.
- 5) **Molecular diagnostics** includes genetics, proteomics and metabolomics.⁴¹ Tests in the molecular diagnostics category investigate the molecular relationships within organisms (e.g., link between genes and function of metabolic pathways, drug metabolism and disease development), with a primary focus on the study of DNA, RNA and proteins. Within molecular diagnostics, genetic tests focus on how genes affect health status, while proteomic tests study the functions, structures and chemical modifications of proteins (the molecules responsible for performing the majority of cellular functions). Proteomic tests can be used to investigate associations between various protein types and bodily levels and onset or progression of disease. The emerging category of metabolomic testing examines the body's ability to use and excrete chemicals or metabolites (e.g., lipids, sugars/carbohydrates).⁴² When combined with genomic and/or proteomic data, metabolomic data will help clinicians better characterize cause and effect relationships for disease development. The already substantial molecular diagnostics market is growing at a rate of about 25% per year and is anticipated to undergo rapid expansion.^{43,44} Molecular diagnostics are expected to lead to major advancements in pharmacological therapy, such as the customization of drug selection and dosing for more personalized health interventions and patient management.

⁴⁰ Immunochemistry. Abbott Park, IL: Abbott Laboratories, 2004. Accessed November 2, 2004 http://www.abbottdiagnostics.com/Your_Lab/default.cfm?syscat_id=28&path=1.

⁴¹ Adams A. Metabolomics: small molecule 'omics. *Scientist* 2003;17(8):38.

⁴² RFA: metabolomics technology development. Rockville, MD: National Institutes of Health, 2004. Accessed November 1, 2004 <http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-002.html>.

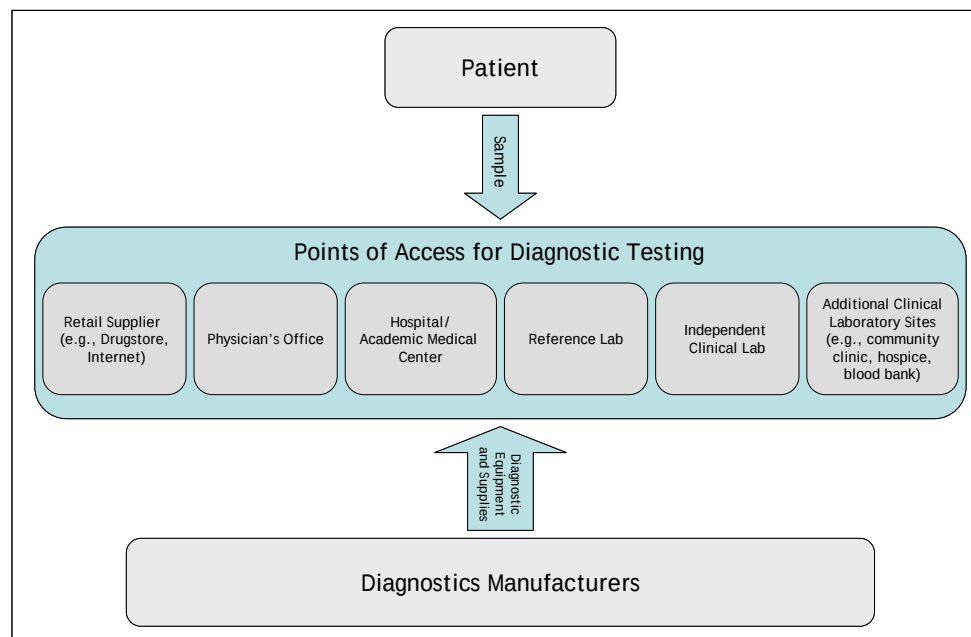
⁴³ Quirk WR. The in-vitro diagnostics industry: overview and emerging opportunities. Toronto, Canada: RBC Capital Markets, 2003.

⁴⁴ Ross JS, Ginsburg GS. The integration of molecular diagnostics with therapeutics. *Am J Clin Path* 2003;119(1):26-36.

E. Settings of Use

To understand the utility and value of diagnostics within health care, it is important to understand the primary customers of the industry and the many ways of obtaining diagnostic services. Consumers of diagnostics include individual patients, physician practices, hospitals, reference laboratories, academic medical centers, nursing homes and other facilities such as hospices and blood donation centers. As shown in **Figure 1.5**, there are multiple points of entry into the diagnostics supply chain, depending on the customer's needs and level of technical and resource capability.

Figure 1.5
Points of Entry in the Diagnostics Supply Chain



Source: The Lewin Group, Inc.

There are currently more than 186,000 clinical laboratories in the US alone where diagnostics are used. The diversity of locations where diagnostics can be accessed is demonstrated in **Figure 1.6**. The number of settings by type is not indicative of the volume of tests performed at that site of service. While the majority of diagnostic tests are used within physician offices, hospitals, clinics and other health care facilities, **individual patients** can purchase some diagnostics directly from retail outlets, such as drugstores and Internet sites, and conduct their own tests in the privacy of their homes. The most frequently purchased home testing diagnostics include blood glucose monitors and pregnancy tests.⁴⁵ Patients also may purchase diagnostics that allow them to collect samples and send them directly to a reference lab for processing and analysis, as is the case with home-based drug abuse tests and some tests for sexually transmitted diseases.

⁴⁵ Lewis C. Home diagnostic tests: the ultimate house call? FDA Consumer Magazine 2001;35(6)..

Figure 1.6
Sites of Clinical Laboratory Service by Type in the US (2004)

Type of Laboratory	Number	Percent
Ambulatory Surgical Centers	3,229	1.7%
Community Clinic	6,717	3.6
Comp, Outpatient Rehabilitation Facility	205	0.1
Ancillary Testing Site in Health Care Facility	2,712	1.5
End-Stage Renal Disease Dialysis Facility	3,657	2.0
Health Fair	482	0.3
Health Maintenance Organization	657	0.4
Home Health Agency	8,308	4.4
Hospice	1,285	0.7
Hospital	8,749	4.6
Independent	5,162	2.8
Industrial	1,647	0.9
Insurance	49	0.02
Intermediate Care Facility for Mentally Retarded	856	0.5
Mobile Laboratory	1,096	0.5
Pharmacy	2,423	1.3
School/Student Health Facility	1,771	0.9
Skilled Nursing Facility/Nursing Facility	14,792	7.9
Physician Office	103,378	55.4
Other Practitioner	2,239	1.2
Tissue Bank/Repositories	36	0.02
Blood Banks	361	0.2
Rural Health Clinic	982	0.5
Federally Qualified Health Center	247	0.1
Ambulance	1,993	1.1
Public Health Laboratories	119	0.06
Other	13,582	7.3
Total	186,734	100.0%

Source: Clinical Laboratory Improvement Amendments. Baltimore, MD. Centers for Medicare & Medicaid Services; 2004 August.

For tests that require involvement of a health care provider, **physician practices** are often the next access point. Physicians may offer blood work or other basic tests within the confines of their office (through POCT or benchtop/near-patient diagnostics), or they may collect a sample and send it directly to a reference lab for analysis or more complex and esoteric tests. The majority of diagnostic testing is conducted within **hospitals**, either within central labs that process many samples daily or at other sites, particularly the patient's bedside. Diagnostic testing in the hospital setting represents about 60% of the diagnostic industry's revenue.⁴⁶ Diagnostic equipment used in this setting can range from small, specialized POCT instruments to complex instruments that are comparable in size to small automobiles. **Other health provider settings**, such as nursing homes, other long-term care facilities, public health clinics and other health care agencies, represent additional access points for testing.

⁴⁶ Smith RE 1998.

When diagnostic capabilities are needed beyond those provided in hospitals and physician practices, analysis is conducted in **reference labs**. While reference labs comprise only 2.8% of all clinical labs within the US, these facilities are responsible for 32% of the diagnostic industry's revenue, due to their focus on processing large volumes of diagnostic tests for a broad client base.⁴⁷ Reference labs generally perform both routine testing and esoteric testing. The largest reference labs may conduct more than 4,400 different types of tests, ranging from high-throughput routine tests (e.g., routine culture, cholesterol tests, Pap smears) to complex or specialized diagnostic tests for Lyme's disease, cancer, cardiovascular disease and HIV.

Limited numbers of specialized tests for rare disorders also may be marketed by certain academic medical center laboratories or reference labs. Analyte specific reagents (ASRs) and test procedures and components developed in-house by laboratories are two mechanisms to address the need for tests for these rare diseases. While a hospital/academic lab or reference lab might develop a component and testing procedure independently, ASRs are produced by a diagnostics manufacturer. These tests are discussed in greater detail in **Section IV**.⁴⁸

F. Value of Diagnostics to Health Care and Health Status

Diagnostics are an indispensable and increasingly valuable component of high quality health care. When asked about the tools necessary to substantially improve health care quality, health care executives have ranked diagnostics fourth, directly following information technology, which ranked first, and physical infrastructure improvements in emergency rooms and other patient care departments, which ranked second and third respectively.⁴⁹ While diagnostics are most commonly considered to be tools for establishing a diagnosis, their application, contribution to quality care and value across all phases of patient care are much more expansive and often under-recognized (see **Section II** and **Section VII**).

In addition to the value to individual patients, diagnostics also are responsible for larger scale contributions to the nation's hospitals, health systems and networks and public health. Diagnostics directly and indirectly influence health quality, resource utilization, health outcomes and costs. The role of diagnostic tests as standards of care (e.g., as incorporated into clinical practice guidelines) and as quality measures to track the adequacy of health services by health insurers, health care systems and national accrediting bodies, underlines essential and multifunctional contribution to patient care (see **Section VII**). Further, protection of the public's health involves heavy reliance on diagnostics to detect infectious diseases such as West Nile virus and SARS and potential bioterrorism threats such as anthrax, smallpox and botulism.

⁴⁷ Smith RE 1998.

⁴⁸ FDA has been involved in regulation of tests kits and systems since passage of the Medical Device Amendments of 1976. Until 1997, FDA was not actively involved in regulation of in-house, so-called "home brew," tests or in regulation of the building blocks sold and used to create these tests. In 1997, FDA published a final rule classifying the building blocks of in-house tests as analyte specific reagents (ASRs) and subjecting manufacturers of ASRs and the laboratories using them to incremental regulation. The purpose of this rule was to clarify FDA oversight for in-house tests in relation to the oversight provided by CMS under CLIA and to ensure that these ASRs would be made consistently according to the agency's quality system regulations. Analyte specific reagents; Small entity compliance guidance; Guidance for industry. February 26, 2003. Rockville, MD: US Food and Drug Administration, 2003. Accessed April 12, 2005. <http://www.fda.gov/cdrh/oivd/guidance/1205.html>.

⁴⁹ Blendon R, Schoen C, DesRoches CM, et al. Confronting competing demands to improve quality: a five-country hospital survey. *Health Affairs* 2004;23(5)119-35.

Diagnostic information is an invaluable foundation for decisions made by the spectrum of health stakeholders, including patients, clinicians, health care providers, health care purchasers and public health officials for patient-specific and population-wide health care procedures, services and measures. Recent advances in the biological sciences, genomics, computing and telecommunications have enhanced the capacity for diagnostic innovation and have set the stage for new health information processing and health services paradigms (see **Section VII**).

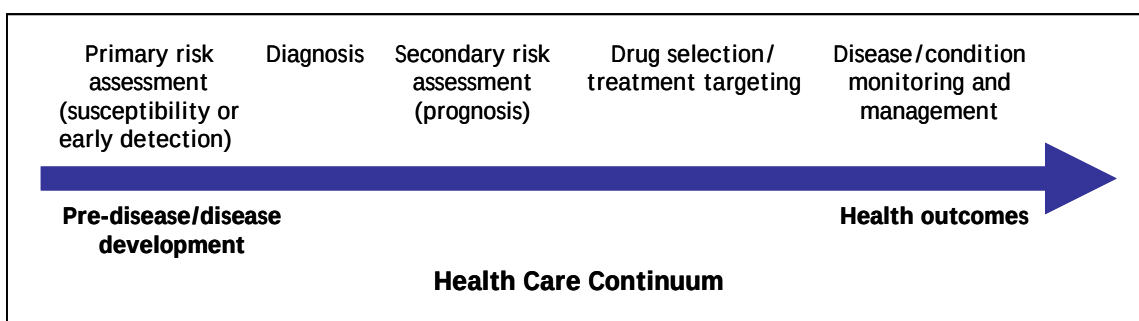
This report is intended to provide insight into the diagnostics industry, including the factors affecting innovation for new products and the diffusion and access to diagnostic technologies (e.g., product development, markets for diagnostics, health regulatory and payment systems). To illustrate the value of diagnostics, a detailed explanation of the utility and value of diagnostics at all phases and levels of health care will be provided. Throughout this report, the current and future abilities of diagnostics firms to develop new products and contribute to individual health, health services and systems and local and national economies are discussed in the context of existing enhancers and challenges. An understanding of these factors is essential for developing effective policies that enable diagnostics firms to continue to innovate and provide novel solutions for addressing national and global health challenges in the context of rising patient demand and cost containment measures.

II. Current and Future Use of Diagnostic Products

A. Primary Uses of Diagnostics

Diagnostics provide key and sometimes critical information at multiple points along the health care continuum, from risk assessment and early diagnosis to treatment, patient follow-up and disease management (see **Figure 2.1**). While clinicians and laboratory professionals often classify diagnostics according to test type (e.g., general chemistry, immunochemistry, microbiology, coagulation, hematology, molecular), considering for *what* diagnostics are used and *how* they inform patient decision-making helps to convey their value. Principal uses include primary risk assessment (including predictive and early disease identification applications), diagnosis, secondary risk assessment (prognosis), drug selection and treatment targeting applications and disease/condition monitoring and management. Each of these applications is described in this section. Diagnostics are discussed in this functional manner throughout this report and in greater detail in **Section VII**.

Figure 2.1
Principal Uses of Diagnostics Across The Health Care Continuum
from Earliest Stages of Disease to Health Outcomes



Source: The Lewin Group, Inc.

1. Primary Risk Assessment

a. Predictive Applications/Screening

At the earliest stages, or even years before a disease might emerge, diagnostics can detect nascent disease or determine which patients are at increased risk for developing certain diseases (e.g., breast cancer, melanoma, nonpolyposis colorectal cancer). Determination of increased risk may allow patients and their health care providers to take measures to prevent or reduce this risk of developing a disease/condition, including increased medical monitoring, lifestyle changes and, in certain cases, preventive interventions.⁵⁰ In addition to preventing or minimizing the severity of disease and its effects on mortality, morbidity and quality of life, these measures can, when used appropriately, alleviate downstream health care spending that would have been induced by such disease.

⁵⁰ Genomics and population health: United States 2003. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, 2004. Accessed October 22, 2004. <http://www.cdc.gov/genomics/>.

b. Early Disease Detection

Detection of emerging disease before symptoms appear or at early symptomatic stages confers significant opportunities for early prevention and treatment. Accurate early detection, disease identification and assessment of health status can translate into reduced morbidity and mortality, improved quality of life and reduced treatment costs associated with detection and treatment of disease during later stages. For instance, early detection of colorectal cancer (e.g., using fecal occult blood testing) is associated with more successful treatment and increased survival rates.⁵¹ The value of diagnostics for early disease detection is examined more thoroughly in **Section VII**.

2. Diagnostic

In diagnosis, one or multiple tests are used, typically in combination with patient history and health practitioner experience, to identify a particular existing disease or condition (e.g., heart attack, diabetes, cystic fibrosis). Some tests or test combinations may identify comorbidities in addition to the primary diagnosis, providing information that can inform selection among alternative treatments or adjusting a treatment regimen. Used for this purpose, diagnostics provide clinicians with information essential to making appropriate treatment and patient care decisions.

3. Secondary Risk Assessment - Prognostic

Diagnostic tests also may be used to assess the degree of disease progression or severity and the likelihood of recovery or risk of future adverse health outcomes (e.g., recurrent stroke, cancer relapse). This prognostic information frequently is used to inform treatment decisions tailored to individual patient health status/needs. Prognostic assessment also can include testing for certain comorbidities (e.g., hypertension, cardiovascular disease, acute respiratory infection), the presence of which may inform alterations in treatment options and therapeutic regimen.⁵²

4. Drug Selection/Treatment Targeting

In certain health conditions, a patient's genetic profile or other biological predispositions may influence individual response to a drug. Emerging pharmacogenetic, pharmacogenomic and other molecular diagnostics (see glossary in **Appendix A**) use information about genetic variability to allow accurate and targeted treatment selection tailored to individual needs.⁵³ Knowing which treatments are likely to be successful for a particular patient can allow health practitioners to avoid prescribing potentially harmful or ineffective treatments, resulting in

⁵¹ Colorectal cancer: early detection. Atlanta, GA: American Cancer Society, 2004. Accessed December 8, 2004. http://www.cancer.org/docroot/CRI/content/CRI_2_6X_Colorectal_Cancer_Early_Detection_10.asp?sitearea=&level=.

⁵² de Castro FR, Torres A. Optimizing treatment outcomes in severe community-acquired pneumonia. *Am J Respir Med* 2003;2(1):39-54.

⁵³ Paul NW, Roses AD. Pharmacogenetics and pharmacogenomics: recent developments, their clinical relevance and some ethical, social and legal implications. *J Mol Med* 2003;81:135-40.

improved patient health outcomes and cost savings resulting from more effective health decision-making.⁵⁴

5. Disease/Condition Monitoring and Management

Certain chronic diseases require continuous monitoring to avoid serious disease or treatment complications, maintain safe and effective bodily levels of therapeutic drugs and screen for emerging resistance to medications or co-occurring infection (e.g., septic infection) or other disease. Commonly used for these purposes, diagnostics are instrumental in helping clinicians and patients manage complex, currently incurable or later-stage diseases or conditions. Effective disease monitoring and management often is linked to reduced health care utilization and costs and improved patient quality of life (see **Section VII**).^{55,56}

B. In Vitro Diagnostics: Overview of Future Trends and Directions

Each of the main ways of using diagnostics has the potential to mediate patient health outcomes and inform clinical decisions in important ways. The significance of diagnostics is anticipated to increase as they evolve with other interventions and with health information technology. Emerging and future diagnostics will have wide-ranging impacts on all aspects of health care; further, they will help to advance new fundamental concepts of care and improve the quality of health services. Key trends and directions in diagnostics are introduced below and discussed in greater detail in **Section VII**.

1. Predict Disease Before Symptoms Appear

Diagnostics continually are evolving to enable more sensitive and specific detection of disease at earlier stages via measurement of biological chemicals, proteins, metabolites (e.g., cholesterol, glucose) and infectious organisms. Today, many gene-based and other molecular diagnostics are emerging that enable identification of susceptibility to disease long before symptoms occur. As noted above, these diagnostics offer new opportunities for disease prevention and treatment.

The chief catalyst of this evolution has been the Human Genome Project (HGP). In 2000, a published draft sequence of the entire human genome was presented and honored by President Clinton at a White House ceremony.⁵⁷ The sequence of the human genome serves as a foundation for understanding how our genes influence human health and disease, as well as our response to many pharmaceuticals and other health care interventions. The years of research leading to this landmark accomplishment not only are resulting in expanded understanding of disease pathways and processes, but are leading to major advances in clinical medicine, medical technology, computer science, information technology that contribute to improved health and quality of life.

⁵⁴ Rusnak JM, Kisabeth RM, Herbert DP, McNeil DM. Pharmacogenomics: a clinician's primer on emerging technologies for improved patient care. *Mayo Clin Proc* 2001;76(3):299-309.

⁵⁵ Testa MA, Simonson DC, Turner RR. Valuing quality of life and improvements in glycemic control in people with type 2 diabetes. *Diabetes Care* 1998;21:C44-52.

⁵⁶ Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans for poor glycemic control. *Diabetes Care* 1997;20:1847-53.

⁵⁷ The Human Genome Project completion: frequently asked questions. Bethesda, MD: The National Human Genome Research Institute, National Institutes of Health, 2004. Accessed October 25, 2004. <http://www.genome.gov/11006943>.

Progress in understanding individual disease susceptibility has enabled development of more targeted interventions and opened the door for a new generation of molecular diagnostic tests applicable to multiple stages of disease. These tests enable prevention and earlier treatment that can delay or reduce adverse health outcomes and health spending associated with later-stage disease.

For example, genetic testing for BRCA I and II mutations can indicate individual risk for developing breast or ovarian cancer (discussed in greater detail in **Section VII**). This knowledge enables women and their health providers to take steps to minimize risks and avert future adverse health outcomes. Preventive options for such patients, depending on risk level, may range from behavioral/lifestyle changes (e.g., exercise, diet, regular self breast examination), increased medical surveillance for high-risk individuals and, in certain cases, consideration of preventive mastectomy or ovary removal.⁵⁸

The potential scope and approximate timeframe for large-scale clinical applications of genomic health care (including susceptibility diagnosis) were described by the Director of the Human Genome Project at NIH, Francis Collins, in his 2003 testimony before the Subcommittee on Health, the Committee on Energy and Commerce and the US House of Representatives:⁵⁹

While it always is somewhat risky to predict the future, I want to leave you with my view of where I believe genomic medicine is headed. In the next ten years, I expect that predictive genetic tests will exist for many common conditions in which interventions can alleviate inherited risk, so that each of us can learn of our individual risks for future illness and practice more effective health maintenance and disease prevention. By the year 2020, gene-based designer drugs are likely to be available for conditions like diabetes, Alzheimer's disease, hypertension, and many other disorders. Cancer treatment will precisely target the molecular fingerprints of particular tumors, genetic information will be used routinely to give patients more appropriate drug therapy, and the diagnosis and treatment of mental illness will be transformed.

The CDC Office of Genomics and Disease Prevention currently recognizes genetic tests for more than 1,000 health conditions, of which some 800 have been validated for clinical testing.^{60,61} While impressive, it represents only a fraction of the potential scope of genetic testing for human health. About 90% of currently available genetic tests are for sometimes rare single-gene disorders (e.g., glucose-6-phosphatase deficiency, Huntington's disease), while 95% of human diseases are not caused by single genes.⁶²

Although validation of multi-gene diseases is extremely complex and resource intensive, significant R&D is occurring in such areas as heart disease, diabetes, asthma and Alzheimer's disease. Fuller understanding of genomic and related information (e.g., proteomic,

⁵⁸ The Human Genome Project completion: frequently asked questions, 2004.

⁵⁹ The Future of Genomics. Statement of Francis S. Collins, MD, PhD, Director, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services. Testimony before the Subcommittee on Health, Committee on Energy and Commerce and United States House of Representatives, 2003. Accessed October 25, 2004. <http://www.genome.gov/11007447>.

⁶⁰ Genomics and Population Health: United States 2003, 2004.

⁶¹ Gene Tests. Seattle, WA: 2004. Accessed September 19, 2004. www.geneclinics.org.

⁶² Ibid.

metabolomic) will enhance our ability to manage these complex diseases. **Figure 2.2** notes rapidly expanding areas of scientific inquiry, from which future diagnostics related to complex diseases/conditions are likely to emerge.

Figure 2.2
Rapidly Expanding Areas of Scientific Inquiry

Term	The Study of ...
<i>Genomics</i>	All of the genes in a person or an organism
<i>Glycomics</i>	Carbohydrate-protein interactions at the cellular level, particularly in cell-cell and cell-tissue interactions.
<i>Metabolomics</i>	The body's metabolic reactions to stress and/or disease
<i>Pharmacogenetics</i>	The effects of genetic variation on differential efficacy and side effects of drugs
<i>Pharmacogenomics</i>	Genetic variation in biomarkers, targets or target pathways, particularly the use of tests for these in conjunction with drug therapies
<i>Proteomics</i>	The proteins produced by genes
<i>Transcriptomics</i>	All of the RNA transcripts produced by the genome at one time

Note: Definitions for these terms are evolving and not yet standardized.

Some observers predict that, within the next five to seven years, genetic information will become standard in patient medical records and susceptibility tests will be validated and available for multiple multi-gene/complex disease indications. Our growing knowledge of the interactions of genes, the environment and individual health behaviors will place greater emphasis on prevention of disease. This shift toward prevention in disease management ideology will be influenced in large part by the continued evolution of rapid, more accurate and better integrated novel diagnostics.^{63,64,65}

Many experts remain skeptical about the implementation of gene-based and related molecular diagnostics, citing potential challenges, limitations and unintended consequences resulting from the use of such diagnostics. For instance, some have raised concern regarding the difficulty of validating the clinical utility of some gene-based tests (especially how use of the test affects health outcomes).⁶⁶ Using diagnostic tests that lack appropriate clinical characterization may result in unacceptable levels of false positive and false negative test results and subsequently unnecessary actions by patients and health practitioners. Many also have noted the need to increase educational efforts for health practitioners regarding these emerging diagnostics and

⁶³ Lea D. A new world view of genetics service models. On J Issues Nurs 2000;5. Accessed October 21, 2004. http://www.nursingworld.org/ojin/topic13/tcp13_6.htm.

⁶⁴ Col NF. The use of gene tests to detect hereditary predisposition to chronic disease: Is cost-effectiveness analysis relevant? Med Decis Making 2003;23:441-8.

⁶⁵ Paegel BM, Blazej RG, Mathies RA. Microfluidic devices for DNA sequencing: sample preparation and electrophoretic analysis. Curr Opin Biotechnol 2003;14:42-50.

⁶⁶ Coverage and reimbursement of genetic tests and services. Draft report. Public comment draft. Washington, DC: US Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, April 2005.

their proper interpretation.^{67,68,69} Other concerns include cost and cost-effectiveness considerations, unique regulatory and reimbursement hurdles for gene-based diagnostics and certain social, ethical and legal considerations associated with these technologies. Many of these important considerations are discussed in **Sections IV, V and VI** of this report.

2. Predict Beneficial and Adverse Treatment Effects

Pharmacogenetic (PGx) diagnostics are gene-based diagnostic tests used to determine individual benefits or harms of taking certain medications. One such use of PGx links individual genetic variation to information on drug metabolism (drug breakdown and processing in the body).⁷⁰ For instance, patients who process drugs too rapidly (ultra-rapid metabolizers) may not receive enough of a drug from the standard dose to achieve therapeutic effect, whereas those who process drugs too slowly (slow metabolizers) are at risk for increased side effects, drug-related toxicities and adverse health outcomes.

Emerging PGx capabilities are precipitating an ideological shift within the medical community from a “one size fits all” drug treatment approach to that of “right amount of the right drug for the right patient.”⁷¹ To help scientists and clinicians understand how genetic variations may relate to treatment outcomes, databases that compile and present such information are now becoming publicly available. One such database is PharmGKB: The Pharmacogenetics and Pharmacogenomics Knowledge Base, managed at Stanford University, which houses searchable gene, drug, disease and pathway information.^{72,73} As the relationships between genetic variation, treatment and clinical outcomes are better understood, such databases may adapted for routine use in clinical practice in the future.

Currently, main applications for PGx diagnostic information include:⁷⁴

- 1) Identify those who can benefit most from a particular drug
 - via genetic variations influencing rate and efficacy of drug metabolism
- 2) Identify those at risk for atypical adverse reactions
 - via genetic variations influencing rate and efficacy of drug metabolism

⁶⁷ Coverage and reimbursement of genetic tests and services, 2005.

⁶⁸ Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Affairs* 2004;23(1):77-87.

⁶⁹ Phillips KA, Veenstra DL, Ramsey SD, et al. Genetic testing and pharmacogenomics: issues for determining the impact to healthcare delivery and costs. *Am J Manag Care* 2004;10(7 Part 1):425-32.

⁷⁰ Paul 2003.

⁷¹ Poste G. Molecular diagnostics: a powerful new component of the health care value chain. *Expert Rev Mol Diagn* 2001;1.

⁷² Royle R, Dombrowski SM. Etext on Health Technology Assessment (HTA) Information Resources: Pharmacogenomics. Bethesda, MD: National Information Center on Health Services Research and Health Care Technology (NICHSR), 2001. Accessed October 22, 2004. <http://www.nlm.nih.gov/nichsr/eha/chapter14.html>.

⁷³ PharmGKB: Pharmacogenetics and Pharmacogenomics Knowledge Base. Stanford, CA: Stanford University, 2004. Accessed October 22, 2004. <http://www.pharmgkb.org/home/overview.jsp>.

⁷⁴ Melzer D, Raven A, Detmer DE, et al. My very own medicine: what must I know? Information policy for pharmacogenetics. Cambridge, UK: University of Cambridge, Department of Public Health and Primary Care, 2003. Accessed October 22, 2004. <http://www.phpc.cam.ac.uk/epg/IP.html>.

- via other genetic variations related to drug response, e.g., cardiac channelopathy mutations that increase risks for sudden cardiac death (see **Section VII**)
- 3) Identify biomarkers or pathways for specific therapies
 - 4) Inform selection of the optimal dose or treatment frequency necessary to achieve desired therapeutic effect in an individual patient⁷⁵

The majority of available PGx markers relate to differential drug metabolism.⁷⁶ A well-known example involves testing acute lymphoblastic leukemia patients for one of 12 known mutations that cause abnormally low levels of thiopurine 5-methyltransferase (TPMT),^{77,78} an enzyme that metabolizes 6-mercaptopurine, a drug often used to treat this cancer. In patients with TPMT deficiency, 6-mercaptopurine can accumulate in tissues and cause potentially fatal adverse effects. If PGx testing shows TPMT activity to be low or nonexistent, clinicians can alter the dose of 6-mercaptopurine and avoid complications.⁷⁹

Although PGx diagnostics only now are beginning to emerge, PGx may influence the health care of at least 15% of the US population by 2018. In some cases, PGx diagnostics may be developed independently to identify risks and benefits associated with certain drugs or classes of drugs, e.g., genetic variations in the CYP P450 drug metabolizing enzymes or HER2/neu testing for prescription of the cancer drug Herceptin (discussed in **Section VII**). As genetic/genomic data increasingly is incorporated into human clinical trials, diagnostic and drug combinations also are anticipated to become more common.⁸⁰ Available pharmaceuticals target only about 500 of the 30,000 (<2%) human genes, suggesting significant room for expanding the use of diagnostics to guide targeted treatments.⁸¹

While PGx diagnostics can help ensure that certain patients receive optimal treatment, proper management and reimbursement for procedures involving genetic information (e.g., by third-party payers, employers and others) also is critical to ensure appropriate access to available treatments (**Sections IV, V and VII**).⁸² In addition to these considerations, PGx diagnostics are susceptible to many of the challenges inherent to predictive genetic tests including social, ethical and legal implications (**Section VI**), validation of clinical utility, establishment of medical necessity for test reimbursement, transparency of interpretation and

⁷⁵ PGx information, when coordinated with selection, dose and timing of therapy is sometimes referred to as *theranostics*, an emerging field of molecular diagnostics.

⁷⁶ Ibid.

⁷⁷ Coverage and reimbursement of genetic tests and services, 2005.

⁷⁸ Armstrong VW, Shipkova M, von Ahnen N, Oellerich M. Analytical aspects of monitoring therapy with thiopurine medications. *Ther Drug Monit* 2004;26:220-6.

⁷⁹ Carroll WL, Bhojwani D, Min DJ, et al. Pediatric acute lymphoblastic leukemia. *Hematology (Am Soc Hematol Educ Program)* 2003:102-31.

⁸⁰ Ibid.

⁸¹ Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research: a blueprint for the genomic era. *Nature* 2003;422:835-47.

⁸² Royle R 2001.

certain cost considerations.⁸³ Addressing these challenges will be essential to successful integration of PGx diagnostics into routine health care practice.

As use of PGx data becomes integrated into clinical practice guidelines, electronic medical records and decision support systems, clinicians will increasingly include PGx in routine treatment decisions. Where supported by available evidence, increasing use of PGx holds great potential to yield better treatment selection and disease management strategies.⁸⁴

3. Enable Personalized “Real-Time” Treatment and Disease Management Regimens

For many chronic diseases and conditions (e.g., heart disease, arthritis, abnormal renal function, certain viral infections), treatment is ongoing, and clinicians and patients must maintain adaptable treatment regimens in order to respond to changes in the disease course. Diagnostic tests, especially those that provide rapid or real-time results, can be an essential part of individualized treatment and disease management. Current examples of the many available disease management diagnostics include the following:

- **Blood glucose and glycated hemoglobin tests for monitoring diabetes:** effective control of glucose levels is associated with a significant reduction in common, serious complications of diabetes (e.g., eye disorders, kidney disease, limb amputation).⁸⁵
- **Therapeutic drug monitoring tests to select drugs for resistant HIV strains:** monitoring blood levels of antiretroviral drugs and detecting emerging resistance to drug therapies for HIV/AIDS patients improves the safety and effectiveness of a chosen regimen, including reduced drug toxicity and improved patient care.⁸⁶
- **Cholesterol (and other lipid) testing to monitor the effectiveness of lipid-lowering therapy:** detection and tracking of elevated cholesterol levels may indicate that a change in dosage or drug is necessary to avoid onset or progression of heart disease.

In each of these examples, diagnostic information informs treatment decisions and allows clinicians to reduce the likelihood of unnecessary adverse events. Many more diseases and conditions will be managed using customized, real-time approaches. As medicine becomes increasingly personalized, health information technology and integrated communication networks will enable better channeling of patient diagnostic information to inform the timing and nature of evidence-based health interventions.⁸⁷ Disease management diagnostics are evolving into point-of-care devices or integrated home testing instruments (e.g., using personal

⁸³ Veenstra DL, Higashi MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci* 2000;2(3):E29.

⁸⁴ Khoury MJ. Genetics and genomics in practice: the continuum from genetic disease to genetic information in health and disease. *Genet Med* 2003;5:261-8.

⁸⁵ The State of Health Care Quality: Industry Trends and Analysis. Washington, DC: National Committee for Quality Assurance, 2004. Accessed October 22, 2004. <http://www.ncqa.org/communications/SOMC/SOHC2004.pdf>.

⁸⁶ Duong M, Golzi A, Peytavin G, et al. Usefulness of therapeutic drug monitoring of antiretrovirals in routine clinical practice. *HIV Clin Trials* 2004;5:216-23.

⁸⁷ Shuter J, Kalkut GE, Pinon MW, et al. A computerized reminder system improves compliance with Papanicolaou smear recommendations in an HIV care clinic. *Int J STD AIDS* 2003;14(10):675-80.

digital assistants) that track changes in certain disease markers and communicate results more readily to health practitioners.⁸⁸ These trends in disease management should result in improved control of symptoms and disease progression, greater treatment effectiveness and more comprehensive health care options for patients with chronic conditions.

4. Facilitate Point-of-care and Near-patient Testing

Point-of-care testing (POCT) and near-patient testing allow physicians to conduct rapid diagnostic tests while the patient waits, rather than sending samples to hospital or other centralized laboratories. Such rapid diagnostics equip health practitioners with information on patient health status and care options during the office and hospital visits. This immediate responsiveness reduces delays in effective health decision-making, allows rapid response to critical situations such as heart attack or trauma, as well as routine and noncritical situations, and can reduce downstream health care costs.⁸⁹ Examples of POCTs already in use include:

- blood glucose tests for monitoring diabetes
- cardiac marker testing (e.g., troponin, myoglobin) for rapid assessment of heart injury/heart attack
- blood clotting tests for pre-surgical risk assessment
- HIV antibody testing

The evolution of rapid HIV antibody testing over the past 20 years provides a useful example of the evolution and utility of POCTs. In 1985, the first HIV antibody test was approved by the FDA. This initial HIV test involved an enzyme immunoassay laboratory test of patient blood to detect antibodies to the HIV virus. In 1994, the FDA approved the first oral specimen HIV antibody test, which measures antibodies collected from the tissues of a patient's cheek/gums.⁹⁰ While it marked an important innovation in HIV antibody testing, this method still required processing in a central laboratory and substantial waiting time for the patient to receive test results.⁹¹ HIV testing made the jump to POCT in 2002 when the FDA approved an immunoassay test that could identify HIV infection in 20 to 40 minutes using a whole blood finger-prick sample.⁹² This diagnostic exhibits many elements of conventional POCT testing, including small size (similar to many OTC pregnancy tests), portability and processing simplicity. In 2004, the FDA approved a second-generation immunoassay test that employed

⁸⁸ Kerkenbush NL. A comparison of self-documentation in diabetics: electronic versus paper diaries. AMIA Annu Symp Proc 2003:887.

⁸⁹ The State of Health Care Quality: Industry Trends and Analysis, 2004.

⁹⁰ HIV/AIDS historical time line 1991-1994. Rockville, MD: US Food and Drug Administration, 2004. Accessed December 7, 2004. <http://www.fda.gov/oashi/aids/miles91.html>.

⁹¹ Statement on FDA approval of AIDS virus test system based on oral fluid samples. Rockville, MD: US Food and Drug Administration, 1994. Accessed October 15, 2004. <http://www.fda.gov/bbs/topics/NEWS/NEW00503.html>.

⁹² FDA approves new rapid test kit. Rockville, MD: US Food and Drug Administration, 2002. Accessed October 15, 2004. <http://www.fda.gov/bbs/topics/NEWS/2002/NEW00852.html>.

similar testing technology that uses a cheek swab instead of whole blood, for taking the least invasive specimen possible.⁹³

Consumer expectations for diagnostics, such as rapid results, increased automation, simpler operation and enhanced portability/reduced size will continue to drive development of POCT devices.⁹⁴ Evolving technologies such as nucleic acid amplification techniques, microarrays and multiplexed technologies will provide a strong scientific foundation for the next generation of POCT diagnostics.⁹⁵ POCT diagnostics will continue to play a significant role in health decision-making, particularly in areas where rapid and accurate response is closely tied to health outcomes (e.g., diagnosis of heart attack, assessment of trauma patients, identification of certain infectious diseases including antibiotic resistant strains) and where ready access to testing can improve patient compliance and continuity of care.⁹⁶

5. Enable Home Testing

Advances in point-of-care, convenient and rapid diagnostic testing also have opened the door to home applications. These tests can be completed in the home, or they can involve self-collection of blood, saliva, urine or other specimens that are shipped directly to the manufacturer or a reference laboratory for rapid turn-around. To date, the FDA has approved nearly 500 home-based tests for over-the-counter (OTC) purchase.⁹⁷ While diagnostics such as pregnancy tests and ovulation predictor kits still account for approximately 33% of this market, diagnostics for a variety of other conditions now occupy a considerable segment of the market.^{98,99}

Examples of such diagnostics are tests that detect:

- lipid levels to gauge risk for heart disease
- illegal drugs or other abused drugs
- antibodies to viruses and other infectious diseases
- tests that allow assessment of blood thinning and/or clotting
- fecal occult blood tests that indicate colorectal cancer

Although home testing for management of chronic diseases is expected to remain an important area of diagnostic development, there has been a shift in recent years toward home testing to

⁹³ FDA approves first oral fluid based rapid HIV test kit. Rockville, MD: US Food and Drug Administration, 2004. Accessed October 15, 2004. <http://www.fda.gov/bbs/topics/news/2004/NEW01042.html>.

⁹⁴ Tudos AJ, Besselink GJ, Schasfoort RB. Trends in miniaturized total analysis systems for point-of-care testing in clinical chemistry. *Lab Chip* 2001;1:83-95.

⁹⁵ Marsh P, Cardy DL. Molecular diagnostics: future probe-based strategies. *Methods Mol Biol* 2004;266:167-89

⁹⁶ Yang S, Rothman RE. PCR-based diagnostics for infectious diseases: uses, limitations, future applications in acute-care settings. *Lancet Infect Dis* 2004;4:337-48.

⁹⁷ Device evaluation information: IVD OTC list. Rockville, MD: US Food and Drug Administration, 2002. Accessed October 15, 2004. <http://www.fda.gov/cdrh/ode/otctable.html>.

⁹⁸ Lewis C. Home diagnostic tests: the ultimate house call? Rockville, MD: US Food and Drug Administration Consumer Magazine, 2001. Accessed October 15, 2004. http://www.fda.gov/fdac/features/2001/601_home.html.

⁹⁹ With home testing, consumers take charge of their health: tests available for home use. Washington, DC: American Association for Clinical Chemistry, Lab Tests Online, 2004. Accessed October 15, 2004. <http://www.labtestsonline.org/understanding/features/hometesting-2.html>.

screen for or diagnose certain conditions (e.g., HIV, colorectal cancer, chlamydia).¹⁰⁰ This may be particularly relevant to diseases that pose social or personal concerns for some individuals (e.g., sexually transmitted diseases) or as an alternative to testing methods that are more invasive or associated with low patient compliance (e.g., colonoscopy for detection of colon cancer). Of course, these tests are not necessarily substitutes for tests conducted by physicians, but they are becoming more accurate and reliable over time. By enabling testing for many patients who would not otherwise seek testing by physicians, they provide a point of entry and awareness for patients to seek care.¹⁰¹

An example of these benefits is home-based osteoporosis screening (currently available in the UK), which involves collecting specimens at home and shipping them to a reference laboratory for analysis.¹⁰² This approach allows those with limited mobility or access to transportation to obtain results conveniently at home. Similarly, home testing for chlamydial infection not only allows individuals to obtain test results privately and seek treatment if results are positive, but increases the likelihood that males will be tested for this disease. Males typically are less compliant with chlamydia testing recommendations and can remain asymptomatic for long periods.^{103,104} Earlier and more comprehensive identification and treatment of infected individuals provides opportunities for treatment before complications such as infertility and pelvic inflammatory disease occur and limit the spread of chlamydia infection.

Web-based interfaces are anticipated to better link patients, health practitioners and laboratories, facilitating more comprehensive home testing processes.¹⁰⁵ Some fertility and glucose monitoring diagnostics already are available that allow individuals and their physicians to track changes in health status and conveniently share information using personal digital assistants or other data storage and communication devices.^{106,107} Where applicable, these diagnostic options will continue to redefine physician-patient relationships and the role of the patient in health decision-making as new diagnostic interfaces continue to emerge.

6. Public Health, Environmental, Bioterrorism Applications

Public health, environmental and bioterrorism-related diagnostics are used to detect infection/disease in individuals and for tracking population-level outbreaks. These applications are introduced as follows and discussed in greater detail in **Section VII**.

¹⁰⁰ What to expect: the future of home testing. Washington, DC: American Association for Clinical Chemistry, Lab Tests Online, 2004. Accessed October 15, 2004.
<http://www.labtestsonline.org/understanding/features/hometesting-5.html>.

¹⁰¹ Lewis C 2001.

¹⁰² Ibid.

¹⁰³ Bloomfield PJ, Steiner KC, Kent CK, Klausner JD. Repeat chlamydia screening by mail, San Francisco. *Sex Transm Infect* 2003;79:28-30.

¹⁰⁴ Ford CA, Viadro CI, Miller WC. Testing for chlamydial and gonorrheal infections outside of clinical settings: a summary of the literature. *Sex Transm Dis* 2004;31:38-51.

¹⁰⁵ What to expect: the future of home testing, 2004.

¹⁰⁶ May K. Home monitoring with the ClearPlan Easy Fertility Monitor for fertility awareness. *J Int Med Res* 2001;29:14A-20A.

¹⁰⁷ Keshavjee K, Lawson ML, Mallow M, et al. Technology failure analysis: understanding why a diabetes management tool developed for a Personal Digital Assistant (PDA) didn't work in a randomized controlled trial. *AMIA Annu Symp Proc* 2003:889.

In public health, diagnostics have an array of applications, including population-level genetic screening of newborns, rapid identification of pathogens in disease outbreaks and identification of organisms that have developed antimicrobial resistance and determining risk of future epidemics. Advances in understanding the genetics and lifecycles of humans and infectious organisms have enabled development of increasingly sophisticated diagnostics for detecting public health threats.^{108,109} As novel diagnostics continue to emerge in this area, public health threats can be characterized and contained more quickly and efficiently, affecting fewer individuals in improving public health management options.

Response to bioterrorism and/or infectious disease represents a specialized area within public health that presents unique challenges and considerations. Diagnostics contribute to two key factors related to bioterrorism response: a) rapid detection of the causative pathogen or toxin; and b) initiation of proper containment and treatment measures. Newly developed rapid detection diagnostics (e.g., for anthrax, smallpox, SARS, West Nile virus), may help decrease the time between introduction of a pathogen and detection, enabling faster and more effective threat response.^{110,111,112} Many of these emerging diagnostics also are being adapted for field use in emergency situations, ideally allowing containment efforts to begin before an infected person ever enters a health care facility.

Additional environmental/public health applications of diagnostic tests include monitoring biological and chemical levels in water and soil, surveillance of disease among marine and land animals and controlling growth of certain microorganisms that become harmful when present in massive numbers.^{113,114} Toxic biological or chemical agents in water or soil also may become incorporated into human food sources and have detrimental downstream effects on public health and national or global economies.¹¹⁵ Assessing the health of various marine and land animals also may be vital to protecting our agricultural supply chain and human health. A prominent example of this is mad cow disease (i.e., bovine spongiform encephalopathy), which can cross over to humans via consumption of contaminated cattle products in the form of variant Creutzfeldt-Jakob disease, a progressive and fatal neurodegenerative condition.^{116,117} Monitoring livestock using emerging diagnostics offers opportunities for rapid disease identification and timely response before unnecessary harm to livestock and humans can

¹⁰⁸ Khoury MJ 2003.

¹⁰⁹ Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naïve HIV-1-infected persons in 10 US cities. *J Infect Dis* 2004;189:2174-80.

¹¹⁰ Baeumner AJ, Leonard B, McElwee J, Montagna RA. A rapid biosensor for viable *B. anthracis* spores. *Anal Bioanal Chem* 2004;380:15-23.

¹¹¹ Sofi Ibrahim M, Kulesh DA, Saleh SS, et al. Real-time PCR assay to detect smallpox virus. *J Clin Microbiol* 2003;41:3835-9.

¹¹² Casman EA. The potential of next-generation microbiological diagnostics to improve bioterrorism detection speed. *Risk Anal* 2004;24:521-36.

¹¹³ Blackburn BG, Craun GF, Yoder JS, et al. Surveillance for waterborne-disease outbreaks associated with drinking water – United States, 2001-2002. *MMWR Surveil Summ* 2004;53(8):23-45.

¹¹⁴ Casper ET, Paul JH, Smith MC, Gray M. Detection and quantification of the red tide dinoflagellate *Karenia brevis* by real-time nucleic acid sequence-based amplification. *Appl Environ Microbiol* 2004;70:4727-32.

¹¹⁵ Ibid.

¹¹⁶ Priola SA, Vorberg I. Molecular aspects of disease pathogenesis in the transmissible spongiform encephalopathies. *Methods Mol Biol* 2004;268:517-40.

¹¹⁷ Centers for Disease Control and Prevention. Creutzfeldt-Jakob disease not related to a common venue – New Jersey, 1995-2004. *MMWR Morb Mortal Wkly Rep* 2004;53(18):392-6.

occur.¹¹⁸ Given the critical links between certain environmental chemicals and biological agents and human health, improved surveillance and control of these agents will translate into fewer incidents of disease in humans.

Use of diagnostics for these applications informs appropriate treatment and containment efforts to reduce the spread of infection. Diagnostics development in this area has focused on rapid and accurate results, as well as portable, easy-to-use instruments. Technological advances in these have great potential for cross-over into other segments of diagnostics and health care more broadly, increasing flexibility and responsiveness to changing health care needs.

7. Technology and Testing System Integration

Consumer and health care provider needs and competition in the diagnostics industry drive development of more accurate, rapid, reproducible and higher throughput diagnostics. Many emerging and future diagnostic devices will incorporate these elements, as well as greater flexibility and technology integration, ease of use and compatibility with other instruments or information resources (e.g., electronic medical records, health databases). Future diagnostics will allow health practitioners to capture a much broader range of information relevant to patient health and respond to changing health needs with greater precision.

Emerging technologies, such as DNA or protein microarrays and real-time PCR, are useful for associating expression of various biological products/biomarkers with health status or disease. As new biomarkers are validated, and as the significance of various combinations of biomarkers (in the context of specific disease indications) is better understood, these technologies are being adapted rapidly for a range of diagnostic applications. Although such technologies primarily are employed in R&D at present, some currently are used in assessment of health/disease status, testing the blood supply and organ/cell transplant donors and monitoring levels of infectious, environmental or bioterrorism agents, among other applications.

“Multiplexing,” which involves conducting tests for more than one biomarker in the same vessel, is another expanding trend. This testing paradigm also is being developed in array formats, where multiple multiplex tests can be performed on the same platform or chip. Aside from producing a consolidated set of biomarker data for clinicians, this testing strategy conserves resources (e.g., disposables, reagents) that would be necessary to conduct some or all of these tests independently. Multiplexing has ushered in a new group of diagnostics known as “tandem products,” which combine, for instance, identification of infectious disease pathogens and (drug resistant) strain identification to allow clinicians to prescribe the most beneficial antimicrobial agent.¹¹⁹

As diagnostics become increasingly integrated and capable of generating vast amounts of data, analytical advances and ease of interpretation will facilitate adoption and diffusion of these technologies into routine clinical practice. For example, interpretation of a genetic or biomarker assay that includes several hundred tests may be too complex for use in general medical practice without companion software or information processing to assist with analysis and presentation of diagnostic results. Even though many genetic tests only have to be completed

¹¹⁸ Bradley R, Liberski PP. Bovine spongiform encephalopathy (BSE): the end of the beginning or the beginning of the end? *Folia Neuropathol* 2004;42(Suppl A):55-68.

¹¹⁹ Poste G 2001.

once (because genetic information does not change), as products that identify many hundreds or thousands of markers (e.g., “whole genome scans”) emerge, sophisticated analytical tools will be necessary to decipher the relationships between genetic makeup and disease risks.¹²⁰

Continued advances, such as in electronic medical records and decision support software, will assist clinicians in extracting meaning from such increasingly complex diagnostic results.^{121,122} Already, computerized systems assist with processing certain laboratory tests, and similar systems will decrease diagnostic interpretation time, allowing for more rapid translation into appropriate prevention or treatment efforts.^{123,124} To the extent that information systems for health care providers can keep stride with advances in diagnostic throughput, these technologies hold the potential to dramatically augment patient care delivery.

¹²⁰ Revolutionary genome sequencing technologies – the \$1000 genome. Request for application. The National Institutes of Health. <http://grants.nih.gov/grants/guide/rfa-files/RFA-HA-04-003.html>.

¹²¹ Hellman R. A systems approach to reducing errors in insulin therapy in the inpatient setting. *Endocor Pract* 2004;10(Suppl 2):100-8.

¹²² Garthwaite EA, Will EJ, Bartlett C, et al. Patient-specific prompts in the cholesterol management of renal transplant outpatients: results and analysis of underperformance. *Transplantation* 2004;78(7):1042-7.

¹²³ Ronco G, Vineis C, Montanari G, et al. Impact of the AutoPap (currently Focalpoint) primary screening system location guide use on interpretation time and diagnosis. *Cancer* 2003;99:83-8.

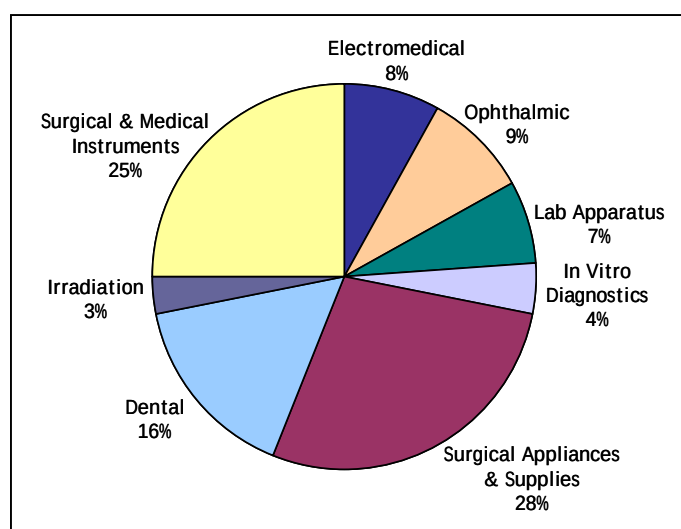
¹²⁴ Vassilakos P, Carrel S, Petignat P, et al. Use of automated primary screening on liquid-based, thin-layer preparations. *Acta Cytol* 2002;46:291-5.

III. Profile of the Diagnostics Industry

A. Scope and Magnitude of the US and International Diagnostics Industry

Companies that manufacture in vitro diagnostics as their primary business line represented 4% of the medical device and diagnostics industry in 2001, according to US Department of Commerce data (**Figure 3.1**).¹²⁵ While the IVD industry represents a relatively small portion of the health care technology sector and the medical device and diagnostics industry in particular, it is an industry in which the US excels. Further, it continues to exhibit considerable growth in domestic and international markets. The worldwide market for IVDs is projected to be \$28.6 billion in 2005, the US share of which will exceed \$11.2 billion.¹²⁶

Figure 3.1
Distribution of Firms by North American Industrial Classifications, 2001



Source: US Department of Commerce.

1. The Global Market

In 2003, the US accounted for 43% of the total international market share for IVDs, the largest percentage for any one country (**Figure 3.2**).¹²⁷ In 2004, the US was the largest exporter of IVD substances, with an estimated \$3.4 billion in products entering the global market. The US export market for these substances has grown steadily from \$2.1 billion in 1998 to \$3.4 billion in 2004, with a compound annual growth rate (CAGR) of 8% (**Figure 3.3**). In addition to being the largest exporter of IVD substances, the US is also one of the largest consumers. In 2004, the US imported a total of \$1.2 billion worth of IVD substances. European markets dominated US imports in 2003 with the UK, Japan, France, Germany and Sweden making up \$1.0 billion of total US imports (**Figure 3.4**). Among the sub-sectors of the IVD industry, tests for cancer

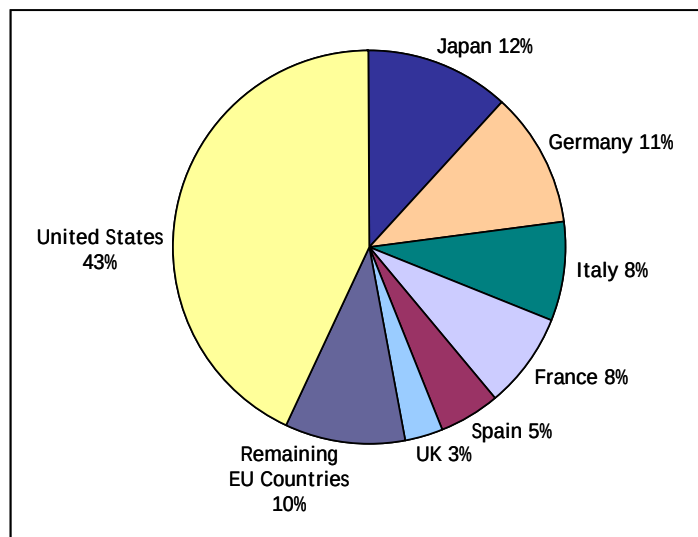
¹²⁵ County business patterns. Washington, DC: Department of Commerce, 1998-2001. Accessed September 1, 2004. <http://www.census.gov/csd/susb/susb01.htm>.

¹²⁶ The Worldwide Market for In Vitro Diagnostic Tests. Hartford, CT: Kalorama Information, 2002.

¹²⁷ Though the projected US market share for the IVD market in 2005 is 39% (nearly 4% less than the actual market share in 2003), this decline partially is attributable to growing competition from countries such as China, India and those in Latin America and Eastern Europe that are anticipated to account for larger percentages of the worldwide market in 2005.

detection and blood processing are forecast to grow the fastest, by 10% and 11%, respectively, from 1997 to 2005 (**Figure 3.5**).¹²⁸ With \$3.4 billion in exports and \$1.2 billion in imports, the US IVD industry had a net trade surplus of \$2.2 billion in 2004, a year in which there was a record national trade deficit of \$617.7 billion for all goods.¹²⁹ The US IVD industry posted an increasing trade surplus every year from 1998 to 2004 (**Figure 3.6**).

Figure 3.2
2003 International *In Vitro* Diagnostics Market Estimates



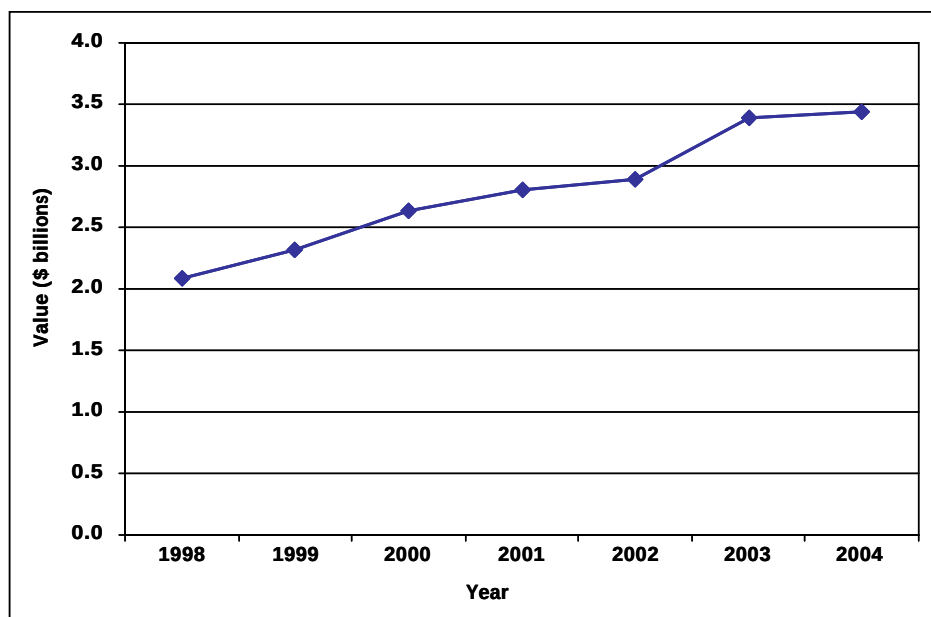
Adapted from:

1. European IVD market estimates 2003. Brussels, Belgium: European Device Manufacturers Association, 2004.
2. The Worldwide Market for In Vitro Diagnostic Tests. Hartford, CT: Kalorama Information, 2002.

¹²⁸ Smith RE 1998.

¹²⁹ Annual trade highlights. Washington, DC: US Census Bureau, 2003. Accessed August 1, 2004.
<http://www.census.gov/foreign-trade/statistics/highlights/annual.html>.

Figure 3.3
Total Exports of US IVD Industry, 1998-2004



Source: Annual trade highlights. Washington, DC: US Census Bureau 2003.

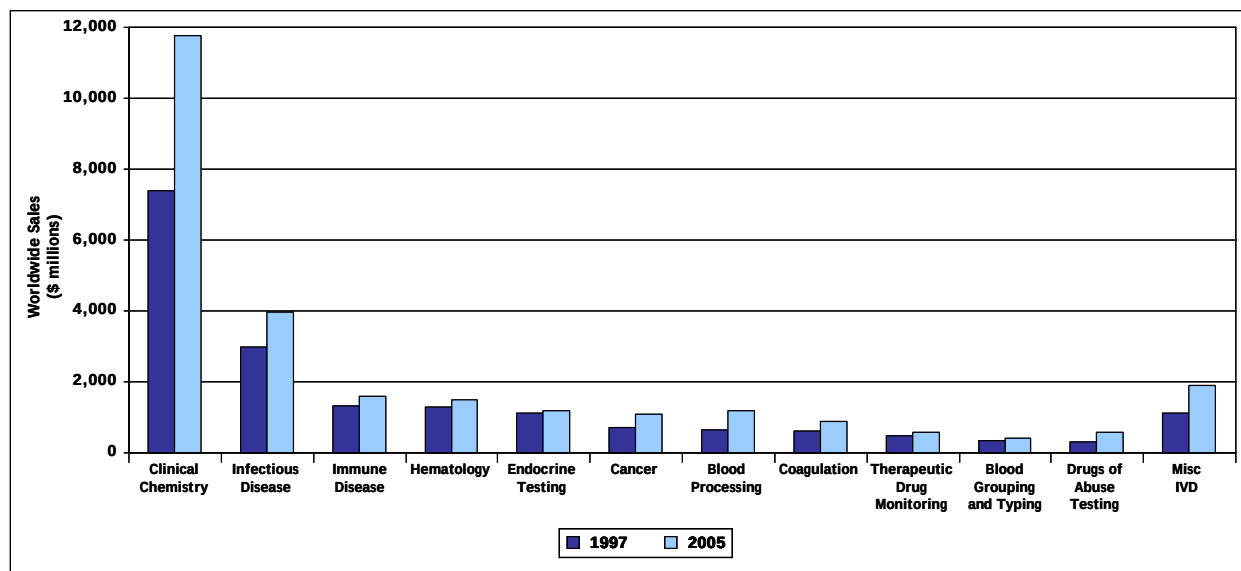
Figure 3.4
US Imports of the IVD Industry: Top 10 Countries, 2004

Country	2004 Value (millions of dollars)
United Kingdom	367.42
Japan	220.24
France/Germany*	168.72
France	168.72
Sweden	83.46
Canada	78.21
Ireland	51.86
Finland	21.12
Australia	14.61
Russia	14.04

* France/Germany indicates Atlantic region ports; All other Germany Baltic Region Ports; etc.

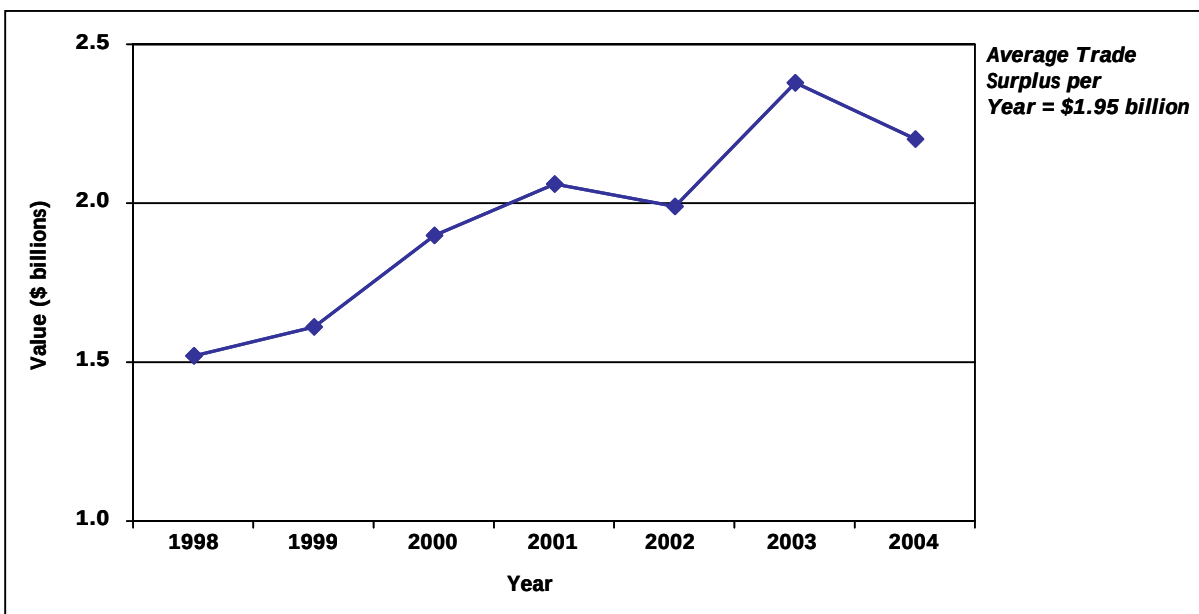
Source: US Census Bureau. US Imports of Selected Merchandise, 2004.

Figure 3.5
Estimated Worldwide IVD Market, by Clinical Segment, 1997 and 2005



Source: Smith, RE. *The Diagnostics Outlook to 2005*. London: Datamonitor PLC 1998.

Figure 3.6
US IVD Industry Trade Surplus, 1998-2004



Source: US Census Bureau. *US Imports of Selected Merchandise*.

Growth of the diagnostics industry has continued, despite trade barriers and market constraints such as inadequate intellectual property rights and price controls.¹³⁰ Regulatory hurdles for exports to EU countries increased in 2003 with its In Vitro Diagnostics Directive (IVDD). The IVDD added diagnostics to existing medical device legislation and new requirements for the translation of diagnostic product instructions into 11 or more distinct languages of the EU.¹³¹ Despite the increase in regulatory oversight, three of the top four overseas destinations for US products in 2003 were EU member countries France, Germany and the UK (**Figure 3.7**).

Figure 3.7
US Exports of the IVD Industry: Top 10 Countries, 2004

Country	2004 Value (millions of dollars)
France/Germany*	737.86
Japan	457.00
United Kingdom	353.62
France	273.49
Canada	268.82
Belgium	173.56
Netherlands	126.14
India	102.10
Australia	87.99
Italy	81.53

* France/Germany indicates Atlantic region ports; All other German Baltic Region Ports; etc.

Source: US Census Bureau. US Imports of Selected Merchandise, 2004.

2. US Diagnostics Industry

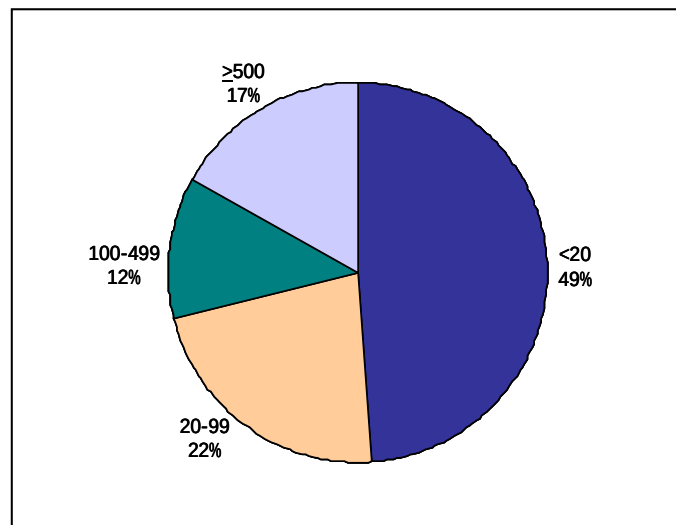
The US diagnostics industry comprises a diverse range of companies, varying by types of products, revenue, number of employees and investment in R&D. While some diagnostics firms focus on particular diseases (e.g., cervical cancer), larger firms typically have highly diversified product lines and research portfolios. Companies range in size from one-person start-ups to multinational corporations with thousands of employees. While larger companies account for the greatest share of the market, 49% of the diagnostics firms employed fewer than 20 people in 2001 (**Figure 3.8**).¹³²

¹³⁰ Arakaki E. Diagnostics. Washington, DC: United States Department of Commerce International Trade Administration. Export America, 2002. Accessed September 1, 2004. <http://www.export.gov/exportamerica>.

¹³¹ Dati F. The new European directive on in vitro diagnostics. Clin Chem Lab Med. 2003 Oct;41(10):1289-98.

¹³² County business patterns 1998-2001.

Figure 3.8
Distribution of US IVD Firms by Number of Employees, 2001



Source: County Business Patterns. Washington, DC: Department of Commerce, 1998-2001.

a. Distribution of US Diagnostics Firms by Product Classification

Products of the diagnostics industry may be divided roughly into the two broad categories of devices and substances. The device side of the industry develops and manufactures the devices, instruments and other products that analyze specimens (from blood, urine, tissue, etc.). These devices can range from hand-held glucose monitors to analyzers the size of automobile minivans. In order to process samples, diagnostic devices require specific substances, called reagents. For example, reagents are the chemicals that are used to mark cancer cells with fluorescence so that they can be distinguished from healthy cells under a microscope, to increase the volume of a blood sample so that fewer blood draws are needed from a patient or to purify samples so that more accurate results can be obtained.

Many diagnostic devices and instruments, including those used in large labs, are considered capital equipment, whose value is amortized over time, sometimes a decade or longer. As such, sales of these products may not reflect current trends of the diagnostics market. Furthermore, government trade statistics frequently categorize IVDs with *in vivo* diagnostic equipment, (e.g., MRI machines and ultrasound scanners), which confounds efforts to isolate market trends for IVD devices. In contrast, sales of reagents and other substances, which are consumed and restocked as needed, provide a better means of monitoring the market for diagnostics. The US Department of Commerce tracks the companies that produce and sell diagnostic substances under code 325413 of the North American Industrial Classification (NAIC) coding system. This code specifically refers to companies engaged in the production of substances that are used only for those diagnostic tests that take place in test tubes, Petri dishes or diagnostic devices.¹³³

Within the NAIC coding system, there are eight distinct product classes of diagnostic substances, including reagents, blood bank products and coagulation products (**Figure 3.9**). In

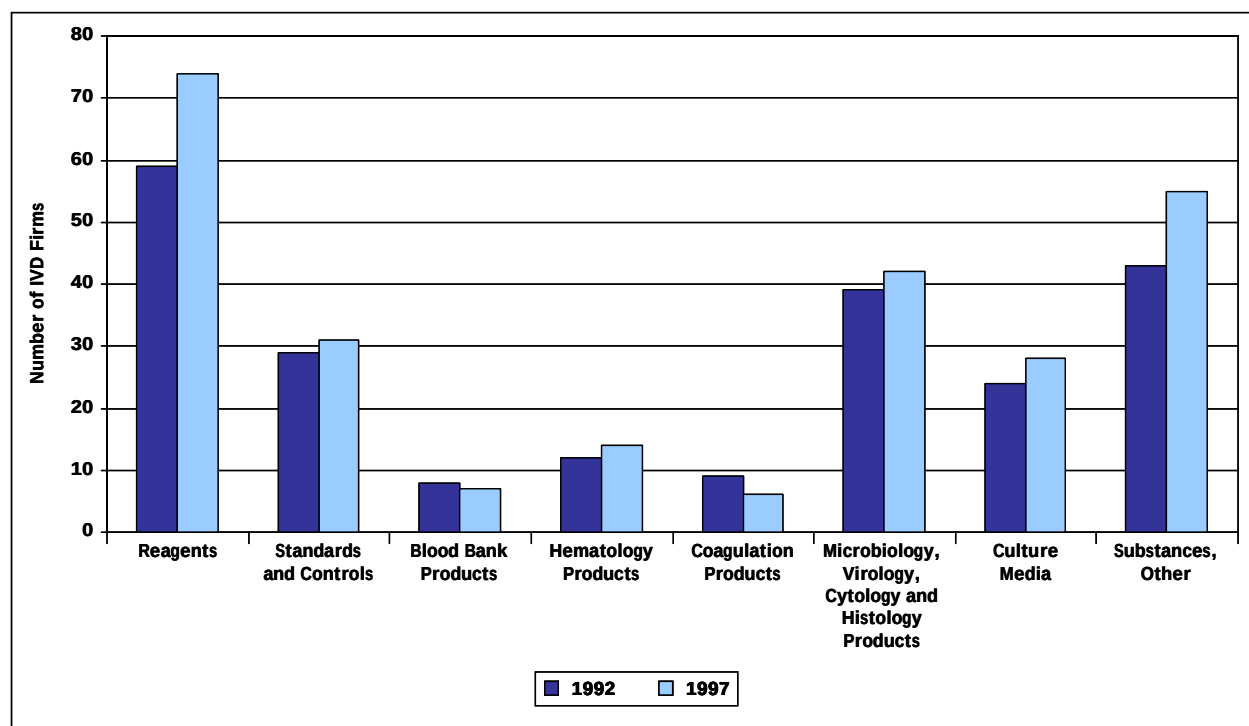
¹³³ Diagnostic substances mfg industry report. Twinsburg, OH: Harris InfoSource International, 2003. Accessed September 15, 2004. <http://www.harrisinfo.com/purdue/DiagnosticSubstancesMfg.pdf>.

1992 and 1997, the Census Bureau provided estimates of the number of firms engaged in the production of each category of products. During that five-year interval, fewer companies with shipments of at least \$100,000 were engaged in the production of products in every category, except for coagulation and blood bank products (**Figure 3.10**). However, the value of these product shipments increased across all categories except for the “other substances” category. These measures indicate that, while fewer companies were engaged in production, the overall value of production continued to grow. Later Census Bureau data indicate that the decrease in the number of diagnostics companies continued from 1997 to 2001 (**Figure 3.11**).

Figure 3.9
IVD Substances by NAIC Code

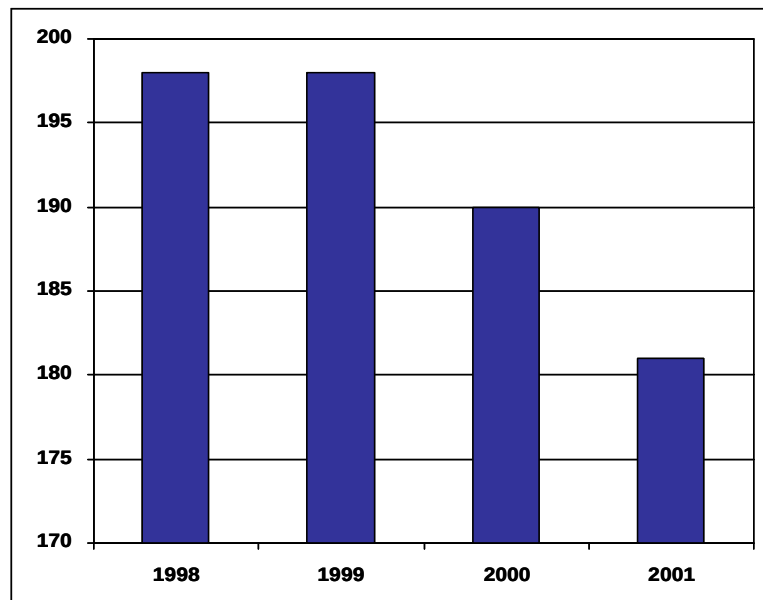
NAIC Code	Substance
32513	Substances
325413011	Reagents
3254130221	Standards and Controls
3254130331	Blood Bank Products
3254130351	Hematology Products
3251430351	Coagulation Products
3254130461	Microbiology, Virology, Serology, Cytology, and Histology Products
3254130571	Culture Media
32541306	Substances, Other

Figure 3.10
IVD Industry Product Lines, 1992 and 1997



Source: *In vitro diagnostic substance manufacturing. Annual Survey of Manufacturers*. Washington, DC: US Census Bureau, 1997.

Figure 3.11
Number of US IVD Companies, 1998 to 2001



Source: County Business Patterns. Washington, DC: Department of Commerce, 1998-2001.

b. Employment Trends of the US Diagnostics Industry

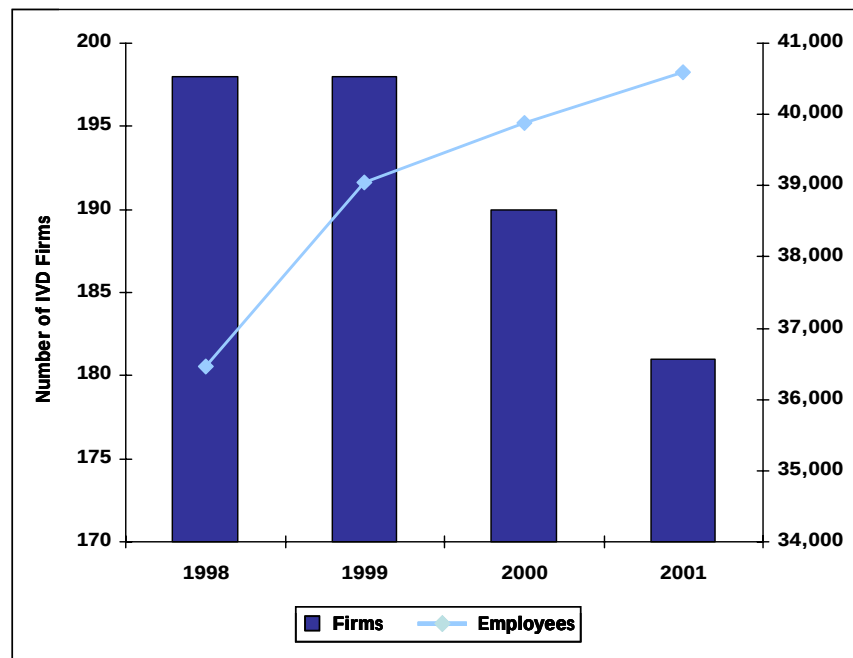
In addition to its production, the diagnostics industry contributes to the US economy by employing a workforce across varying levels of education at salaries well above the national average. Employees in this industry range from manufacturing and production workers to doctoral-level researchers. As a whole, the diagnostic substances manufacturing industry employs more than 40,500 people, only one-third of whom work directly in production.¹³⁴ In 2001, the average salary in the diagnostics industry was \$63,000, comparable to \$62,000 in the pharmaceutical manufacturing industry and 80% higher than the average salary of \$35,000 of all working Americans that year.¹³⁵

The number of companies identified as diagnostic substance manufacturers decreased by 8.6% from 1998 to 2001, while total employment grew by 10% (**Figure 3.12**). These trends were not uniform across all sizes of companies. The number of employees who worked for companies with fewer than 500 workers declined by 30% during this period. At the same time, the number of workers who were employed by companies with more than 500 workers increased by 14%.

¹³⁴ In vitro diagnostic substance manufacturing. Annual Survey of Manufacturers. Washington, DC: US Census Bureau, 1997. Accessed August 1, 2004. <http://www.census.gov/mcd/asmhome.html>. (Pub. No. EC97M-3254C).

¹³⁵ County business patterns 1998-2001.

Figure 3.12
Number of IVD Firms and Total Employment, 1998-2001



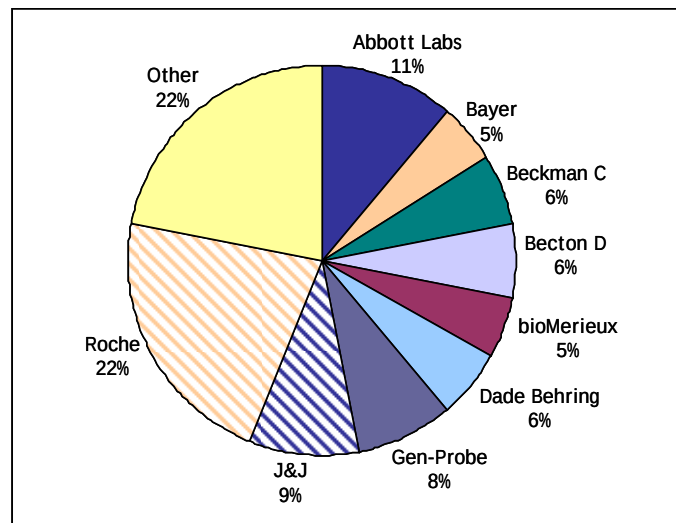
Source: County Business Patterns. Washington, DC: Department of Commerce, 1998-2001.

The trends in production, employment and number of diagnostics companies partially is explained by the merger and acquisition (M&A) activity of the late 1990s through 2003. In 2002, nine companies accounted for 78% of the US diagnostics market (**Figure 3.13**).¹³⁶ With only 22% of the market share left for the approximately 170 other companies, there are clear incentives for M&A for companies of all sizes. In the 1990s, consolidation through M&A provided companies with the means to develop and expand existing product lines. While M&A activity has increased over the past 10 years, market forecasts indicate that this trend will begin to slow starting in 2005, mostly due to the decreasing number of diagnostics firms and increasing maturity for several of the industry's market segments.¹³⁷

¹³⁶ Quirk WR. The in-vitro diagnostics industry: overview and emerging opportunities. Toronto, Canada: RBC Capital Markets, 2003.

¹³⁷ Smith RE 1998.

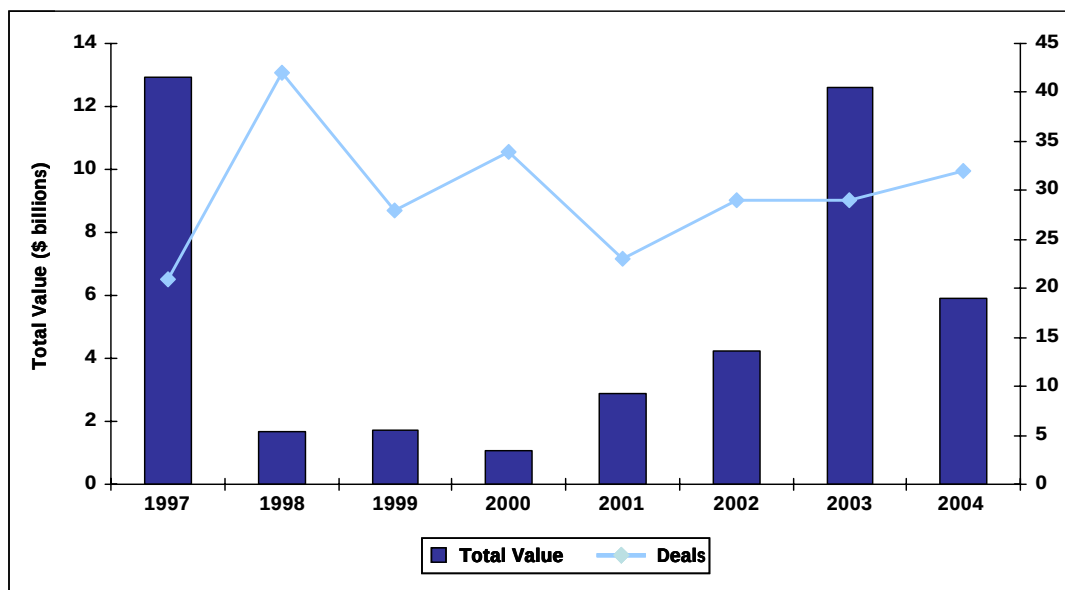
Figure 3.13
US IVD Market Share, 2002



Adapted from: Quirk WR. *The in-vitro diagnostics industry: overview and emerging opportunities*. Toronto, Canada: RBC Capital Markets, 2003.

M&A activity in the diagnostics industry explains some of the employment shift from smaller to larger companies. The high number of M&A transactions between 1998 and 2002 and the low corresponding dollar volume indicates that many smaller firms were acquired by larger ones (Figure 3.14). The most extreme volume-to-dollar ratio in this time frame was in 2000, when 34 diagnostics firms were acquired for a total cost of less than \$1.08 billion (average price of \$31.8 million). The average value of acquisitions increased from 2001 until 2003, with more recent M&A data suggesting a slowing of this trend. During the first half of 2004, 32 companies were acquired for a total of \$5.9 billion, for an average price of \$183.9 million.

Figure 3.14
Mergers and Acquisitions Transaction Volume, IVD Industry, 1997-2004



Source: Proprietary Data from Windhover Information's Strategic Transactions Database.

B. Financing Opportunities in the US Diagnostics Industry

In this highly technical and competitive sector, diagnostics firms face considerable challenges in bringing new technologies to market. These firms require significant capital to finance the R&D, regulatory process, manufacturing scale-up and marketing necessary to advance a new product through the pipeline. While start-up companies typically depend on capital financing prior to marketing of a product, companies with products at all stages of development and marketing use capital financing streams. In general, there are four categories of capital investment, which are not mutually exclusive:

- **Seed investment:** for a company in its embryonic stages, typically up to \$500,000.
- **Start-up investment:** as the company completes its product development and begins initial marketing, approximately \$500,000 to \$1 million.
- **Early-stage funding:** as the company enters the market, but has yet to earn substantial revenue, approximately \$500,000 to \$15 million.
- **Late-stage/mezzanine investment:** for expansion, generally leading to initial public offering (IPO) in 3-18 months or an acquisition, approximately \$2 million to \$20 million.

Discussed below are the private and public equity markets for diagnostics firms and their potential impact on the industry.

The venture capital (VC) market plays an essential role in the diagnostics industry. VC financing represents one of the main sources of funding for start-up companies that have yet to market a revenue-producing product. VC financing for diagnostics start-ups appeared to have stagnated by the end of 1999, partially due to consolidation among the larger companies.¹³⁸ The high dollar amounts of VC investments from 2001 to 2003, compared with the lower number of VC transactions, indicate that more early-stage funding was occurring than seed or start-up investments (**Figure 3.15**). During this time, VC financiers were well aware of the hurdles facing diagnostics firms seeking to bring a product to market, particularly those posed by FDA regulation, third-party payment and the length of time typically required for adoption of new technology by the medical profession.¹³⁹ This contributed to the migration of VC financing toward companies with well-established product lines and clear paths to adequate reimbursement.¹⁴⁰ VC activity in 2004, indicated a return of investments, for seed or start-up ventures, partially due to promising advances in proteomics as well as diagnostics for cancer and cardiovascular disease.¹⁴¹

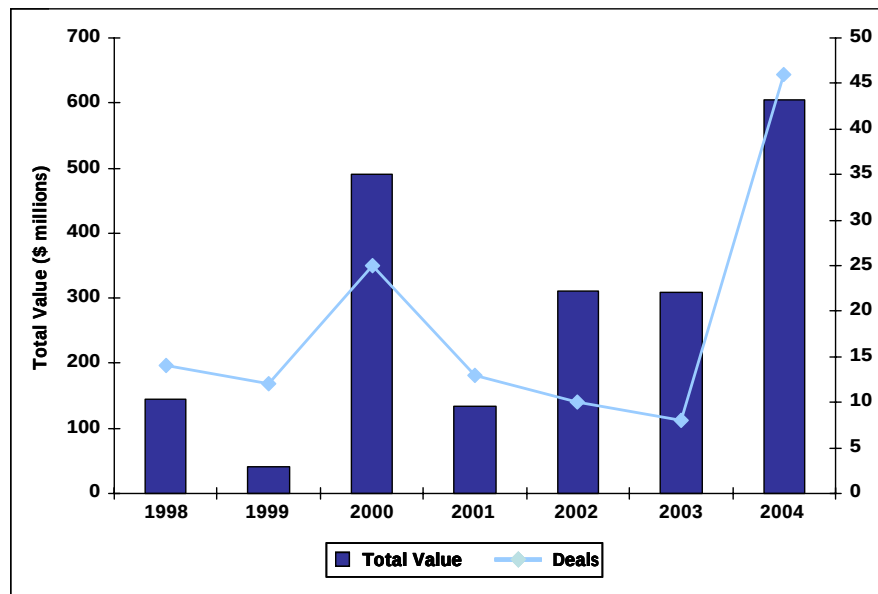
¹³⁸ Diller W. A buyer's market in diagnostics. In *Vivo: The Business and Medicine Report* 1999;51-103.

¹³⁹ Lytton M. It's time to re-examine the diagnostics opportunity. *Start-Up: Windhover's Review of Emerging Medical Ventures*, 2003;41.

¹⁴⁰ The Lewin Group. Report 1: The State of the Industry. 2000.

¹⁴¹ Lytton M 2003.

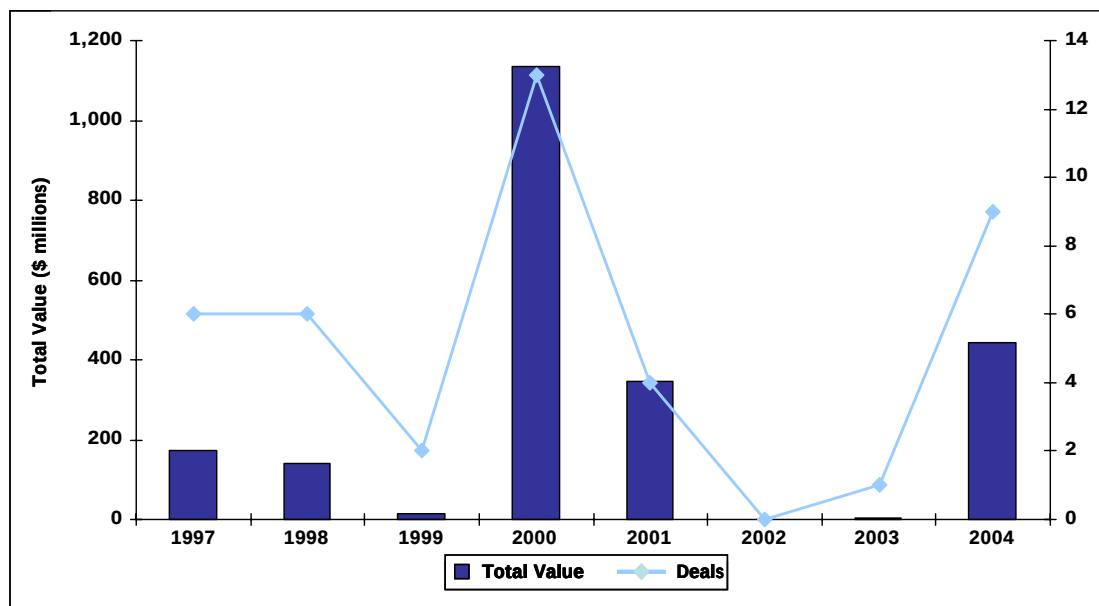
Figure 3.15
Value and Volume of Venture Capital Financing, IVD Industry, 1998-2004



Source: Lewin Analysis of Data from Deal Making, *In Vivo: The Business and Medicine Report*, 1998-2004.

The number of diagnostics firms that have entered public markets through IPOs since 1997 has been modest. The most activity in number of IPOs and dollar volume occurred in 2000, when 13 IPOs were offered, compared to only two from the previous year (**Figure 3.16**). In 2002, a down year for the US stock market, no diagnostics firms entered the public sector. In 2003, there was only one IPO, valued at \$2.8 million. Despite these few years of low market entrance by IVD firms, 2004 indicated the start of a recovery with nine IPOs raising a total of \$442 million.

Figure 3.16
Value and Volume of Initial Public Offerings, IVD Industry, 1997-2004

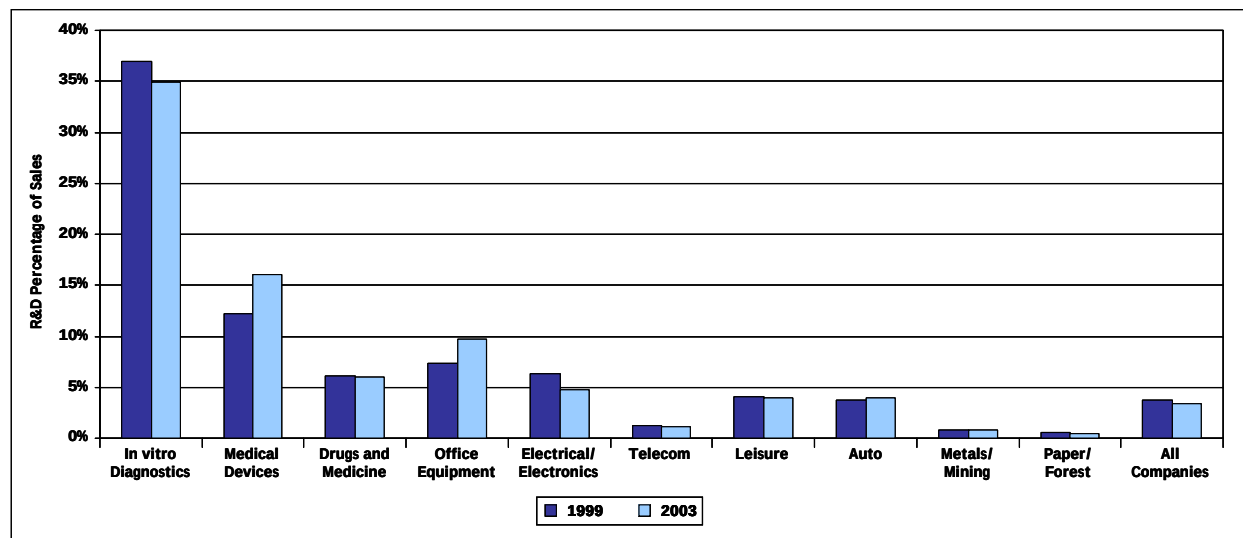


Source: Proprietary Data for Windhover Information's Strategic Transactions Database.

C. Research and Development

The amount of money that diagnostics companies invest in R&D provides some insight into the financial capital dynamics of the IVD industry. According to data from Standard & Poor's Compustat for 2004, companies that produce IVD substances invested approximately 35% of their revenue into R&D. This compared to an average of 11% for the medical devices and diagnostics industry as a whole, 16% for the pharmaceutical industry, and 3.3% for all US industries in 2003 (**Figure 3.17**). Companies that are investing in R&D but have not yet begun to generate revenue (i.e., start-ups and other small firms) are not included in these calculations, which may mean that investment in R&D is higher than these estimates suggest.

Figure 3.17
R&D as Percentage of Sales for Selected Industrial Sectors



Includes a representative sample of IVD and other company types selected by primary business line.

Source: Proprietary data from COMPUSTAT (North America) Database, Standard and Poor's, 2003.

Due to the uncertainties associated with R&D, including the potential for failure and unforeseen delays in the process, these activities can pose significant risk to investors and company survival. Among smaller, publicly-traded companies (those with annual sales of less than \$5 million) the investment in R&D is disproportionately high (**Figure 3.18**). The smallest, typically new companies, can invest amounts that are 200% or more of their revenue into R&D. Of course, companies with established and profitable product lines tend to invest a smaller percentage of revenue into R&D and are less susceptible to the effects of delays or failures associated with any single product. For example, two of the largest diagnostics firms, with \$7.4 and \$2.2 billion in sales respectively, invested 9.8% and 8.9% of their revenue into R&D.^{142,143} Even so, these are substantial percentages compared to other industries and many companies in the health care product sector, and the actual dollar figures (more than \$725 million and \$195 million for the two companies presented here) are substantial financial contributions.

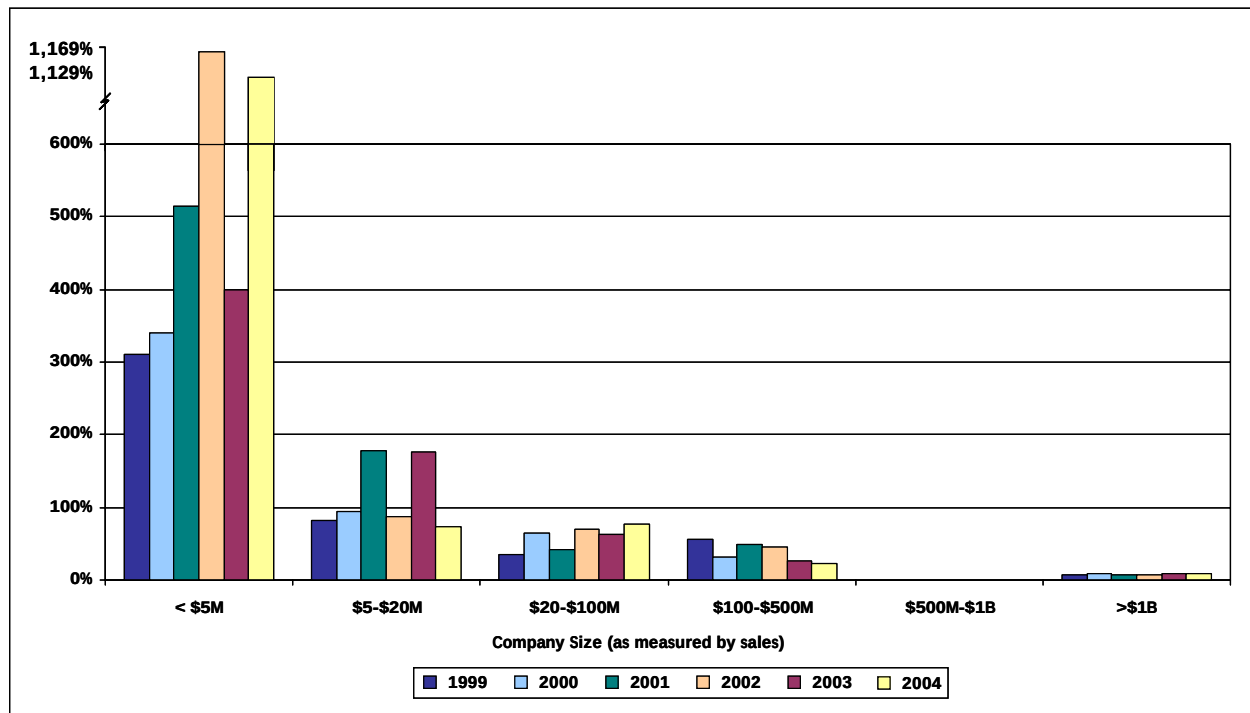
¹⁴² Annual report. Basel, Switzerland: Roche Diagnostics, 2003. Accessed October 1, 2004.

http://www.roche.com/home/figures/fig_annualrep_2003.htm.

¹⁴³ Drawing out information from within. Fullerton, CA: Beckman Coulter, 2003. Accessed October 1, 2004.

http://ir.beckmancoulter.com/ireye/ir_site.zhtml?ticker=BEC&script=11903&item_id='annual.htm'.

Figure 3.18
IVD R&D Spending as Percentage of Sales by Company Size, 1999-2004



Source: Proprietary data from COMPUSTAT (North America) Database, Standard and Poor's, 2003.

D. Main Customers of the Diagnostics Industry

The diagnostics industry serves a diverse customer base with products of considerable range in size, purpose, capabilities and price. Direct customers include reference laboratories, research laboratories, physicians' offices, hospital laboratories, nursing homes, long-term care facilities, clinics and individual consumers. The needs of each of these customers vary considerably from basic clinical chemistry tests to esoteric, highly complex processes such as nucleic acid amplification testing (NAT). Large academic medical centers and reference labs typically have the diagnostic tools to process thousands of specimens for a wide variety of conditions on a daily basis. At the other end of the spectrum, individuals using home testing kits use much smaller devices, such as those for detecting pregnancy or monitoring glucose levels.

The types of products used by each customer may vary greatly, even when they are used to test for the same condition. For instance, a blood glucose monitor in a hospital may have more advanced features than one used by an individual to test at home. Large hospital labs and reference labs typically have large chemistry systems that can process blood, urine and cerebrospinal fluid specimens for a wide variety of tests, including clinical chemistry, immunochemistry, hematology, microbiology, coagulation/hemostasis, genetic testing and molecular diagnostics.

In **hospitals**, the majority of diagnostic testing occurs in central labs, which are responsible for nearly 60% of the diagnostic industry's revenue.¹⁴⁴ Inpatient labs handle information from virtually every patient, even if only a basic blood test. After a sample is collected and sent to the

¹⁴⁴ Smith RE 1998.

lab, it is processed by a lab technician or technologist trained to handle the complexities of lab tests and equipment. With diagnostic instruments that may rival the size of an automobile, central labs typically are focused on simultaneous processing of multiple tests and samples.

Not all lab tests in a hospital are performed in a central lab. POCT is moving many of the tests traditionally conducted in the central lab to the bedside and other sites, enabling more rapid diagnosis and treatment. With advances in information technology, POCT also allows for transmission of diagnostic information from the patient's bedside to central labs, where it may be further reviewed by laboratory staff and incorporated into medical records. POCT devices typically are smaller and more specialized for particular types of tests. For example, new POCT technology in the emergency department (ED) can substantially reduce the amount of time needed to diagnose a heart attack. During a heart attack, distressed cardiac cells secrete the protein troponin into the patient's blood stream. By measuring the levels of troponin while standing at the patient's bedside, physicians can begin appropriate treatment immediately; this can be crucial to limiting damage to the heart muscle. According to a recent study of more than 200 patients presenting with chest pain to an ED in a community-based tertiary care facility, using cardiac POCT yielded results 55% faster than tests sent to the central lab.¹⁴⁵

Many **physician practices** have basic diagnostic devices on-site for throat cultures and basic blood work. Laboratories located in physician practices comprise 55.4% of all laboratories in the US.¹⁴⁶ The diagnostic devices used in physician practice labs are usually much smaller those in hospitals (earning them the title of "benchtop" instruments), and they generally offer a smaller subset of diagnostic tests. Physicians also may use POCT devices in their offices to make faster clinical decisions. As many of the smaller physician practices are not staffed with lab technologists or technicians, the testing process generally is simplified in this setting so that the practice staff can easily obtain results without complex handling of reagents.

When volume or technological constraints limit the diagnostic testing capabilities of a hospital or physician practice, specimens may be sent to a **reference lab**. With an even greater emphasis on volume processing than hospital labs, reference labs receive specimens from hospitals, physician practices and individual patients for analysis. These facilities generally provide routine testing, such as cholesterol tests, blood tests, Pap smears, HIV tests, urinalyses, pregnancy tests and substance abuse tests. Reference labs also may conduct tests that require extremely sophisticated equipment or a substantial amount of professional attention. Referred to as "esoteric tests," there may be less demand for these tests than for more traditional lab tests. Examples of esoteric tests include metabolic studies, genetic tests and certain toxicology tests.

While the majority of diagnostic tests are conducted by clinicians and laboratory personnel, **individual consumers** also purchase diagnostics for private use in their homes. The market for home testing devices expanded from \$1.19 billion in 1994 to \$4.8 billion in 2002.^{147,148} Among home testing devices approved by the FDA are those that measure cholesterol levels, glucose levels, vaginal pH levels, blood clotting time (for patients on blood thinning drugs such as

¹⁴⁵ Caragher TE, Fernandez BB, Jacobs FL, Barr LA. Evaluation of quantitative cardiac biomarker point-of-care testing in the emergency department. *J Emerg Med* 2002;22(1):1-7.

¹⁴⁶ Laboratories by type of service. Baltimore, MD. Centers for Medicare & Medicaid Services; 2004 August. Accessed November 30, 2004. <http://www.cms.hhs.gov/clia/factype.pdf>.

¹⁴⁷ With home testing, consumers take charge of their own health. Washington, DC: American Association for Clinical Chemistry. Accessed May 2004. www.labtestsonline.com.

¹⁴⁸ Quirk WR 2003.

warfarin) and the presence of fecal occult blood (for detecting colon cancer). The FDA also has approved home testing devices that test for hepatitis C virus (HCV) and HIV, as well as for detecting menopause, pregnancy and drug abuse. The most frequently used home testing devices include blood glucose monitors for diabetics, pregnancy tests and cholesterol tests. These home testing devices allow consumers to collect and analyze a sample without interacting with an outside lab. Another type of home testing device requires that a sample be sent to an independent lab for analysis, with results reported directly to the consumer several days or weeks later.

Consumers of home testing devices may use the results obtained from these tests to make health-related decisions with or without consultation from a physician. These devices also may motivate consumers to seek health care, such as following the positive result of a home-based pregnancy test. While the FDA requires that home testing devices be sufficiently user-friendly to ensure that consumers can use them independently of a clinician, improper use of even a perfectly functioning device may lead to inaccurate results. For this reason, the FDA recommends that patients talk with their doctor about the results of any home testing device, especially if results fall into an abnormal range.¹⁴⁹ There is additional concern over the level of consumer protection for Internet-based sales of home testing devices, similar to the concern over pharmaceuticals purchased on-line. In response, the FDA has issued a “buyer-beware” notice, urging consumers to use caution when purchasing a home testing device from an Internet storefront.¹⁵⁰ Despite concerns over incorrect use and improper sale of some home testing devices, those devices that are approved by the FDA for home use provide individuals with a convenient way of learning more about their health at a cost that may be lower than an insurance co-payment for a similar test ordered in a doctor’s office.

In addition to home testing devices, 34 states now provide consumers with the option of ordering diagnostic tests from labs without the written approval of a clinician. With this direct access testing, individuals may go directly to a reference lab for the collection and processing of their samples, and results are provided directly to the consumer without consultation with a physician. The availability of tests depends on the lab providing the services, but they can range from basic blood tests for cholesterol level or thyroid function to complex genetic tests. According to the Clinical Laboratory Improvement Advisory Committee, which reports directly to the US Secretary of Health and Human Services, consumers of direct access testing cite convenience, privacy and cost as reasons for seeking this type of testing.¹⁵¹

E. Main Factors Affecting Diagnostic Product Development

The considerable investment of the diagnostic industry in R&D reflects not only the costs of scientific and technical advancements, but of validating products to meet regulatory and, increasingly, reimbursement requirements. In the US, market approval by the FDA and reimbursement by Medicare, other government payers and private payers are increasingly subject to greater evidence requirements. Companies must demonstrate more often that new technology is cost-saving, and sometimes more cost-effective, compared to more established

¹⁴⁹ Lewis C. Home diagnostic tests: the ultimate house call? FDA Consumer Magazine 2001;35(6). Accessed September 1, 2004. http://www.fda.gov/fdac/601_toc.html.

¹⁵⁰ Buying diagnostic tests from the internet: buyer beware! Rockville, MD: US Food and Drug Administration, 2001. Accessed September 1, 2004. http://www.fda.gov/cdrh/consumer/_buyerbeware.html.

¹⁵¹ Direct access testing-overview. Atlanta, GA: Clinical Laboratory Improvement Advisory Committee, March 2003. Accessed September 1, 2004. <http://www.phppo.cdc.gov/cliac/cliac0303.aspx#t17>.

technology. Obtaining evidence demonstrating the safety and effectiveness of new diagnostic devices generally requires more resource-intensive and lengthy clinical studies. In this section, some of the hurdles to product development in the diagnostics industry are examined, including regulatory and reimbursement requirements and competition within the industry.

1. Regulatory Requirements

Regulation of diagnostics in the US is primarily the responsibility of the FDA, although CMS and other agencies have key regulatory roles affecting laboratory testing and other aspects affecting these products. The success of developing, validating and marketing diagnostics depends in great measure on the ability of manufacturers to navigate certain complex and interrelated regulatory requirements. Regulatory requirements for diagnostics are discussed in greater detail in **Section IV**.

The unit within the FDA that is responsible for regulating most diagnostics is the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), part of the Center for Devices and Radiological Health (CDRH). In addition to OIVD, the FDA Center for Biologics Evaluation and Research (CBER) has a role in regulating certain IVDs, particularly those used in the collection, processing, testing, storage or administration of blood and other biological products.

Regulatory jurisdiction and processes for diagnostics depends on several factors, including the type of device or substance for which approval is being sought and the level of oversight necessary to ensure its safety, effectiveness and appropriate use. There are four primary regulatory pathways for diagnostics: a) premarket notification, otherwise known as the 510(k); b) premarket approval application (PMA); c) classification as an analyte specific reagent (ASR); and d) humanitarian use devices.

As it does for other medical devices, the FDA categorizes these products into three classes. Class I products are considered to present minimal potential for harm and face lesser regulatory scrutiny, such as sterile specimen containers and medicine droppers. Class II diagnostics usually are similar to existing devices on the market for which there is considerable information available on safety and effectiveness, for example, pregnancy test kits. Class III diagnostics generally are novel or present greater potential risk; examples are immunohistochemistry kits and HIV test kits. Class III diagnostics are subject to the most regulatory scrutiny and are generally subject to a premarket approval (PMA) process based on a review of available evidence that the device is safe and effective for its intended use. The evidence collection and review processes for these technologies are often more resource-intensive and time consuming.

ASRs are biological or chemical reagents that are used to identify or quantify substances in biological specimens. These building blocks of diagnostic tests are used by some laboratories to develop their own in-house tests. Manufacturers of ASRs must restrict their sale to certain laboratories designated as “high complexity” under CLIA. Most ASRs are categorized as Class I devices. However, laboratory-developed tests, including those incorporating ASRs, are not regulated by the FDA as such, but are subject to the test performance standards of CLIA. CLIA is administered by CMS, the Federal Trade Commission and state laws (as specified by CLIA, OIVD is responsible for categorizing laboratory tests for CMS).

There are multiple important current regulatory issues pertaining to diagnostics, many of which are addressed in **Section IV**. Among these are FDA's resource and ongoing capacity for processing regulatory submissions, ability of the FDA regulatory process to accommodate technological advances, e.g., uncertainty related to regulation of pharmacogenomic-based products and large bundles ("arrays") of tests, disparities in FDA and CLIA regulation of tests that are functionally similar and appropriateness of current federal informed consent regulations for using patient samples in studies of diagnostics.

2. Coverage and Reimbursement Requirements

Once a diagnostic receives market clearance from the FDA, it still may have to obtain coverage from government and private payers for reimbursement, especially in cases of new technology where existing codes are not applicable. Even where coverage of diagnostics is not at issue, reimbursement by third-party payers often is inadequate, not accounting for the cost of providing the test or the value conferred by it. In its 2000 report, *Medicare Laboratory Payment Policy Now and in the Future*, the Institute of Medicine (IOM) noted that, as the largest purchaser of clinical laboratory services in the US, Medicare's reimbursement policies influence those of other third-party payers. The IOM found that:

[Medicare] payments for some individual tests likely do not reflect the cost of providing services, and anticipated advances in laboratory technology will exacerbate the flaws in the current system. Problems with the outdated payment system could threaten beneficiary access to care and the use of enhanced testing methodologies in the future.¹⁵²

Payments associated with the codes used to bill for clinical lab services may not be at levels that are commensurate with the costs of developing and bringing the technology to market. Further, payment levels may not reflect the additional value to patient health inherent in the technology, especially certain novel diagnostics such as those for genetic or molecular testing. When a more advanced diagnostic test becomes available, it often is reimbursed at the same rate as a less effective or outdated test. This reimbursement structure does not encourage companies to develop new or novel diagnostics and may dampen innovation (these reimbursement issues are addressed in greater detail in **Section V** of this report).

Tests that can predict how a patient will respond to particular drug therapies exemplify how reimbursement may fail to keep up with improvements in diagnostic technology. As described in detail in **Case Study IV**, the diagnostic technology for predicting which breast cancer tumors will respond to the drug Herceptin has improved substantially since the drug's introduction in 1998. The initial diagnostic test, an immunohistochemistry (IHC) assay, was used to detect tumor cells that over-produce the HER-2/neu protein. Concerns over the ability of IHC to definitively identify those tumors that are most likely to respond to Herceptin have been well documented in published medical literature.^{153,154} Newer tests use a technology called

¹⁵² Wolman DM, Kalfoglou AL, Leroy L. Medicare laboratory payment policy now and in the future. Washington, DC: Institute of Medicine, Committee on Medicare Payment Methodology for Clinical Laboratory Services, January 2000. Accessed September 1, 2004. <http://www.iom.edu/report.asp?id=5547>.

¹⁵³ Larsimont D, Di Leo A, Rouas G, et al. HER-2/neu evaluation by immunohistochemistry and fluorescence in situ hybridization in breast cancer: implications for daily laboratory practice. *Anticancer Res* 2002;22(4):2485-90.

¹⁵⁴ Gancberg D, Jarvinen T, di Leo A, et al. Evaluation of HER-2/NEU protein expression in breast cancer by immunohistochemistry: an interlaboratory study assessing the reproducibility of HER-2/NEU testing. *Breast Cancer Res Treat* 2002;74(2):113-20.

fluorescence *in situ* hybridization (FISH) to directly measure an individual's level of HER-2/neu gene expression. When used alone or to confirm the positive results of an IHC assay, FISH has been shown to be more effective in predicting tumor responsiveness to Herceptin than IHC assays alone.^{155,156} Despite technological advances in testing for over-expression of the HER-2/neu gene, and evidence indicating FISH to be more objective than IHC, FISH was assigned to a reimbursement code developed in 1989 that does not sufficiently capture the increased resources needed for the new FISH testing method. Resolution of the reimbursement for this type of testing still was pending with the CMS in 2004, and regional disparities continue to exist among private payers.¹⁵⁷

3. Competition

Although the diagnostics industry is highly competitive, certain factors increase the competitive challenges, particularly for the smaller innovative companies. In the industry, the top nine companies account for 78% of the market, narrowing opportunities for smaller companies.¹⁵⁸ Other factors that have been known to influence the level of competition within the diagnostics industry include actual and perceived uncertainties, risks and benefits inherent in pursuing certain regulatory (i.e., 510[k], PMA and ASR registration) and reimbursement pathways for similar products (when such options exist). In some instances, factors such as familiarity with these processes, access to capital and lack of transparent guidance in emerging areas of technology may result in an uneven playing field for competing companies. Further, the customer base of the industry has undergone changes that affect purchasing power and demand for diagnostics. Laboratory customers of the industry have undergone consolidation and are more likely to be members of group purchasing organizations (GPOs), which tend to establish contracts with larger companies to reduce administrative costs, thereby making it easier for a lab to purchase from larger companies than smaller ones.¹⁵⁹

One of the factors affecting competition in the diagnostics industry is its heavy reliance on patents. Due to the highly technical and research-intensive environment of the industry, patents offer protection for companies that undertake risky R&D to ensure that they benefit exclusively from the success of their efforts for the life of the patent (typically amounting to 20 years). Without the prospect of patent protection, there would be little incentive for diagnostics firms to undertake R&D projects at considerable expense and risk.

An unintended effect of patents is that they may slow further innovation by blocking R&D efforts along avenues patented by other companies.¹⁶⁰ This was the case with genetic testing for the BRCA1 and BRCA2 genes, the presence of which are associated with an elevated risk for developing breast or ovarian cancer. The US Patent and Trademark Office (USPTO) issued patent rights for BRCA1 and BRCA2 to a privately owned diagnostics firm. These rights

¹⁵⁵ Cianciulli AM, Botti C, Coletta AM, et al. Contribution of fluorescence in situ hybridization to immunohistochemistry for the evaluation of HER-2 in breast cancer. *Cancer Genet Cytogenet* 2002;133(1):66-71.

¹⁵⁶ Hammock L, Lewis M, Phillips C, Cohen C. Strong HER-2/neu protein overexpression by immunohistochemistry often does not predict oncogene amplification by fluorescence in situ hybridization. *Hum Pathol* 2003;34(10):1043-7.

¹⁵⁷ Zarbo RJ, Hammond ME. Conference summary, Strategic Science symposium. HER-2/neu testing of breast cancer patients in clinical practice. *Arch Pathol Lab Med* 2003;127(5):549-53.

¹⁵⁸ Quirk WR 2003.

¹⁵⁹ Smith RE 1998.

¹⁶⁰ Heller MA, Eisenberg RS. Can patents deter innovation? The anticommons in biomedical research. *Science* 1998;280:698-701.

included the gene sequences and any resulting applications developed from them, including laboratory tests and targeted drug therapies. The patents allow the firm to control breast cancer susceptibility testing and research and also were found to affect development and provision of potentially more cost-effective testing strategies.¹⁶¹ Despite this instance in which patents appear to have constrained development of new diagnostics, the overall effect of patents on the progress of biomedical R&D generally is positive. In 2003, a committee of the National Research Council, a branch of the National Academy of Sciences, issued a report entitled *Patents in the Knowledge-Based Economy*, in which biomedical patents were found to be increasing in number and complexity, but not to the level that derails R&D or prohibits firms from developing new products. Among the mechanisms for working within the construct of existing patents employed by pharmaceutical, diagnostic and biotechnology firms, the committee highlighted negotiation and creation of collaborations with patent holders, use of existing public tools and submission of judicial challenges for patents thought to be too broad in scope as viable and realistic solutions.¹⁶²

As certain diseases are found to involve multiple genetic anomalies and express several biological markers, diagnostics companies may have to collaborate with several patent holders to develop a new product in a process known as “royalty stacking.” In an extreme example, the cost of royalties and licensing fees may surpass the value of the product under development, forcing a company to abandon R&D. The National Research Council reported that, while royalty stacking theoretically may serve as a barrier to innovation, that termination of product development for this reason is relatively rare.¹⁶³

Another side to the role of patents for diagnostics is similar to that of much of the medical device industry in general. For many diagnostics, competing companies can “invent around” existing patents, generating a new or revised product that achieves the same purpose as an existing diagnostic without infringing upon its patent. In these instances, the protection of the remaining patent life of a diagnostic may be undermined or made irrelevant. While this confers the benefits of rolling innovation to patients and health care providers, it results in shorter product lifecycles, placing an even greater premium on timely regulatory approval, coverage and adequate reimbursement.

The use of patents in the diagnostics industry, therefore, is both a hindrance and an advantage to companies. Patent protection is essential to innovation because it provides economic incentives through provision of exclusive rights. Since the diagnostics industry is highly technical, however, patents may block one company from using a patented technology for the development of an unrelated product. As the fields of genomics and proteomics grow and more diagnostic technology becomes genetically focused, the patent environment may lead to a continued decrease in the number of companies able to develop new products. Furthermore, as diseases are increasingly found to be the result of multiple genes, royalty fees stemming from patents may be cost prohibitive, especially to smaller companies developing products using several genetic markers. The extent of gene-based patent protection and its subsequent effects

¹⁶¹ Sevilla C, Julian-Reynier C, Eisinger F, et al. Impact of gene patents on the cost-effective delivery of care: the case of BRCA1 genetic testing. *Int J Technol Assess Health Care* 2003;19(2):287-300.

¹⁶² Cohen WM, Merrill SA, eds. *Patents in the knowledge-based economy*. Washington, DC: The National Academies Press, 2003. Accessed September 1, 2004. <http://www.nap.edu/catalog/10770.html>.

¹⁶³ Ibid.

on commercial development and marketing of products derived from patented genes is currently unknown by the National Human Genome Research Institute of the NIH.¹⁶⁴

F. Market Drivers of the Diagnostics Industry

Due to the complex and varied needs of its customer base, the diagnostics industry is affected by multiple market drivers. As noted above, regulatory hurdles, along with reimbursement policies of government and private payers, significantly affect the diagnostics industry. Other important market drivers include changes in the structure and workflow of hospital labs, as pressures to reduce costs and streamline utilization alter the use and demand for diagnostic technology. The industry also must be responsive to changes in the need for new products, such as those that identify infectious diseases like West Nile virus and severe acute respiratory syndrome (SARS), and be willing and able to adjust research priorities to meet these needs. These dynamics translate into demands on the industry to continually improve their products.

1. Evolving Roles of Reference and Hospital Laboratories

The diagnostics industry not only is directly responsible for the employment of more than 40,000 individuals in the US, but is partially responsible for the demand for those professionals who conduct diagnostic tests. Diagnostic tests used in reference and hospital labs require skilled individuals to analyze specimens in a way that ensures accuracy and reliability. Lab technologists typically have bachelor's degrees with a major in one of the life sciences, while lab technicians typically have an associate degree or certificate. The US Department of Labor estimates that, at least until 2012, there will be more openings for lab technicians and technologists than qualified applicants for these jobs.¹⁶⁵ In 2003, there were approximately 9,300 medical technology openings, yet there were only 4,800 graduates of medical technology programs.¹⁶⁶ Despite continued advances in computing, specimen processing and other aspects of diagnostic technology, the accuracy of many types of tests still depends on the observation and interpretation skills of properly trained professionals. A well recognized example of the importance of a skilled labor force pertains to the Pap smear, commonly used to detect cervical cancer. Pap smears require a specialized lab technologist, a cytotechnologist, to examine slides under a microscope for cancerous or pre-cancerous cells.

Due to the intense concentration required to review these slides, a cytotechnologist may only review up to 100 slides per day, per federal regulations. When they detect abnormal cells on a slide, cytotechnologists refer the slide to a pathologist who decides if the cells potentially are cancerous or atypical due to causes such as infection or sampling errors. The potential for error in interpreting traditional Pap smears is not inconsequential, with clinical studies reporting false-negative rates (i.e., failure to detect cervical cancer when it is actually present) that range from 6% to as high as 55%.¹⁶⁷

¹⁶⁴ The human genome completion: frequently asked questions. Bethesda, MD: National Institutes of Health, National Human Genome Research Institute. Accessed October 25, 2004. <http://www.genome.gov/11006943>.

¹⁶⁵ Clinical laboratory technologists and technicians. Washington, DC: Bureau of Labor Statistics, 2002. Accessed September 1, 2004. <http://www.bls.gov/oco/pdf/ocos096.pdf>.

¹⁶⁶ Peele JD, Trochman A. Remote diagnostics monitors vital signs in the lab. *Med Lab Obs* 2003;35(10):40-2.

¹⁶⁷ Shingleton HM, Patrick RL, Johnston WW, Smith RA. The current status of the Papanicolaou smear. *CA Cancer J Clin*. 1995 Sep-Oct;45(5):305-20.

The potential for error is partly due to the repetitive nature of reviewing slides. As a result, the American Society of Cytopathology provides clear parameters for the work environment and work load limits for cytotechnologists in its *Cervical Cytology Practice Guidelines*. In these guidelines, the needs for ergonomic workspaces, adequate supervisory and support staff and personalized work load limits, depending on the skill and abilities of each cytotechnologist, are addressed.¹⁶⁸ Advances in diagnostic technology also have improved the error rate and provided quality assurance systems for laboratories. Among the advances, changes in the way samples are collected have resulted in clearer slides for cytotechnologists to review. Liquid-based specimen collection has eliminated problems with cells clumping together on a slide. Through processing of liquid based specimens, cytotechnologists are able to visualize cells more clearly, resulting in more definitive diagnoses.¹⁶⁹ Another advance occurred in 2003, when the FDA approved a computerized system that can identify potentially cancerous cells and flag them for the cytotechnologist. Referred to as computer-assisted screening or morphometric analysis, this technology does not replace the need for highly trained laboratory personnel, but it has been shown to increase and expedite the ability of cytotechnologists to correctly identify abnormalities when they do exist.^{170,171} A recent study demonstrated productivity gains in cervical cancer screening rates using a computer-assisted screening system, while matching or exceeding the sensitivity and specificity of manual screening.¹⁷²

The need for diagnostics that reduce workloads for existing laboratory personnel was underscored by a 2001 report from the General Accounting Office (GAO, now the Government Accountability Office) on the adequacy of the supply of laboratory personnel. Among its findings, the GAO concluded that:

[T]echnological advances that facilitate increased automation may enhance productivity by substituting for some workers even as the demand for the particular service, test, or procedure continues to rise.

In addition, the GAO found that automation of existing testing procedures will allow nonlaboratory personnel or less skilled personnel to complete tests.¹⁷³ The shortage of qualified laboratory personnel pushes the industry to develop devices and systems that streamline existing processes through automation and other technological advances.¹⁷⁴ In this way, the diagnostics industry is enabling expansion of the capacity of the existing laboratory workforce.

The diagnostics industry also is driven by workforce constraints in other areas of health care. Since the latter half of the 1990s in particular, attention of public and private payers has increased on preventive care and evidence-based medicine. Indeed, there are now so many

¹⁶⁸ Cervical cytology practice guidelines. American Society of Cytopathology. Acta Cytol 2001;45(2):201-26.

¹⁶⁹ Rosenthal DL. Cervical disease screening and detection: emerging technologies in molecular diagnostic assays. Medical Laboratory Observer 2004;36(9):10-6.

¹⁷⁰ Parker EM, Foti JA, Wilbur DC. FocalPoint slide classification algorithms show robust performance in classification of high-grade lesions on SurePath liquid-based cervical cytology slides. Diagn Cytopathol 2004;30(2):107-10.

¹⁷¹ Wilbur DC, Prey MU, Miller WM, et al. Detection of high grade squamous intraepithelial lesions and tumors using the AutoPap System: results of a primary screening clinical trial. Cancer 1999;87(6):354-8.

¹⁷² Biscotti CV, Dawson AE, Dziura B, et al. Assisted primary screening using the automated ThinPrep Imaging System. Am J Clin Pathol 2005;123(2): 281-7.

¹⁷³ Supply of selected health workers. Washington, DC: US General Accounting Office, October 2001. Accessed September 1, 2004. <http://www.gao.gov/new.items/d02137r.pdf>. (GAO Publication No. GAO-02-137R).

¹⁷⁴ Diller W. Robust times for diagnostic companies. In Vivo: The Business and Medicine Report 2004;4:18-20.

preventive care guidelines that a 2003 study published in the *American Journal of Public Health* reported that physicians would have to spend 7.4 hours of each working day just providing those services recommended by the US Preventive Services Task Force (USPSTF) before addressing other patient needs. Physicians can be so pressed for time that they are unable to provide many of the recommended services of the USPSTF, several of which involve diagnostic tests.¹⁷⁵ In order to best serve their patients in spite of time constraints, clinicians increasingly are seeking diagnostics that help with clinical decision-making in a more user-friendly manner.¹⁷⁶ In particular, there is increased demand for diagnostic tests that minimize the need for clinicians to interpret and extrapolate the information necessary for a diagnosis. By providing data from lab tests in a more useful format (such as through flagging test results that fall outside of normal ranges), diagnostics are increasing the capacity of the health care workforce by decreasing the amount of time that clinicians must spend deciphering lab results.

2. Emerging Public Health Applications

The diagnostics industry responds to changes in disease patterns such as the emergence and spread of infectious diseases, including contemporary ones such as SARS and West Nile virus. Increasing globalization and international jet travel provide more opportunities for the spread and mutation of pathogens. As such, there is greater need for rapid development and deployment of diagnostics, including those that detect diseases that typically are not seen within the US. The 2003 SARS epidemic highlighted the need for diagnostic tests that can identify infections quickly, so that potential carriers can be quarantined and exposure to others minimized. For these reasons, the World Health Organization used rapid identification of infected individuals as a key performance measure in its selection of diagnostic tests for SARS.¹⁷⁷ The resulting diagnostic test is able to detect SARS in as little as three-to-four hours by using a nucleic acid testing assay to detect the virus in nasal swabs and throat cultures even before patients show symptoms of the disease.¹⁷⁸ The ability to detect SARS in hours as opposed to days is remarkable, especially considering that the earliest diagnostic tests for SARS were most effective between nine and 11 days following onset of symptoms.¹⁷⁹

The emergence of West Nile virus (WNV) and its impact on the blood donation system also illustrates the need for diagnostics that can quickly identify potential pathogens. WNV originates with an infected mosquito biting a human and, while the disease is not transmitted person to person through normal contact, it can be transmitted through donated blood products. In 2002, the CDC reported 23 cases of WNV in recipients of blood transfusions, seven of whom later died from their illness.¹⁸⁰ In response to the emergence of WNV in the US, the National Institute of Allergy and Infectious Diseases (NIAID) accelerated its research agenda on WNV, including the provision of funds for small biotechnology companies to develop rapid

¹⁷⁵ Yarnall KS, Pollak KI, Ostbye T, et al. Primary care: is there enough time for prevention? *Am J Public Health* 2003;93(4):635-41.

¹⁷⁶ McQueen MJ. Overview of evidence-based medicine: challenges for evidence-based laboratory medicine. *Clin Chem* 2001;47(8):1536-46.

¹⁷⁷ Update 30-status of diagnostic test, significance of "super spreaders", situation in China. Geneva, Switzerland: World Health Organization, April 2003. Accessed September 1, 2004. http://www.who.int/csr/sars/archive/2003_04_15/en/print.html.

¹⁷⁸ Poon LL, Wong OK, Chan KH, et al. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). *Clin Chem* 2003;49(6 Pt 1):953-5.

¹⁷⁹ Fouchier RA, Osterhaus AD. Laboratory tests for SARS: powerful or peripheral? *CMAJ*, 2004;170(1):63-4.

¹⁸⁰ Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med* 2003;349(13):1236-45.

tests for WNV from human, animal or mosquito samples.¹⁸¹ The CDC reported in 2003 that implementation of national screening of the blood supply under an investigational exemption for WNV substantially reduced the risk of infection for blood transfusion recipients with 163 infected units of blood removed from the supply.^{182,183}

Considerable research potential for the diagnostics industry also rests in the area of biodefense. In 2001, the NIAID launched a biodefense research program to spur the development of drugs, vaccines and diagnostic tools. In 2004, the program's estimated research budget was \$1.6 billion, with \$64 million specifically earmarked for diagnostics, especially those that facilitate the rapid detection of exposure to possible bioterror agents.¹⁸⁴ Funding of biodefense initiatives through this program has increased eight-fold from the 2002 fiscal year, constituting the single largest increase for any program in the history of NIH. According to the director of NIAID, the federal government is actively pursuing relationships with companies in the private sector, including diagnostics firms, in order to speed innovative products through the pipeline.¹⁸⁵ Still, companies often are hesitant to develop a product that may never be purchased or profitable, and the market for biodefense diagnostics remains uncertain. To avert this disincentive to product development, and to ensure that the most advanced biodefense diagnostics are available if needed, the federal government is exploring options such as guaranteeing that products will be purchased, regardless of the actual level of need.¹⁸⁶

G. Expectations for Diagnostics

Users of diagnostics seek products that are smaller, faster and more accurate than their current products and that fit into existing workflow patterns and increase productivity through automation or ease of use.

1. Accuracy of Diagnostics

While no test is perfectly accurate in all instances, there is a constant push in the diagnostics industry to improve detection of diseases and health conditions. The accuracy of a test most often defined is in terms of sensitivity and specificity. The sensitivity of a test refers to its ability to detect a disease or condition when it is truly present. A "false negative error" occurs when a test fails to detect a disease or condition when it is truly present. The specificity of a test refers to its ability to rule out a disease or condition when it is truly not present. A "false positive error" occurs when a test indicates that it has detected a disease or condition when it truly is not present. False positive and false negative errors can result in unnecessary clinical and economic burdens to patients and the health care system. A false positive error may prompt a clinician to order additional unnecessary diagnostic tests or procedures such as a scan or a biopsy, resulting in unnecessary expense and patient discomfort or anxiety. A false negative error can miss an opportunity to detect a condition or disease that could have been prevented or treated, enabling

¹⁸¹ NIAID research on West Nile virus, fact sheet. Bethesda, MD: National Institute of Allergy and Infectious Diseases, April 2004. Accessed September 1, 2004. <http://www.niaid.nih.gov/factsheets/westnile.htm>.

¹⁸² Centers for Disease Control. Update: detection of West Nile virus in blood donations---United States, 2003. *Morbidity and Mortality Weekly Report* 2003;52(38):916-9.

¹⁸³ Pealer LN, Marfin AA, Petersen LR 2002.

¹⁸⁴ Fauci AS. Statement on biodefense. Bethesda, MD: National Institute of Allergy and Infectious Diseases, 2003. Accessed September 1, 2004. http://www2.niaid.nih.gov/biodefense/about/directors_statement.htm.

¹⁸⁵ Fauci AS. Biodefence on the research agenda. *Nature* 2003;421(6925):787.

¹⁸⁶ Fauci AS. Biodefence on the research agenda. 2003.

it to progress to adverse health outcomes and the need for health care interventions and greater costs.^{187,188} Tradeoffs in the levels of acceptable sensitivity and specificity may vary and be appropriate depending on the application (e.g., higher sensitivity may be more desirable for certain screening applications to reduce the possibility of missing a serious disease in asymptomatic patients). Although making such tradeoffs is not always necessary or possible, it can change the clinical utility of the test as the application changes.

The ability to detect disease with more reliability has greatly increased in the past two decades, partially due to advances in the understanding and application of genetics. Early HIV tests such as enzyme immunoassays (EIA) and enzyme-linked immunosorbent assays (ELISA) detected the virus through the presence of antibodies circulating in the bloodstream. These tests generally were unable to detect very early cases of HIV, because several weeks or months may pass before a person who has contracted the virus develops enough antibodies to be detected by a diagnostic. Newer tests, however, are able to detect antibodies at much lower levels, leading to earlier detection of HIV than was possible with older tests.¹⁸⁹ The use of NAT to detect the genetic material of viruses before the body forms antibodies against them has further reduced the window of infection for HIV and other viruses.¹⁹⁰ As is the case for many diagnostics, testing for HIV continues to evolve, with more accurate and user-friendly tests.

2. Rapid Results

Rapid test results often are demanded by clinicians and consumers. From at-home glucose testing by diabetes patients to testing for the biomarker troponin that ED physicians use to determine whether a patient is having a heart attack, results for certain tests are sought within minutes to make diagnosis and treatment decisions. Even when rapid results are not essential to prevent immediate harm or death, they have proven to be useful in generating patient compliance and follow-up care. Prior to rapid tests for HIV (which can provide results in as little as 20 minutes), patients had to wait up to a week to receive results. The FDA has estimated that up to 8,000 patients per year who underwent standard HIV testing never returned to learn their results.¹⁹¹ Provision of results in minutes, as opposed to hours or days, can increase the number of patients who receive treatment for serious health problems simply because they will wait for the results and receive post-test counseling. For HIV and other conditions, diagnostics that provide faster results without sacrificing accuracy will replace slower diagnostics as the standard of care.

¹⁸⁷ Steigman CK, Vernick JP. The pap smear: a victim of its own success? *Med Lab Obs* 2002;34(8):8-14.

¹⁸⁸ Medicare coverage~MCAC. Baltimore, MD: Centers for Medicare & Medicaid Services 2000. Accessed December 1, 2004. <http://www.cms.hhs.gov/mcac/8b1-i19.asp>

¹⁸⁹ Ly TD, Laperche S, Brennan C, et al. Evaluation of the sensitivity and specificity of six HIV combined p24 antigen and antibody assays. *J Virol Methods* 2004;122(2):185-94.

¹⁹⁰ Busch MP, Glynn SA, Stramer SL, et al.; NHLBI-REDS NAT Study Group. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. *Transfusion* 2005;45(2):254-64.

¹⁹¹ Wider use of rapid HIV test. *FDA Consumer Magazine* 2003. Accessed September 1, 2004. http://www.fda.gov/fdac/departs/2003/303_upd.html#hiv.

Rapid results also have been cited as a driver for decreasing overcrowding in hospital EDs.¹⁹² As ED overcrowding becomes more of an issue for quality and access to health care, diagnostics that facilitate timelier triage and discharge of patients will become even more of a necessity in hospitals and other highly-trafficked health care centers.

3. Point-of-care Testing

As an application of rapid testing, POCT moves diagnostic tests that traditionally have been conducted in a lab to a location near the patient, whether at the patient's bedside, just outside the emergency room, in an exam room at a doctor's office or in one's home. Results often are obtained faster with POCT devices, because trips to and from the central lab are eliminated. As concerns over laboratory staff shortages grow, POCT has the potential to shift some of the testing burden from lab staff to other clinicians. In some instances, the transition to more POCT may be accompanied by potential tradeoffs between convenience and accuracy. Other concerns arise regarding assigning responsibility for maintenance of POCT devices, including regular quality control assessments and training auxiliary staff to use POCT devices.¹⁹³ Further, the availability and extent of coverage and reimbursement of tests by third-party payers are affected by the shift in site of care (e.g., inpatient to outpatient care or physician office, or from those sites to the home).¹⁹⁴ The adoption of POCT may vary depending on the setting. For patients in the ED or intensive care unit, where turnaround time can be critical, POCT may be adopted more quickly than on regular hospital floors or in physicians' offices.

The demand for POCT devices spurs the diagnostics industry to produce products that are smaller, faster and easier to use, but often more sophisticated in design than diagnostics traditionally found in laboratories. POCT devices that can be incorporated into the existing routine of patient care are more likely to be adopted by clinicians. For this reason, the devices cannot be heavy, large or have unusual requirements, such as specialized power supplies. Since clinician encounters with patients generally transpire in the range several minutes to a half-hour, POCT diagnostics must produce results in this timeframe to be useful. Results obtained after the encounter are not as likely to be used in clinical decision-making. Finally, since the primary users of POCT are clinicians, these diagnostics must be user-friendly for nonlaboratory personnel to operate, which means that any complex handling and processing of samples and reagents must be eliminated. As with many consumer-directed technologies (e.g., calculators, laptop computers and cellular phones), the process of making products smaller, faster and more user-friendly can be time consuming and costly in design and manufacture.¹⁹⁵

¹⁹² Proudlove NC, Gordon K, Boaden R. Can good bed management solve the overcrowding in accident and emergency departments? *Emerg Med J.* 2003;20(2):149-55.

¹⁹³ Diller W. Cardiac diagnostics and the challenges of ER testing. In *Vivo: The Business and Medicine Report* 2003:43-57.

¹⁹⁴ O'Brien JA. Point-of-care testing. *Med Lab Obs* 2000;32(12):38-43.

¹⁹⁵ Macfarlane I, Davis F. Building blocks for the point-of-care-boom. IVD technology. Canon Communications. 2002.

H. Diagnostic Technology Trends and Pipeline

1. Recent FDA Approvals of Diagnostics

Diagnostics that recently have gained FDA approval represent advances in rapid testing, POCT, automation and detection of infectious diseases. Devices approved by OIVD in 2004 included:¹⁹⁶

- A home testing device for **diabetics** to monitor their glycated hemoglobin levels, resulting in more effective diabetes management
- Several diagnostics for detecting **illegal substances**, such as marijuana, cocaine, methamphetamines and opiates
- A diagnostic that can detect antibodies to the **West Nile virus**
- Multiple tests for **cardiac disorders**, such as congestive heart failure, heart attack and coronary heart disease
- The first fully automated analyzer for amplified NAT

2. Improved Navigation of the Regulatory Process

Diagnostics firms are becoming more adept at navigating the regulatory process. While the FDA has been able to reduce the number of days it takes to deliver a final decision on a PMA application through organizational and administrative changes, diagnostics companies also have reduced the number of non-FDA days required in the process. By developing applications with more scientific evidence and by communicating earlier in the regulatory process with the FDA, diagnostics companies also are responsible for significant reductions in the length of time from submission to final rule (see **Section IV**).

Diagnostics firms also have benefited from the ability to combine several related devices into a single FDA application. By combining devices that are complementary or that may be used for multiple indications, diagnostics firms can reduce significantly the time and expense consumed in the regulatory process. This practice is referred to as “bundling.” For example, multiple analytes may be bundled so that one application can be submitted for a test that can detect multiple diseases such as toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex. Similarly, reagents can be bundled if they are used together to complete a testing process.¹⁹⁷ However, many emerging molecular diagnostics that can involve hundreds or thousands of simultaneous tests pose new challenges to FDA regulation of bundled tests and to the diagnostics manufacturers that must navigate these new tests through the regulatory process.

¹⁹⁶ Annual report fiscal year 2003. Rockville, MD: Office of Device Evaluation and Office of In Vitro Diagnostic Device Evaluation and Safety, 2003. Accessed September 1, 2004.
<http://www.fda.gov/cdrh/annual/fy2003/ode/>.

¹⁹⁷ Bundling multiple devices or multiple indications into a single submission. Rockville, MD: Center for Devices and Radiological Health, November 2003. Accessed September 1, 2004.
<http://www.fda.gov/cdrh/mdufma/guidance/1215.html>.

3. Collaborative Developments

Many diagnostics companies perceive strong incentives to form partnerships with pharmaceutical companies to produce diagnostic and therapeutic combinations based on the use of biomarkers. The identification and measurement of biomarkers may enable more accurate prediction of patient response to particular drug therapies, resulting in fewer adverse events from inappropriate use of pharmaceuticals and better patient outcomes. Anticipation that successful identification of biomarkers may reduce R&D timelines for some new drugs is fueling the study of biomarkers. While the diagnostics industry currently is pursuing biomarker research, some in the pharmaceutical industry remain cautious over concerns that biomarkers that enable targeting patient sub-groups might reduce markets for particular drugs.¹⁹⁸ It is becoming more common for diagnostics manufacturers to collaborate to develop, manufacture and market products. These relationships allow for some degree of specialization, leveraging of individual strengths for targeted collective efforts and more effective resource allocation, including for R&D, performance or clinical testing, and developing combined product offerings that are more beneficial than an individual test alone.

¹⁹⁸ Diller W. Roche's challenging biomarker strategy. In Vivo: The Business and Medicine Report 2004:53-65.

IV. US Regulation of Diagnostics

Diagnostics are classified by the FDA as medical devices. Therefore, the regulations pertaining to medical devices also pertain to diagnostics. In addition, there are supplemental regulations specific to diagnostics, such as certain requirements for labeling and establishing safety and effectiveness, and non-FDA regulations such as the Clinical Laboratory Improvement Amendments (CLIA) that apply to most laboratory testing.

This chapter describes the current framework for regulation of diagnostics, including a description of primary regulatory paradigms and the FDA units responsible for their implementation. Key issues pertaining to the regulation and approval of diagnostics are discussed, as well as current trends and their implications for product innovation and access for health practitioners and patients.

A. FDA Regulation of Diagnostics

The FDA has the primary authority for regulation of marketed diagnostics in the US. While this FDA authority derives from the same legislation governing the regulation of drugs, far fewer regulatory controls applied to medical devices, including diagnostics, prior to 1976. In the last three decades, FDA regulation of these products has become increasingly complex, due to numerous legislative, regulatory and judicial decisions.¹⁹⁹

The unit within the FDA that is responsible for regulating most diagnostics is the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD). Formerly known as the Division of Clinical Laboratory Devices, OIVD was established in 2002 within CDRH and works with the Office of Device Evaluation (ODE) to ensure that diagnostics allowed on the market comply with the Federal Food, Drug, and Cosmetic (FD&C) Act. OIVD is responsible for regulating IVDs, with the exception of those used in the collection, processing, testing, storage or administration of biological products (including blood and blood products), including all retrovirus tests, such as for HIV. CBER has the complementary role of regulating medical devices used in the collection, processing, testing, storage or administration of biological products (including blood products), including IVDs for such purposes. CBER regulates IVD tests for blood donor screening and banking and all IVD diagnostic tests and medical devices related to HIV1, HIV 2 and other retroviruses.²⁰⁰

OIVD seeks to regulate IVDs throughout their total product life cycle (TPLC). OIVD also is responsible for categorizing laboratory tests as specified by CLIA. These responsibilities include assigning new, commercially marketed laboratory tests and test systems to one of three CLIA complexity categories: a) waived; b) moderate; or c) high complexity.²⁰¹ This function was carried out by other agencies on behalf of CMS and was returned to FDA in 1999.²⁰²

¹⁹⁹ Merrill RA. Regulation of drugs and devices: an evolution. *Health Affairs* 1994;13(3):47-69.

²⁰⁰ Kochman SA. CBER 510(k) issues. Rockville, MD: Office of In Vitro Device Evaluation and Safety, Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed online November 5, 2004. <http://www.fda.gov/cdrh/oivd/presentations/042004-KOCHMAN.html>. For full details, see 21 CFR 864.9050 through 864.9875.

²⁰¹ Tests are evaluated for complexity based upon seven criteria: knowledge; training and experience; reagents and materials preparation; characteristics of operational steps; calibration, quality control and proficiency testing

B. Primary Regulatory Paradigms for In Vitro Diagnostics

1. Classification of Diagnostics by Risk

As with other medical devices, the FDA assigns diagnostics to three classes, according to the level of control the agency believes is necessary to regulate test safety and effectiveness. As described below, diagnostics in Class I are subject to *general controls*, those in Class II are subject to *special controls* in addition to general control requirements and those in Class III are considered by the FDA to be of high risk or without established predicates.

- **Class I diagnostics** require the lowest level of regulation. These devices, such as sterile specimen containers and medicine droppers, are considered to present minimal potential for harm and face lesser regulatory scrutiny. *General controls* include requirements for basic registration and listing of diagnostics, premarket notification [510(k)], prohibition of inappropriately marketed products, record keeping, reporting of device failures and compliance with Good Manufacturing Practices (GMP). GMP requirements were established in the Quality System (QS) regulation (under Section 520 of the FD&C Act) and require manufacturers of devices to have a quality system for design, manufacture, packaging, labeling, storage, installation and servicing. This includes the establishment of specifications and controls for diagnostics and a system by which to address complaints. These data are subject to inspection by the FDA as part of the general controls over medical devices/diagnostics. Most Class I diagnostics have been exempted from premarket notification requirements.²⁰³
- **Class II diagnostics** are subject to special controls, in addition to general controls. New Class II diagnostics usually are similar to existing devices on the market for which there is considerable information available on safety and effectiveness, for example, pregnancy test kits. Special controls include predetermined product-specific standards, design controls, certain postmarket surveillance requirements, associated guidelines or guidance documents, special labeling and/or certain tracking requirements for diagnostics and patients. Most Class II diagnostics require premarket notification.
- **Class III diagnostics** generally are novel devices or have the potential to pose substantial risk to patients; examples are immunohistochemistry kits and HIV test kits. Class III diagnostics generally are subject to a premarket approval process (outlined below).²⁰⁴ In general, a diagnostic must be listed as Class III if one of the following criteria is met: a) regulated as a Class III prior to May 28, 1976 (i.e., considered a transitional device); b) no substantially equivalent predicate; or c) pre-amendment

materials; test system trouble shooting and equipment maintenance; and interpretation and judgment. Waived tests are those determined by CDC or FDA to be so simple that there is little risk of error (e.g., pregnancy tests; fecal occult blood tests; and some urine, glucose and cholesterol tests). Tests of moderate complexity include provider performed microscopy (PPM) procedures.

²⁰² CLIA complexity determinations were made by the FDA as early as 1992, though this authority was moved to the CDC in 1994 before returning to FDA in 1999. However, CMS still maintains the authority for conducting inspections of laboratories.

²⁰³ Medical device exemptions 510(k) and GMP requirements. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed November 5, 2004.
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpdc/315.cfm>

²⁰⁴ In some cases, premarket approval is mandated by the FDA regardless of the existence of predicate devices.

diagnostics that require a premarket approval application.²⁰⁵ Class III diagnostics are subject to the most regulatory scrutiny and generally are subject to a premarket approval (PMA) process, involving a review of available evidence of the safety and effectiveness of a device for its intended use. The evidence collection and review processes for these technologies are often more resource-intensive and time consuming.

2. Main Regulatory Pathways for Diagnostics

There are four primary regulatory pathways for diagnostics: a) premarket notification, otherwise known as the 510(k); b) premarket approval application (PMA); c) classification as an analyte specific reagent (ASR); and d) humanitarian use devices. Humanitarian use devices are pursued infrequently, as these products have special, rigorous regulatory considerations for being classified as such.

The three main regulatory pathways are noted in **Figure 4.1** and discussed below.²⁰⁶

Figure 4.1
Principal Premarket Regulatory Options for Diagnostics

Requirements	510(k)	PMA	ASR
Premarket Review	Establish that the diagnostic is “substantially equivalent” to predicate (90-day review goal)	Establish that the diagnostic is safe and effective (180-day review goal)	Most are exempt and responsible for performance under CLIA high complexity
Good Manufacturing Practices	Periodic field inspection to monitor	Premarket inspection and approval and periodic field inspection to monitor	Periodic field inspection to monitor
Labeling	“For In Vitro Diagnostic Use”	“For In Vitro Diagnostic Use”	Exempt ASRs: “Analyte Specific Reagent; analytical and performance characteristics are not established” Laboratory tests using ASRs must indicate their status as laboratory-developed

Most Class I devices and a few Class II devices are exempt from the 510(k) premarket notification requirements, though not from other general controls. A few Class I devices also are exempt from GMP requirements. Adapted from: Gutman S. The role of Food and Drug Administration regulation of in vitro diagnostic devices—applications to genetic testing. Clin Chem 1999;45(5):746-49.

As noted above, most Class I devices and a few Class II devices are exempt from the 510(k) premarket notification requirements. However, these devices are not exempt from other general controls. All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled and have establishment registration and device listing forms on file with the FDA.²⁰⁷

²⁰⁵ Device classes. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed November 9, 2004. http://www.fda.gov/cdrh/devadvice/3132.html#class_3.

²⁰⁶ Overview of IVD regulation. Rockville, MD: Office of In Vitro Device Evaluation and Safety, Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed November 9, 2004. <http://www.fda.gov/cdrh/oivd/regulatory-overview.html>.

²⁰⁷ A few Class I devices are also exempt from GMP requirements with the exception of complaint files and general record keeping requirements. Devices exempt from 510(k) are: preamendment devices not significantly changed

Premarket Notification (510[k]) is a technical submission made by a product sponsor to the FDA claiming that a diagnostic to be marketed is substantially equivalent to a legally marketed diagnostic (i.e., the diagnostic has a legally marketed predicate for comparison). The Medical Device Amendments of 1976 were enacted with the assumption that FDA approval would not be required for the majority of devices made prior to 1976 or for substantially equivalent post-enactment devices. Congress sought to have regulatory parity between pre- and post-1976 devices by providing for the 510(k) premarket notification requirement, allowing the FDA to determine whether a new product was substantially equivalent to a pre-1976 product. However, no definition of equivalence was specified. As a result, the agency may request reports of clinical experience that demonstrate a new diagnostic poses no more risk (or is less effective) than a previously used one. OIVD also requires submission of data demonstrating clinical utility. Approximately 98% of medical devices entering the market after enactment of the 1976 amendments were processed under the 510(k) provisions, though this proportion decreased during the 1980s.²⁰⁸

A 510(k) must be submitted at least 90 days prior to the planned marketing of a Class I, Class II and some Class III diagnostics for human use (unless the diagnostic is exempt from such requirements). If FDA determines that additional scientific information is required, reviewers may place the submission on hold and request the additional information from the sponsor. Otherwise, if FDA finds that the submitted information demonstrates substantial equivalence to another legally marketed product, the diagnostic is cleared for marketing in the US.

Before clearing a diagnostic via the 510(k) route, FDA review focuses on data submitted to establish device performance, clinical utility and labeling materials. Varying among devices, performance may be defined by such parameters as analytical and/or clinical sensitivity and specificity, bias, repeatability, linearity and limits of detection, as appropriate.²⁰⁹ In many cases, studies using anonymous clinical samples are sufficient for demonstrating substantial equivalence for most diagnostic tests, though occasionally further clinical information is required. These decisions rarely are based on specific parameters and can result in longer and more costly development times for diagnostic manufacturers as they seek appropriate guidance for moving forward with a product development strategy.²¹⁰

There are several categories of 510(k) notification. Traditional submissions take the longest to process (approximately 90 days), though “special 510(k)” (modification to a cleared diagnostic) and “abbreviated 510(k)” (declaration of conformance to recognized standards for a new diagnostic) notifications are possible, when appropriate. “Expedited” or “fast track” notifications can be used in cases where there is significant potential public health importance,

or modified; or Class I/II devices specifically exempted by regulation. “Preamendment device” refers to devices legally marketed in the US by a firm before May 28, 1976, and which have not been: significantly changed or modified since then; and for which a regulation requiring a PMA application has not been published by FDA. Devices meeting this description are “grandfathered” and do not require a 510(k). Class I/II exemptions. Rockville, MD: Office of In Vitro Device Evaluation and Safety, Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed May 25, 2005. <http://www.fda.gov/cdrh/devadvice/3133.html>.

²⁰⁸ Overview of IVD regulation. Rockville, MD: Office of In Vitro Device Evaluation and Safety, Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed November 9, 2004. <http://www.fda.gov/cdrh/oivd/regulatory-overview.html>.

²⁰⁹ Gutman S 1999.

²¹⁰ Overview of IVD regulation, FDA, 2004.

e.g., for high priority applications (such as CBER-regulated HIV tests, certain cancers, West Nile virus and anthrax tests in recent years), and may be processed within 30 days. Third-party reviews, accounting for a small but increasing proportion of 510(k) submissions, may take as little as 15 days of FDA time to process, in addition to the time under review by the third party.

De novo classification (automatic Class III designation and reclassification) is a 510(k) mechanism, mandated by The FDA Modernization Act of 1997 (FDAMA), for classifying new diagnostics that are deemed to be low-risk but do not have a predicate diagnostic on the market. In these instances, a not substantially equivalent (NSE) determination (which classifies the diagnostic as a Class III) must be made by CDRH. If the manufacturer considers that a suitable predicate exists, a reclassification petition can be filed; or, within 30 days of receiving an NSE determination, the manufacturer can submit a request for a risk-based classification determination. Within 60 days of the submitted request, the FDA must make a decision as to which level of control (general or special) is necessary to provide reasonable assurance of the diagnostic's safety and effectiveness.²¹¹ The *de novo* process has been used only in a small number of diagnostics, including those listed in **Figure 4.2**.

Figure 4.2
Recent Examples of Diagnostics Eligible for *de novo* 510(k) Regulation

Diagnostic	Target Application
• Biotinidase test system	• Newborn metabolic disease
• Anti-saccharomyces cerevisiae antibody assay	• Inflammatory bowel disease
• B-type natriuretic peptide	• Congestive heart failure
• Breath nitric oxide test system	• Asthma
• Endotoxin activity assay	• Septic infection
• Factor V Leiden kit	• Cardiovascular disease/stroke
• West Nile Virus IgM capture ELISA assay	• Infectious disease

Source: Chesler R. *Automatic Class III Designation (De novo)*. The US Food and Drug Administration. Accessed November 15, 2004.

Premarket Approval is another mechanism by which new devices may enter the market. A PMA requests approval to market a Class III medical device and is based on a review of available evidence that the device is safe and effective for its intended use. For IVDs, safety is based not on contact of a device with the patient, but on the impact that information generated by the device has on patient management, for example, potential harm from false-positive or false-negative results. As such, the terms safety and effectiveness are linked for IVDs. The FDA reviews PMA submissions on a 180-day timeline, but may require more time for collection of additional information. Panels of outside experts generally review diagnostics that present new or difficult questions relating to safety or effectiveness. The approval of a PMA requires a review of manufacturing processes, inspections of manufacturing facilities, an audit of clinical study sites and a comprehensive review of premarketing data. Since the PMA is established primarily for review of novel diagnostics with no appropriate predicate, their

²¹¹ Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed April 25, 2005.
<http://www.fda.gov/cdrh/modact/classiii.html>.

effects on human health have not been as well characterized as those with predicates that qualify for the 510(k) pathway. As such, the evidence collection and review processes for these technologies are often more resource-intensive and time consuming.

Analyte specific reagents include antibodies, receptor proteins, nucleic acid sequences and other biological or chemical reagents that are used to identify or quantify substances in biological specimens.²¹² These key building blocks of diagnostic tests are used by some labs to manufacture their own in-house tests. In 1997, the FDA published a final rule (62 FR 62260) that classified the components of laboratory-developed tests as ASRs and subjected the manufacturers to incremental regulation. ASR manufacturers must list with the FDA, follow QS regulation, label Class I exempt ASRs appropriately and restrict the sale of these reagents to laboratories designated as “high complexity” under CLIA. Labs must report results of such in-house tests with the standard disclaimer: “This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the FDA.” Exceptions to this regulation of ASRs include those involved in blood screening (generally classified as Class III devices).

Since ASRs involve providing reagents/test materials to only high complexity laboratories conducting these tests and are allowed limited marketing provisions by FDA, this is a constrained regulatory pathway for manufacturers. On the other hand, the ASR pathway supports additional data collection regarding test characteristics that could be used for later 510(k) or PMA submissions.

Humanitarian use devices are for rare diseases or conditions (affecting fewer than 4,000 individuals per year) that require Humanitarian Device Exemptions (HDE). They are subject to institutional review board (IRB) approval and restrictions on their use, cost and labeling, but are exempt from demonstrating effectiveness.

Laboratory-developed tests, often referred to as “home brews,” are not regulated by the FDA, but are subject to the test performance standards of CLIA.²¹³ Under CLIA, laboratory-developed tests are classified into one of three categories: waived complexity, moderate complexity, high complexity. Classification of each test is made with consideration given to the degree of skill, knowledge and training required to perform the test; complexity of material preparation; difficulty and complexity of operating steps for the test; availability of quality control measures; and level of interpretation of results required by laboratory staff.²¹⁴ All laboratory-developed tests are classified as “high complexity,” for which quality requirements must be established and verified in the laboratory and approved by the laboratory director. The regulation of these tests is discussed below.

²¹² Gutman SI. FDA’s role in the regulation of in vitro diagnostic. Presentation May 10, 2003. Rockville, MD: Office of In Vitro Device Evaluation and Safety, Center for Devices and Radiological Health, US Food and Drug Administration, 2003. Accessed November 9, 2004. <http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html>.

²¹³ Test performance standards under CLIA do not cover the range of rigorous safety and effectiveness provisions for FDA approval.

²¹⁴ Program Operations Guidelines for STD Prevention, Medical and Laboratory Services, 2004. Centers for Disease Control and Prevention. Accessed April 5, 2005.: <http://www.cdc.gov/std/program/medlab/ApA-PCmedlab.htm>.

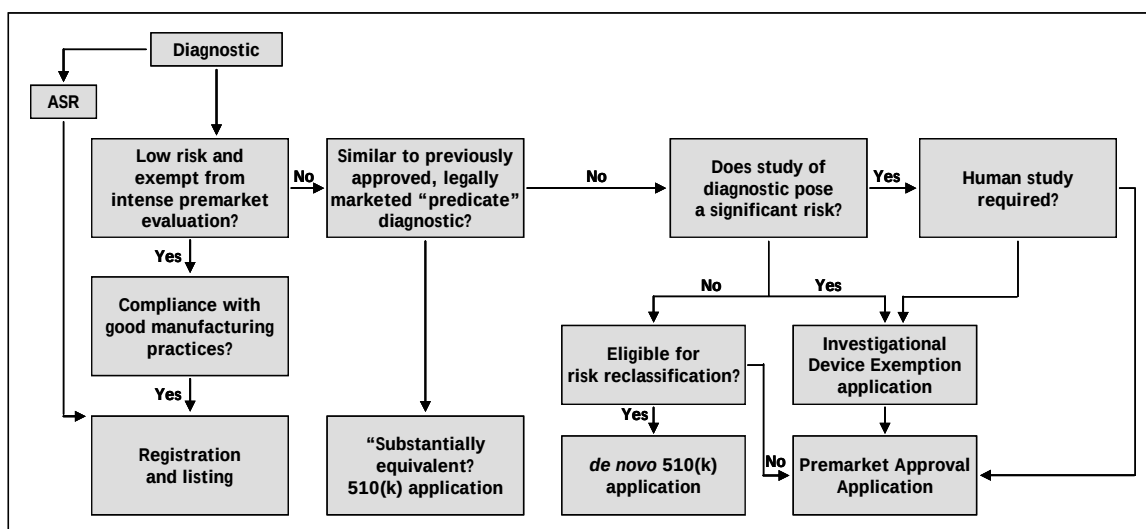
3. Exemptions for Clinical Studies of Diagnostics

Investigational Device Exemption (IDE) allows investigational diagnostics to be used in studies to collect safety and effectiveness data in humans in support of PMA or 510(k) applications. Such exemptions allow limited distribution of diagnostics without complying with certain other sections of the FD&C Act that govern commercial distribution. Although the IDE process does not permit manufacturers to market a test outside of ongoing clinical trials, it does provide significant opportunities for data collection and other advantages, such as eligibility for Medicare reimbursement as a “Category B” device under certain circumstances. It also provides opportunities for clinicians to gain experience using these diagnostics and provide feedback for further refinement and improvement of the technology.

IDE-exempt studies offer another pre-PMA/510(k) data collection opportunity. Many diagnostics are exempt from IDE requirements for conducting studies in support of PMA or 510(k) applications, which reduces regulatory burden for market approval. These exemptions notwithstanding, informed consent and IRB approval may still apply. IDE-exempt sponsors of diagnostic studies still can consult with the FDA to obtain guidance regarding study protocols and improve the likelihood of product approval. If the diagnostic is an incremental improvement to existing technology and can qualify as a “Category B” device, its sponsor (particularly smaller companies) may elect to proceed with the IDE process to obtain that designation and, thereby, be eligible for Medicare coverage for certain costs of studies.²¹⁵ While this Medicare support for “Category B” devices does not defray all costs of studies, it does increase payer awareness of new diagnostics and may increase options for continued reimbursement upon market approval.

Figure 4.3 presents alternate FDA regulatory pathways for development of IVDs.

Figure 4.3
FDA Regulatory Pathways for Development of Diagnostics



Adapted from: Maisel WH. Medical device regulation: an introduction for the practicing physician. *Ann Intern Med* 2004;140:296-302.

²¹⁵ Criteria and procedures for extending coverage to certain devices and related services. Health Care Financing Administration. September 15, 1995. 20 FR 48419.

C. Trends, Challenges and Future Considerations for Diagnostics

Certain trends, challenges and future considerations related to FDA regulation of diagnostics have significant implications for innovation and access. Among these, discrepancies in regulatory materials or outdated guidance documents can increase time to market and development costs for a diagnostic. For example, “clinical utility” is explained differently in several FDA guidances.

1. Trends in Diagnostic Review Times and Currency of Guidance Materials

Regulation and approval of diagnostics is affected by the resources available to the FDA and the Department of Health and Human Services (DHHS). For FY04, CDRH reported that it had a total of 1,059 FTEs, including 713 FTEs for MDUFMA review processes and 346 other FTEs (involved in CLIA, Mammography Quality Standards Act (MSQA) and FDA’s Office of Shared Services), compared to FY03 totals of 1,025, 662 and 363 FTEs in those categories, respectively. For FY05, CDRH projected an overall increase to 1,141 FTEs, including 802 for MDUFMA review and 339 other FTEs.²¹⁶ OIVD ended FY04 with 82 employees. The total number of ODE and OIVD FTEs grew by 15% between FY02 and FY04, as the number of 510(k) submissions that include substantial clinical data increased in tandem. Since third-party review of 510(k) submissions doubled between FY02 and FY04 (127 to 255),²¹⁷ there has been a substantial investment in training of FDA and third-party review staff.

Given limited staff and rapidly evolving technologies, guidance and standards documents quickly can become dated or obsolete. Lack of clear or current guidance can inhibit or slow review times in some areas. Though CDRH has sought to decrease review times and provide the least burdensome path to market for new diagnostics, existing guidances should be reviewed and updated. Almost three-quarters of available review guidances are at least five years old. Problems can arise early in the submission process when documents unclear or outdated or when unanticipated development requirements apply, which in turn can affect resources required for product development and the timeliness of availability of new diagnostics to end-users. Also, primary reviewers have considerable discretion in the amount of data required for submissions and their interpretations of those data.

2. Trends in PMA and 510(k) Review Times for Diagnostics

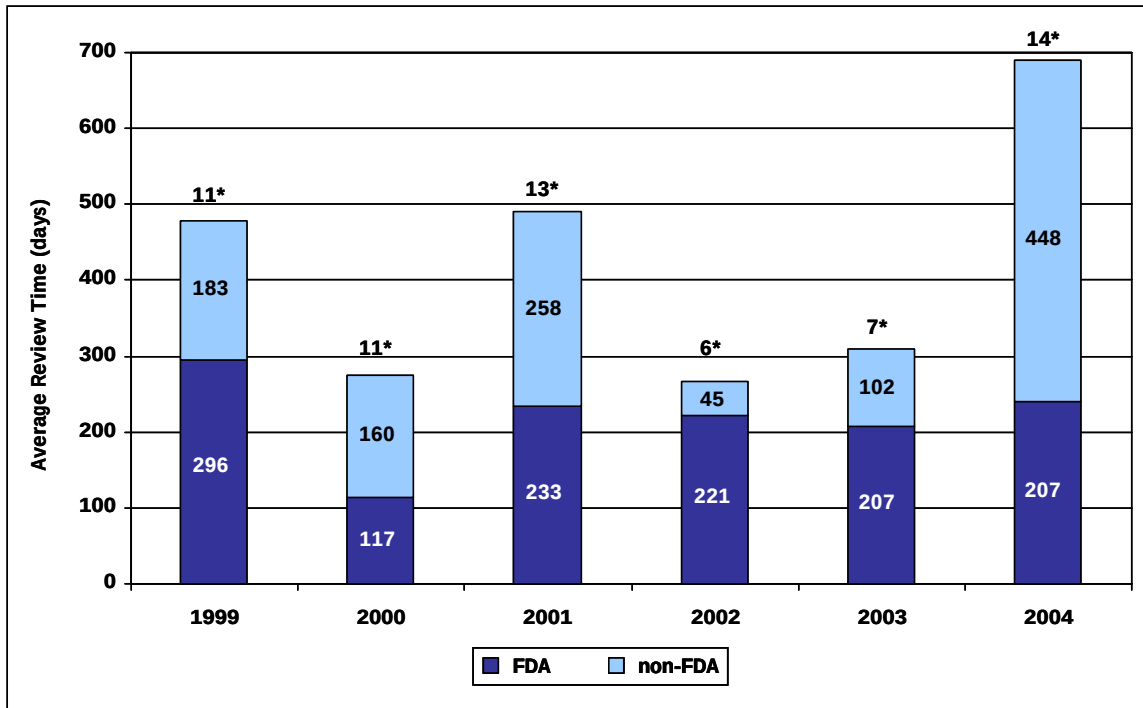
Diagnostics firms are increasingly adept through experience at navigating the regulatory process. By developing applications with appropriate scientific evidence and communicating with FDA earlier as provided by FDAMA, the diagnostics companies and FDA have worked toward reducing the length of time from PMA, PMA supplement and 510(k) submission to final approval or clearance. However, the review process may take longer, given one or more factors, such as the complexity of the technology under consideration, whether it is truly novel and whether it has certain unique features. Further, the mix of submissions for tests of varying

²¹⁶ Medical Device User Fee and Modernization Act of 2002 (MDUFMA). Quarterly update. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2005. Accessed May 25, 2005. <http://www.medicaldevices.org/public/issues/documents/MDUFMAQuarterlyUpdateJan2005.ppt>.

²¹⁷ Office of Device Evaluation Annual Report Fiscal Year 2004. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2005. Accessed May 25, 2005. <http://www.fda.gov/cdrh/annual/fy2004/ode/toc.html>

complexity and different relevant review times (e.g., 30, 90 or 180 days) from year to year make it difficult to elucidate real trends or improvements in FDA review times. **Figures 4.4 and 4.5** show average PMA and PMA supplement review times from 1999 through 2004.

Figure 4.4
PMA Average Review Time for IVDs (1999-2004)

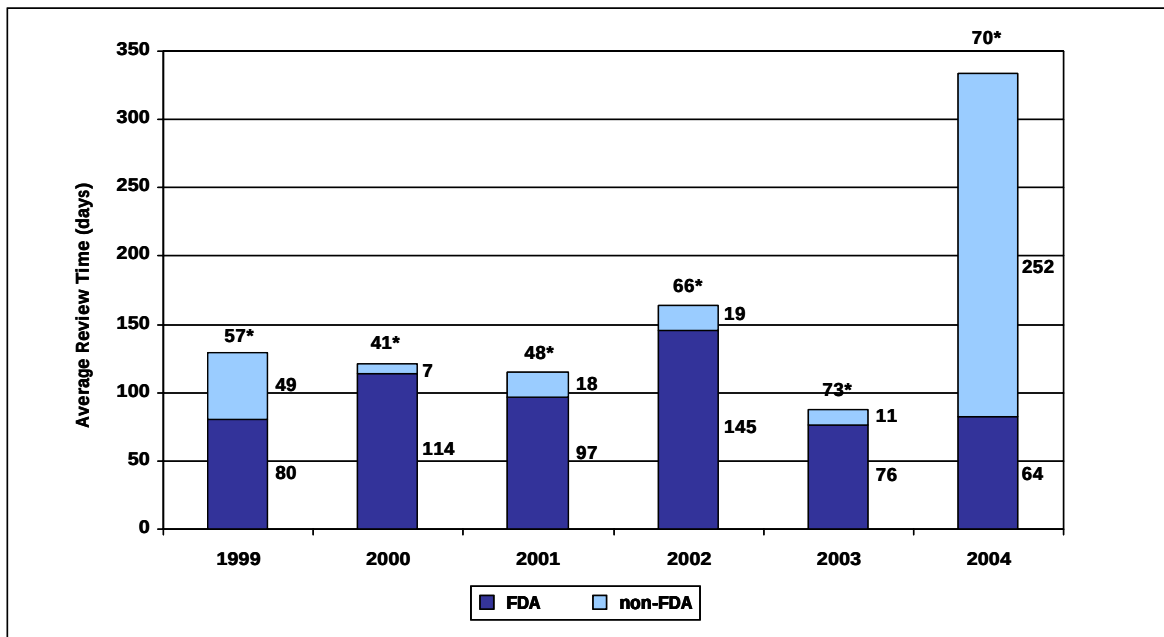


* Number of PMAs received.

Source: Office of Device Evaluation, Center for Devices and Radiological Health, US Food and Drug Administration. 2004.

As shown in **Figures 4.4 and 4.5**, average PMA and PMA supplement review times have varied significantly between 1999 and 2004, with a substantial increase in average non-FDA review time during 2004. As noted above, this is significantly influenced by a variety of factors, making assessment of improvements in review times complex and often misleading. Even so, iterative communications between FDA and the diagnostics industry throughout all phases of development may contribute to the gains in review times, even for particularly complex product reviews. Such communications can help manufacturers to anticipate and avoid potential pitfalls that may slow the review process.

Figure 4.5
PMA Supplement Average Review Time for IVDs (1999-2004)

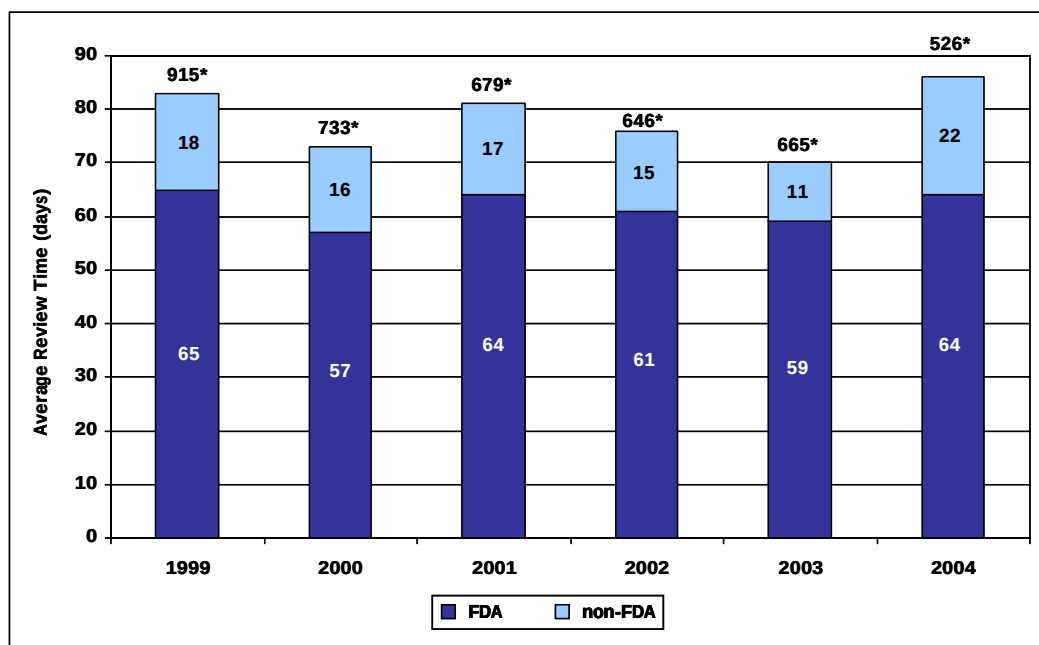


* Number of PMA Supplement Decisions.

Source: Office of Device Evaluation, Center for Devices and Radiological Health, US Food and Drug Administration. 2004.

Average 510(k) review times from 1999-2004 are shown in **Figure 4.6**. Overall review 510(k) times have remained stable over this six year period, with an average total review time of approximately 78 days, of which an average of 62 days involved direct FDA review.

Figure 4.6
510(k) Average Review Time for IVDs (1999-2004)



* Number of 510(k)s received.

Source: Office of Device Evaluation, Center for Devices and Radiological Health, US Food and Drug Administration. 2004.

While the review times from 1999 to 2004 have been relatively consistent, certain diagnostics eligible for the *de novo* 510(k) process could experience significant reductions in overall review times with potential reductions ranging from 183 to 201 days when compared to the PMA process. Recent cooperation between FDA and the diagnostics industry, including development of new mechanisms such as the new “turbo 510(k)” process, illustrate further potential for improving the processing of IVD applications.

3. Turbo 510(k): Toward Efficient Electronic Data Submissions

Recently, OIVD has been working on a pilot program that enables 510(k) applications to be submitted electronically. Known as “turbo 510(k),” the program is scheduled to be available to manufacturers before December 2005. In conjunction with the electronic submission system, OIVD developed a question-and-answer-based model to clarify the data that companies are required to submit. OIVD also is considering extending the turbo approach to PMA applications and *de novo* classification. This new process may reduce the burden of data submissions significantly and improve communications between clinical trial sponsors and FDA, enabling more rapid market access for new diagnostic tests.

4. Increased Emphasis on the ASR Regulatory Pathway

ASR regulation presents a great challenge to the FDA and the diagnostics industry. Since 1995, the FDA has focused greater attention on ASRs. Typically, ASRs are limited to testing at the site of manufacture or by high complexity CLIA-certified reference laboratories.²¹⁸ There continues to be a lack of explicit policy over the regulation of new and emerging technologies in this area, such as gene- or immunohistochemistry-based ASRs.

Most ASRs are considered Class I devices and, thus, do not require FDA approval for distribution but do have specific marketing and other prohibitions.²¹⁹ ASRs are intended to be sold as the building blocks of tests, but cannot have specific claims for medical use attached to them. Provision of instructions for use, certain promotional activities/labeling, claims of specific medical use or sale of other reagents necessary for a reaction in combination with an ASR, would indicate to FDA that the “ASR” is being marketed as a kit or system and is subject to formal FDA approval, e.g., as a 510(k) or PMA.²²⁰

In contrast, test systems/assays developed by laboratories can include ASRs, but are not subject to FDA-enforced limits to approval, GMPs, demonstration of FDA-approved clinical utility, or promotional activities. Laboratory-developed tests are regulated under CLIA (including test performance standards) and by the Federal Trade Commission (FTC) and state laws (advertising, product claims, etc.).²²¹ While compliance with CLIA and FTC regulations involves unique associated burdens, launch of a test/assay as laboratory-developed offers the advantage of more rapid access to market than launch of a test kit/test system subject to FDA review. This difference in regulation can create disincentives for developing tests through more time- and resource-intensive PMA and 510(k) review pathways, which may result in establishment of a

²¹⁸ Gutman S, Feigl DW. The status of ASR regulations. Medical DeviceLink, 2004. Accessed November 10, 2004. <http://www.deviceLink.com/ivdt/archive/04/05/007.html>.

²¹⁹ ASRs used in the detection of infectious diseases are considered Class III and subject to PMA requirements.

²²⁰ Agency Information Collection Activities. 66 Federal Register:1140. 2001.

²²¹ ASRs can be and are commonly used in laboratory-developed tests.

laboratory-developed test or use of ASRs, if available. In some instances, to fulfill special needs, such as newborn screening, or if the request volume for a test is low, laboratory-developed tests might be the only practical means of obtaining such information.

A concern related to the ASR pathway is potentially inappropriate marketing of test kits/systems as ASRs, as summarized in late 2004 by the Director of OIVD:

The greatest abuse [of ASR regulation] may be the increasingly widespread marketing of finished devices as ASRs, thereby allowing manufacturers of detection systems for new analytes to avoid both premarket review and regulations for investigational use. The issue of appropriate regulation is currently under review. Additional rules may not be necessary, however, some clarification of current rules may be based on the different methodologies and regulatory tools available under the two existing authorities for laboratory testing. Under CLIA, tests are subject to regulation through a systems rather than a device specific approach. CLIA focuses on analytical performance and quality control but does not specifically address clinical validation. Under FDA, tests are subject to regulation through a device specific approach. FDA focuses on both analytical and clinical performance but does not specifically address quality control or quality assurance programs required for laboratory testing. FDA recognizes that there is some confusion over the parameters of sales for ASRs and is currently working to produce clearer policy.²²²

Ambiguity regarding ASR regulation poses uncertainty to industry and FDA. Clarification of the definition, classification and oversight of ASRs by FDA would benefit laboratories and manufacturers.²²³ This would elucidate appropriate regulatory pathways and remove uncertainty from product development, though the overall impact on innovation is uncertain.

5. Regulatory Disparities and the Expansion of Laboratory-developed Tests

While it may take manufacturer-produced tests that are subject to FDA approval requirements several years and significant resources to develop data supporting clinical validity and utility, laboratory-developed tests can be developed more rapidly and made accessible to patients with comparatively minimal time and resource constraints. Although certain restrictions apply to in-house tests²²⁴ and third-party payers uniformly may not recognize that these tests do not require FDA approval (creating reimbursement difficulties in some cases), the number of laboratory-developed tests has been growing rapidly.²²⁵ As mentioned above, this creates disincentives for manufacturers to develop tests through FDA approval processes.

6. Increased Emphasis on CLIA Waiver Status

The FDA categorizes commercially-marketed diagnostics under CLIA on the basis of the complexity of the test procedure and the resulting potential risks to public health. However, CLIA regulations consider primarily the analytical validity of laboratory testing through

²²² FDA and the regulation of analyte specific reagents. The American Association of Clinical Chemistry, 2004. Accessed November 17, 2004. <http://64.233.179.104/search?q=cache:SLrvr9NjCmMJ:www.aacc.org/access/ASRs/qanda.stm+%22number+of+ASRs%22+%22analyte+specific+reagents%22&hl=en>.

²²³ Ibid.

²²⁴ For example, tests can only be ordered by practitioners licensed in the state in which the lab resides or test is offered.

²²⁵ 21 CFR 809.30(f).

standards related to personnel qualifications and responsibilities.²²⁶ Certain urine tests, fecal occult blood tests for colorectal cancer detection, self-monitoring blood glucose testing and other diagnostics are waived automatically because the level of expertise required to conduct these tests reliably is minimal (versus, for example, some emerging molecular tests that require significant scientific and technical expertise). Many other diagnostic tests also are waived.²²⁷

Since the inception of CLIA in 1992, the number of waived laboratories has increased from 20% to about 56% today of the 175,000 or more laboratories enrolled.^{228,229} Recent pilot studies (1999 and 2001) conducted by CMS indicated significant quality and certification concerns for more than 50% of existing laboratories under CLIA waiver (e.g., did not conduct tests according to manufacturer's instructions or perform quality control) and that at least 7% of these laboratories were conducting complex tests that exceeded their CLIA certification.²³⁰

In 2002, CMS responded by conducting more frequent on-site visits of CLIA-waived facilities. This should translate into more stringent enforcement of CLIA regulations, including: a) that tests conducted by these laboratories meet compliance requirements; b) that laboratories do not test outside of approved parameters; and c) requiring some laboratories to pay higher fees related to increased diversification of testing.²³¹ While these factors are intended to increase the safety of CLIA-waived laboratory facilities, resulting changes may include reduction in the local/regional availability of some diagnostics and increased time and financial resources associated with finding alternative means of obtaining test results.

7. Informed Consent Regulations for Clinical Trials of Diagnostics

Research on diagnostics can differ from other clinical research in many ways, but perhaps the most important difference is that direct patient involvement may not be required for studies of Class I and many Class II devices. A full study of a diagnostic can be conducted without the research team ever making contact with a patient. This is possible because in usual patient care, a greater volume of a sample is collected from a patient than is actually needed for a lab test. This enables clinical labs to store ("bank") excess specimens for the purposes of future testing, quality assurance or research. Almost all compounds of interest in the specimen can be preserved successfully through freezing or other methods. Diagnostics manufacturers that are designing a study can arrange with a clinical lab to access an adequate bank of specimens. As the chances of physical harm to patients are low or nonexistent, most research on diagnostics is relatively low-risk. In other cases, when fresh specimens are needed for testing, most can be obtained through simple blood draws or other very low-risk procedures.

²²⁶ Sarata A, Shamanski F, Goodwin S, Carr S. The Secretary's Advisory Committee on Genetics, Health, and Society: summary of the October 22-23, 2003 meeting. *J Philos Sci Law* 2004. Accessed online November 9, 2004. <http://www.psljournal.com/archives/all/geneHealth.cfm>.

²²⁷ Currently waived analytes. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration, 2004. Accessed online November 9, 2004. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/analyteswaived.cfm>.

²²⁸ CMS CLIA waived/PPMP laboratory project. Rockville, MD: US Food and Drug Administration, 2004. Accessed November 16, 2004. www.fda.gov/clia/cowppmp.

²²⁹ In the 1997 revisions to the CLIA waiver provisions, Congress specified that tests approved by FDA for home use also were automatically qualified for CLIA waivers; however, professional-use versions are not waived automatically.

²³⁰ Ibid.

²³¹ Ibid.

Concerns about patient privacy, reflected in passage of The Health Insurance Portability and Accountability Act (HIPAA),²³² have focused greater attention on the level and type of risk associated with research of diagnostics. Of particular interest is whether research involving specimens previously collected from patients, yet requiring no further patient identification or involvement, should be subject to prevailing standards regulating human subjects research.

Of particular relevance to IVDs is the contrast between two sets of regulations intended to protect individuals who participate in clinical research. The general regulations for protecting the rights and welfare of human subjects involved in research conducted or supported by DHHS are contained in Title 45 CFR Part 46, known as the “Common Rule.” However, clinical investigations involving products regulated by the FDA are subject to the more conservative FDA regulations for protection of human subjects, i.e., Title 21 CFR Part 50 (Protection of Human Subjects) and Title 21 CFR Part 56 (Institutional Review Board review and approval). Federal support is not necessary for these FDA regulations to apply (when clinical investigations subject to FDA jurisdiction is federally funded, both the DHHS Common Rule and the FDA protection of human subjects regulations apply).

Among the factors that make the FDA regulations more stringent than those of DHHS are differences in the definition of the subjects of clinical research and in exemptions to informed consent by subjects. For the Common Rule, a human subject is a living individual from whom an investigator conducting research obtains data through intervention or interaction. For the FDA regulations, this can be a subject on whom, *or on whose specimen*, an investigational device is used. For the Common Rule, there are several exemptions to informed consent, including collection or study of pathological or diagnostic specimens, if the sources are publicly available or if the subjects cannot be identified directly or through identifiers linked to the subjects. However, for the FDA regulations, the exemptions for informed consent are very narrow, consisting primarily of emergency or life-threatening situations.²³³ Requirements for IRBs are more conservative for FDA regulations as well, providing fewer waivers than those for DHHS. The FDA regulations make it highly difficult to avoid having to seek informed consent for the study of specimens, even for specimens that are leftover from an earlier draw or sample and that have been anonymized or de-linked from their sources.

The rationale for the separate sets of regulations for human subjects protection is not entirely clear. In most research circumstances, an inability to identify subjects directly or link to them through identifiers suffices for an exemption from the Common Rule. In contrast, because FDA submissions are intended to support marketing claims, the agency may consider that it must be able to validate submitted data for particular human subjects. Further complicating the environment for research of IVDs involving human specimens are federal privacy protections under HIPAA and varying state laws. There appears to be no common framework for regulations and institutional policies applying to this form of research. The requirements for

²³² HIPAA covers communication and use of individual and other health information, including requirements for informed consent. HIPAA’s main provisions include: standards for electronic health information transactions; mandate on health plans and providers, and timetable; privacy; pre-emption of state law; and penalties. Pursuant to HIPAA, DHHS published a Privacy Rule that became effective in April 2001. The DHHS Office for Civil Rights has authority for administering and enforcing compliance with the Privacy Rule. CMS has authority for administering and enforcing compliance with the non-privacy HIPAA rules.

²³³ Hojvat SA. Human specimen repositories requirements of 21 CFR 50 & 56. Biological specimens and personal data. April 2005. Accessed May 31, 2005. http://www.uh.edu/pharmacy/ohrp/ppt/Sally_Hojvat-Houston_Presentation_forApril_22%20_2005.ppt.

procuring and using specimens also depend on the type of biological substances involved, the circumstances of procuring them, the parties involved, and their ultimate use.²³⁴

FDA guidance issued in 1999 on regulating IVD studies may have contributed to uncertainty regarding the need for informed consent. This guidance appeared to suggest that certain studies that were exempt from IDE requirements may have been exempt from IRB review and approval or from informed consent if, for example, the source of a leftover sample or previously collected sample were unknown.²³⁵ However, recent actions by the FDA indicate that neither the FD&C Act nor any relevant regulations address specimens that are left over, anonymized or unlinked; therefore informed consent regulations should not be ignored for any FDA-regulated study.^{236,237}

The prevailing regulations require that informed consent must be obtained from all individuals whose specimens may be used, a task requiring significant investment of time and resources. These interpretations affect the ability of the diagnostics industry to develop new products efficiently and successfully. The industry has acknowledged the FDA's position on a patient's right to privacy, but contends that informed consent requirements for trials of Class I and II products, as well as some Class III products, where specimens have been collected previously and identifying information is limited to demographic data, will result in fewer and more limited studies of diagnostics.²³⁸ As noted by one industry executive, implications of these regulations reach beyond diagnostics manufacturers:

*[F]ewer laboratories will have the personnel and infrastructure to support informed consent requirements for even the smallest of studies. The increased expense of conducting studies will drive up the cost of new tests for laboratories, patients and the healthcare system as a whole.*²³⁹

These factors not only influence the use of existing diagnostics, but can delay or inhibit development and marketing of new diagnostics. Rising costs of generating evidence to support regulatory decisions can raise the hurdle to innovation for diagnostics manufacturers.

FDA staff are examining the feasibility of potential means of increasing agency flexibility or discretion for informed consent requirements pertaining to archived or leftover specimens in the context of studies of IVDs regulated by FDA.²⁴⁰

²³⁴ Bernstein SW. Perspectives from those who regulate tissue banks. The moderator's perspective. Accessed May 31, 2005.

<http://www.columbia.edu/itc/hs/medical/bioethics/cire/conference/confMay04/wednesday/PanellI/Bernstein.pdf>.

²³⁵ Guidance for FDA staff. Regulating in vitro diagnostic device (IVD) studies. December 17, 1999. Rockville, MD: US Food and Drug Administration. Accessed May 31, 2005. <http://www.fda.gov/cdrh/comp/ivdreg.pdf>.

²³⁶ Smith KM. New perspectives on informed consent in IVD clinical trials. IVD Technology 2002;June:22. Accessed May 1, 2005. <http://www.devicelink.com/ivdt/archive/02/06/005.html>.

²³⁷ Tarosky M. Bioresearch monitoring. Accessed June 1, 2005. www.fda.gov/cdrh/oivd/presentations/041905-tarosky.ppt.

²³⁸ Moxey-Mims MM, Serge MJ, Melvin MN, et al. Informed consent in clinical trials of in vitro diagnostic devices: perspectives from the FDA and manufacturers. Clin Chem. 2001;47(10):1753-7.

²³⁹ Ibid.

²⁴⁰ Hojvat SA 2005.

In the meantime, various groups have called for a more uniform approach for regulating human subjects research. In its 2001 report on ethical and research issues involving human subjects, the National Bioethics Advisory Commission stated:

Even when current protections apply, the interpretation of the federal regulations can vary unpredictably, depending on which federal agency oversees the research This has slowed the diffusion of basic protections and made it almost impossible to develop consistent interpretations of the basic protections or those relevant to especially problematic research Nor has there been a unified response to emerging areas of research, such as large-scale work on medical records and social science databases or on stored human biological materials.²⁴¹

There is great need and opportunity to harmonize and improve the multiple sets of regulations on informed consent. FDA can address a key aspect of these by re-examining the minimal or non-existent risks and the significant potential benefits that could result from more flexible informed consent requirements for using archived or left over de-linked specimens in IVD studies regulated by the agency.

8. Uncertainty Related to Regulation of Pharmacogenomics

As technologies evolve and become more integrated, FDA likely is to receive more combination products for review. For example, growth in the area of pharmacogenomics is anticipated to lead to drugs whose use in patient care depends on prior specific diagnostic information (e.g., patient genetic or other biomarker information).²⁴² Although most IVDs are reviewed through CDRH by OIVD, the new FDA Office of Combination Products (OCP) may become more active in this area as more drugs that have companion diagnostics are co-developed in the future. While FDA has made reasonable progress toward transparency and consistency of combination product review, many questions remain regarding regulation of drug-device combinations, which may have implications for pharmacogenomic and related diagnostics.

An April 2005 drug-diagnostic concept paper issued by the FDA for the purposes of obtaining feedback from industry and other stakeholders outlines key questions pertaining to potential drug-device combinations.²⁴³ This paper suggests that industry sponsors engage the FDA early to determine which regulatory pathway is most appropriate, whether the product is apt to be a combination or non-combination product and if the product is anticipated to be a combination product, whether sequential or simultaneous review of the drug and diagnostic component is most appropriate.

It is possible that, as review of potential drug-diagnostic combination products unfolds, more FDA requirements may be placed on development of these diagnostics than might occur if they were developed separately from a drug (as has occurred historically through the OIVD). As FDA reviews more drug-diagnostic combination products, it will be important to ensure that requirements for such tests do not delay patient access to diagnostics unnecessarily (e.g., while

²⁴¹ Ethical and policy issues in research involving human participants. August 2001. Bethesda, MD: National Bioethics Advisory Commission. Accessed May 31, 2005.
<http://www.georgetown.edu/research/nrcbl/nbac/human/oversumm.html>

²⁴² The combination of Her-2/neu testing with the drug Herceptin is one example of a diagnostic/drug package.

²⁴³ Drug-diagnostic co-development concept paper (draft). The US Food and Drug Administration, Rockville, MD. April 2005. Accessed May 6, 2005: <http://www.fda.gov/cder/genomics/pharmacconceptfn.pdf>.

additional safety or effectiveness characteristics of a drug are validated), expand inappropriately to other unrelated diagnostic categories (e.g., other gene-based or biomarker tests) or inhibit innovation in this emerging area.

9. Bundling of Tests

Evolving genetic and other molecular diagnostics that comprise multiple tests (e.g., multiplexed, microarray or gene chip tests) are likely to encounter an outdated regulatory framework for bundled tests that may complicate their development and market clearance. “Bundling” of tests occurs when similar analytical and clinical data are proposed for use for a group or panel of diagnostic tests submitted for regulatory review.²⁴⁴ For instance, a sponsor developing a chip that tests for 100 unique biomarkers currently must consider the need to submit a 510(k) or PMA for each of these markers versus a consolidated submission. Resolving these challenges will require close, ongoing communication between industry and FDA.

10. Other Emerging Technology Considerations

Diagnostics that enable simultaneous evaluation of large numbers of biomarkers may pose challenges to both industry and FDA. Computer software necessary to process such diagnostic information and communicate it in a manner that will be readily interpretable and actionable by clinicians will be essential for safe and effective use of these products.²⁴⁵ As products that provide broad patient genetic information (perhaps even full genome scans) become available, future diagnostics may involve comparing an individual’s genetic makeup to population genetic and outcomes data to more accurately assess patient risk for many diseases. While such emerging technologies may offer volume-to-cost advantages for the health consumer, they present great challenges to current regulatory capacity. These technologies will require careful and responsive consideration by regulators and may necessitate expanding the definition of diagnostics and their regulatory pathways and market clearance requirements.

11. Increased Emphasis on Postmarket Surveillance and Total Product Life Cycle

Toward enhanced consumer health and protection, FDA recently has pursued a more process-oriented total product life cycle (TPLC) approach that spans the product concept, prototype, preclinical, clinical, manufacturing, marketing, commercial use and obsolescence. Consistent with this approach, the agency has considered incorporating aspects of QS regulation and postmarket surveillance into the review process, along with lowering the usual premarket review hurdle to provide earlier access to new technology.²⁴⁶

The OIVD, with feedback from the diagnostics industry, has been a leader in implementing TPLC concepts. As part of the TPLC program, CDRH formed an IVD Patient Safety Team in 2003. Its purposes are to explore new avenues to obtain timely, useful and accurate postmarket information on the devices CDRH regulates in order to feed this information back to the

²⁴⁴ Examples of currently bundled tests are lipid profiles and liver function tests. The FDA has suggested that analytes cannot be bundled when they present disparate scientific or clinical uses or other concerns (e.g., testing for unrelated disease indications). When clinical circumstances for multiple tests are identical, disparate tests sometimes can be bundled (e.g., screening for multiple infectious diseases).

²⁴⁵ Ibid.

²⁴⁶ Gutman S 2004.

premarket review process and to facilitate the merger of premarket and postmarket activities to smooth the transition to the TPLC concept. This team oversees several others in areas, such as collection and analysis of data on laboratory events/incidents and IVD adverse event reporting (deaths, hospitalizations, voluntary reports).²⁴⁷

The implications of this tradeoff of reduced premarket review for more longitudinal regulatory oversight remain to be seen. While the TPLC approach could speed some IVDs to market, certain harms that may arise subsequent to the time of testing (e.g., from unnecessary or inappropriate use of further diagnostics or therapies based on false positive or false negative diagnostic test results) may not be truly attributable to the diagnostics themselves. It may be particularly difficult for FDA to track such harms and distinguish those that are at least partially attributable to a diagnostic from those that are not. Because of this ambiguity, open communication with industry and other stakeholders prior to incorporating additional regulatory requirements based on postmarket data should help ensure that such requirements do not inhibit availability of proven diagnostics inappropriately.

D. Implications for Diagnostics Industry Innovation

The regulatory framework for IVDs may need to evolve in response to innovation in the diagnostics industry. Growth in diagnostic areas such as genetic testing and pharmacogenomics and the greater diversity of settings in which IVDs are employed (e.g., home testing, hospital, skilled nursing facilities) will continue to raise challenges for FDA and manufacturers.

Addressing existing and emerging challenges will require open and constructive communication between FDA and industry. Stakeholder communications have improved considerably in recent years through initiatives such as the IVD Roundtable, initiated in 1995, which convenes representatives of IVD makers and FDA to address and overcome regulatory barriers and concerns.²⁴⁸ The IVD Roundtable meets approximately quarterly.

Forthcoming guidelines and rules anticipated in the near future (e.g., pertaining to CLIA waiver, ASRs and combination products) should significantly clarify the process of bringing new diagnostics to market. In general, the legislative and regulatory changes to date have enabled more timely reviews with greater postmarket surveillance, which expedites patient access, aids manufacturers in establishing an evidence base to support various product uses and allows regulators to better understand product effectiveness outside of research settings once safety and effectiveness have been established, as appropriate. Similar to other health technology sectors, it is likely that the diagnostics industry will face increased demand for lower costs, standardization, greater accuracy, easier use, less invasiveness, faster processing of results and other quality improvements. In addition to regulators, this demand will arise increasingly from an aging population, third-party payers, purchasers of health services and others focused on quality and accountability.

²⁴⁷ FY 2003 CDRH Annual Report. Rockville, MD: Center for Devices and Radiological Health, US Food and Drug Administration. Updated August 20, 2004. Accessed December 15, 2004.
<http://www.fda.gov/cdrh/annual/fy2003/assuring.html>

²⁴⁸ Report to Congress on the timeliness and effectiveness of device premarket reviews. Washington, DC: Secretary of the Department of Health and Human Services, 2003. Accessed November 17, 2004.
<http://www.fda.gov/cber/mdufma/report0803.pdf>.

E. Diagnostics Regulation: Findings and Recommendations

1. Findings

Important changes have occurred in regulation of diagnostics in recent years. These are intended to improve coordination of the regulatory process within FDA, communication between manufacturers and FDA and access to new diagnostics.

- FDA has developed more efficient means of regulating diagnostics and other devices, including coordinating diagnostics regulation using a total product life cycle approach and a pilot “turbo 510(k)” process for streamlining 510(k) submissions.
- For diagnostics, average PMA and PMA supplement review times fluctuated between 1999 and 2004, with a large increase in average non-FDA review time for both categories in 2004. Average review times for 510(k)s, the most frequent type of submission, were largely consistent during this period. Review times are influenced by many factors, confounding assessments of year-to-year changes. Iterative communications between FDA and the diagnostics industry throughout all phases of development may contribute to achieving and maintaining efficient reviews, even for particularly complex products.

Despite recent gains, many barriers to efficient product development and timely diffusion remain. Certain regulatory requirements, capacity and guidance for development of diagnostics are outdated or insufficient for addressing complex and unique considerations of emerging diagnostics. Among these are the following:

- Laboratory-developed tests (sometimes known as “home brews”) are not subject to the same FDA regulation required of functionally similar tests developed by diagnostic manufacturers, but are subject to performance standards of CLIA, overseen by CMS. This difference in regulation for functionally similar tests can create disincentives for developing tests that would be subject to FDA’s more time- and resource-intensive regulatory pathways.
- Ambiguity regarding regulation of ASRs poses uncertainty to industry and FDA. There is a lack of explicit policy over the regulation of new and emerging technologies in this area, such as gene- or immunohistochemistry-based ASRs.
- Patient informed consent is protected by DHHS regulations applying to all clinical research conducted or sponsored by the federal government and by specific FDA regulations for studies conducted in support of new product submissions. Investigations of diagnostics conducted for FDA submissions rarely require direct patient involvement, as these studies may use “leftover” or “banked” samples from earlier tests. However, even when these samples have been stripped of individual identifying information, the more conservative FDA regulations requiring informed consent for testing these samples can be an unnecessary barrier to beneficial research.

2. Recommendations

The FDA, in conjunction with CMS, the FTC and others as appropriate, should establish a unifying set of regulations for diagnostics and diagnostic components, regardless of their site of production or use.

- These agencies should clarify regulations and oversight pertaining to laboratory-developed tests and manufacturer-produced ASRs, including apparently finished devices marketed as ASRs, to minimize potential risks to safety and public health.
- The FDA, CMS and other stakeholders should develop an equitable process for regulation of tests/test kits and laboratory-developed tests that does not substantively inhibit or preclude development or availability of these tests.

For emerging diagnostics with high potential to affect health care delivery, FDA should develop a more timely and structured process to update existing agency guidance documents that may be outdated and generate new guidance as needed, including pertaining to practical and informative evidence requirements for these diagnostics.

- Applicable federal agencies should expand collaboration with industry and other stakeholders via such means as the IVD Roundtable to identify high priority areas (e.g., for ASRs, banked samples and pharmacogenomics) for guidance development and clarification of regulatory requirements.
- FDA and CMS should maintain communication regarding their respective evidence requirements and timelines for market clearance and reimbursement of diagnostics, respectively, particularly to improve the relevance and efficiency of necessary data collection, as well as the timeliness of patient access to proven technologies.

In collaboration with CMS, the DHHS Office for Civil Rights and other relevant stakeholders, FDA should determine whether there are circumstances under which the informed consent requirements currently applicable to diagnostics studies are unnecessary.

- Providing that patient information safeguards are upheld consistent with HIPAA and other relevant legislation, these agencies and other stakeholders should develop an informed consent waiver process for previously collected, de-identified patient clinical samples. A viable informed consent waiver process would eliminate unnecessary hurdles and costs required to bring diagnostics to market.
- These stakeholders should consider harmonizing the multiple prevailing sets of regulations pertaining to informed consent. Particular attention should be given to unnecessary or inappropriate distinctions between the Common Rule regulations for research conducted or sponsored by DHHS and the regulations applying to clinical investigations involving products regulated by the FDA.

V. US Reimbursement for Diagnostics

Third-party payment by government and private payers has enabled patients to access and benefit from proven new health care technologies and helped to ensure broad markets for these products. However, difficulty in acquiring appropriate coding, coverage and adequate payment can pose significant hurdles to adoption and diffusion of new technologies and may discourage some innovators from pursuing further development of a technology altogether. Key issues regarding reimbursement of diagnostics are summarized below and addressed in this chapter.

- **Utilization and cost pressures** on providers and manufacturers are characteristic of the US reimbursement environment. These pressures may be counterproductive for innovation and optimizing the value that diagnostics can provide to health care, including more informed decision-making, improved outcomes and more efficient resource use.
- **Coding** can influence the availability and demand for new diagnostic tests, because the payment level for a test is determined by the particular code assigned to it. Current coding mechanisms are not designed to reflect the value of a technology to patient health or the health care system. For diagnostics, the processes associated with obtaining new or revised coding can be complex, lengthy and insufficiently open to stakeholders whose input would strengthen the coding decisions.
- **Coverage** establishes the conditions under which third-party payment is provided, including the clinical indications for a new diagnostic and the circumstances of use by physicians and patients. Medicare coverage of diagnostics is decentralized, with most decisions being made by local Medicare contractors, often resulting in variable coverage decisions that differentially affect access to patient care and health care quality. Local Medicare coverage does provide opportunities for patient access, increased clinical experience with technologies and some revenue to support further technology development. Greater efficiencies in the local coverage process would maintain contractor flexibility to provide services responsive to different regions and balance limitations of local coverage with strengths of the national coverage process.
- **Payment** levels for technologies influence their use by providers and access by patients. The Medicare payment process for clinical laboratory services is long overdue for modernization. Existing methods of incorporating new tests into the CLFS used for Medicare payment for diagnostics are archaic, inconsistent and seriously flawed. They fail to reflect the relative value of diagnostics to health care, sending inefficient market signals to innovators, clinicians and payers. Medicare reimbursement decisions also reach beyond the Medicare program, as other payers often follow these decisions. These and other factors often result in underpayment for existing and new diagnostic technologies. Underpayment of diagnostics can precipitate suboptimal care decisions and unnecessary downstream costs.
- **MMA**, The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, calls for some key improvements to coding assignment and payment for new clinical laboratory tests. However, the five-year freeze on payment rates in the Medicare CLFS will cause payment for diagnostics to lag further behind inflation and extend disincentives for innovation adoption and patient access to diagnostics.

A. Overview of US Reimbursement Systems

Difficulty in acquiring appropriate coding, coverage and adequate payment for new diagnostic tests can pose significant hurdles to their adoption and diffusion. The consequences can include reduced patient access to new tests and decreased incentives for manufacturers to engage in further test development.²⁴⁹

This reimbursement process consists of three basic and distinct considerations:

- **Coding:** alphanumeric nomenclature assigned to particular health conditions, services or products, which also is used to designate payment levels for these
- **Coverage:** a decision or policy of a third-party payer to provide payment for a particular service or product under an insured benefit
- **Payment:** levels of payment for covered services or products and methods for deriving these amounts

Coding mediates the success of new diagnostic tests because assignment to a particular code will link the test to a payment level. New diagnostic tests are assigned either to existing codes with established payment levels or to novel codes with new payment levels.

Despite recent improvements, the processes associated with obtaining new codes or revising older ones for diagnostics can be unpredictable and insufficiently transparent, requiring significant planning and resources on the part of manufacturers or other sponsors. Navigating these multi-step, often lengthy coding processes can increase the uncertainty of timely access and market success, increasing risk for product sponsors. This may be particularly so when regulators and other individuals responsible for assigning or making coding changes are not technical experts or otherwise familiar with the rapidly evolving diagnostics.

Coverage policies also play a major role in the success of new diagnostic tests. Coverage policies specify whether or not payers will include a particular technology or service under their insured benefits and pay providers for these. While US public and private payers typically make coverage and payment decisions separately, payers may anticipate significant financial impact resulting from certain coverage determinations.

Payment for diagnostic technologies can affect incentives to develop technology, enter competitive markets and offer new care options. While it is reasonable to expect that the payment level for a technology should reflect its value to patient care, current coding and payment mechanisms often do not reflect value. A new technology that confers greater benefits often is paid the same amount as, or in some cases less than, an existing one sharing the same code. Methods for setting initial payment levels for diagnostic tests and updating existing ones (e.g., cross-walk and gap-fill methods described below) also are nonstandardized and inconsistently applied.

²⁴⁹ The Lewin Group. Report 1: The State of the Industry. 2000.

In recent years, increasing price sensitivity of payers and providers has prompted greater scrutiny of coverage and payment for new medical technology, which often is perceived as a major contributor to increased health care utilization and costs.²⁵⁰ While intended to incorporate quality and provide adequate payment, current reimbursement trends place increasing constraints on providers and diagnostics manufacturers.

This chapter provides an overview of the public and private payer reimbursement systems, issues affecting the diagnostics industry and implications for patient access to new technology.

B. Medicare

1. Overview

Approximately 41 million Americans age 65 and over, some people under age 65 with disabilities and those with end stage renal disease (ESRD) receive health insurance coverage under Medicare. This national health insurance program was created in 1965 as part of the Social Security Act.²⁵¹ In 2004, Medicare expenditures were an estimated \$295.2 billion, or 16.5% of national health care expenditures.²⁵² As the largest single payer in the US, Medicare has great influence in the health care market.²⁵³

Medicare is administered at the national level by the CMS. In Medicare, four main categories of covered benefits, of which Part B is most relevant to diagnostics, as the following.^{254,255}

- **Part A, Hospital Insurance**, includes inpatient hospital care, skilled nursing facilities, hospice and home health care.
- **Part B, Medical Insurance**, includes physician care; outpatient hospital care; laboratory tests, medical supplies; home health care not covered under Part A; and preventive, outpatient physical therapy, mental health and ambulance services.
- **Part C, Medicare Advantage** (formerly known as Medicare+Choice), refers to Part A and B benefits provided by managed care plans to Medicare beneficiaries who choose to enroll in these plans.
- **Part D, Prescription Drug Benefit**, will be implemented in 2006 as part of the MMA.

²⁵⁰ When a technology is covered, payers may restrict payment to use: a) in patients with specifically defined indications; b) in particular health care settings (e.g., traditional laboratories versus point-of-care testing); and c) subject to prior authorization or utilization reviews to ensure appropriate use of a service.

²⁵¹ Medicare information resource. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 9, 2004. <http://www.cms.hhs.gov/medicare/>.

²⁵² Centers for Medicare & Medicaid Services. The 2004 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds. Baltimore, MD: Office of the Actuary, 2004.

²⁵³ Fact sheet: Medicare at a glance. Menlo Park, CA: The Henry J. Kaiser Family Foundation, 2004. Accessed November 2, 2004. <http://kff.org/medicare/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=33319>.

²⁵⁴ Fact sheet: Medicare at a glance, 2004.

²⁵⁵ Talking about Medicare: Medicare at a glance. Menlo park, CA: The Henry J. Kaiser Family Foundation, 2004. Accessed December 9, 2004. <http://www.kff.org/medicare/7067/ataglance.cfm>.

CMS contracts with three main types of non-governmental entities to administer Medicare payment at the local or regional level. At the local level, fiscal intermediaries administer the Medicare Part A benefit and carriers administer the remaining non-institutional and outpatient Medicare Part B benefit. Durable medical equipment regional carriers (DMERCs) administer the benefit for medical equipment and supplies.²⁵⁶ Responsibilities of these contractors include making coverage decisions at local and regional levels and paying claims.

2. Coding

The code assigned to a technology or service determines its payment level. Under Medicare, codes are linked to fixed payment amounts via fee schedules. Codes for most diagnostic tests are included in the Medicare CLFS. Increasingly, certain complex tests (i.e., pathology tests requiring professional interpretation) fall under the Medicare Physician Fee Schedule (MPFS). Although the CLFS was established for Medicare, the same or similar fee schedules and codes often are adopted by other payers, extending the reach and impact of Medicare decision-making.

Codes for diagnostic tests in the CLFS largely are developed under the Current Procedural Terminology (CPT-4) coding system, maintained by the American Medical Association (AMA).^{257,258} Every October, the AMA publishes updated codes, which become effective as of the next January 1. Approximately 1,000 separate clinical laboratory and pathology codes are currently listed in the 80000-89399 CPT-4 code series.²⁵⁹

a. National Coding Systems

CPT codes fall within a larger national coding system known as the Healthcare Procedural Coding System (HCPCS). Under Medicare, HCPCS codes assign payment levels for physician services, clinical laboratory services and medical equipment provided in the outpatient setting. Payers other than Medicare set their own payment levels based on varying contract designs. The HCPCS coding system comprises two principal subsystems, Level I and Level II.

- **Level I: CPT.** CPT is accepted throughout the US for coding of medical procedures and reporting of services performed by physicians and other health care practitioners.
- **Level II: HCPCS/National Codes.** Because CPT does not include codes for all services that are covered by Medicare, CMS developed an additional set of national codes to

²⁵⁶ Medicare Resident & New Physician Training Program: A Comprehensive Guide Designed to Inform Physicians About the Medicare Program. (Sixth edition). Baltimore, MD: Centers for Medicare & Medicaid Services, 2002. Accessed December 9, 2004. <http://www.cms.hhs.gov/medlearn/medicare%20resident-V2.pdf>.

²⁵⁷ The CLFS also contains a small number (fewer than 50) of Level II HCPCS codes, which were created to describe clinical laboratory services that had to be uniquely identified for Medicare purposes. An example of this type of code is G0103, prostate cancer screening; prostate specific antigen (PSA) blood test. This Level II code was introduced effective January 1, 2000, to implement section 4103 of the Balanced Budget Act of 1997 that mandated negotiated rulemaking for laboratory tests. This resulted in a positive national coverage determination for coverage and tracking of expenditures for PSA tests for Medicare beneficiaries.

²⁵⁸ CPT process – how a code becomes a code. Chicago, IL: American Medical Association, 2004. Accessed February 20, 2005. <http://www.ama-assn.org/ama/pub/category/3882.html>.

²⁵⁹ Medicare program: procedures for coding and payment determinations for clinical laboratory tests and for durable medical equipment. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 5, 2004. <http://www.cms.hhs.gov/medicare/hcpcs/codpayproc.asp>.

identify products, supplies and services not included in the CPT. Level II codes are maintained and distributed by CMS, in conjunction with private payer organizations.

Within HCPCS Level I are the following three categories of CPT codes.^{260,261}

- **Category I:** Five digit numerical codes (e.g., 86301) for well-established tests/services with demonstrated efficacy.
- **Category II: Performance Measurement.** *Optional* five digit alphanumerical codes (e.g., 3000F) for tracking the effects of test results or services on quality of care in coordination with established performance measures.
- **Category III: Emerging Technology.** five digit alphanumerical codes ending in “T” (e.g., 0085T) for new or investigational services/procedures with relevance for research, to collect data for FDA approval or to support broader use of the service/procedure. These codes are made available twice a year and, in most cases, are abolished after five years if they have not been awarded Category I status.

For new tests, Category III codes provide an alternative to submitting claims using unlisted or miscellaneous codes that do not offer the opportunity for collecting data on clinical efficacy, utilization and outcomes. Compiling data as claims are submitted for a new test/service can inform policy and be used to evaluate the utility of new technologies and impacts on health care delivery. In practice, however, Category III codes may not facilitate such useful data collection, as payers often view technologies with Category III codes as investigational or experimental and automatically exclude them from payment. Consequently, if claims are rejected, it can become difficult or impossible to collect sufficient evidence to support moving a technology from a Category III to a Category I CPT code, as is the case with many new diagnostics.

A separate national coding system, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), is the principal system for coding patient diagnoses and conditions in the US.²⁶² This coding system enables payers to determine whether a service is medically necessary and appropriate and whether the provider used the correct code(s) for payment of claims.²⁶³ Many emerging diagnostics, such as those involving multiple biomarkers (each with varying implications for disease detection or prognosis) or gene-based predictive tests used to assess risk for future disease, challenge conventional interpretations of medical necessity and may encounter barriers to payment.

²⁶⁰ CPT ® background and categories of CPT® codes. Chicago, IL: American Medical Association, 2004. Accessed February 16, 2005. <http://www.ama-assn.org/ama/pub/category/12886.html>.

²⁶¹ Category II codes. Chicago, IL: American Medical Association, 2005. Accessed February 16, 2005. <http://www.ama-assn.org/ama/pub/category/10616.html>.

²⁶² The ICD-9-CM system is based on the World Health Organization’s International Classification of Diseases, 9th edition, which is used as an international, uniform coding system for mortality and morbidity. In the US, the ICD system has been modified and expanded into the ICD-9-CM for coding disease, conditions and procedures.

²⁶³ Updates and changes to ICD-9-CM codes are the responsibility of the federal interdepartmental ICD-9-CM Coordination and Maintenance Committee, which is co-chaired by representatives of the National Center for Health Statistics (NCHS, part of the CDC) and CMS. NCHS has lead responsibility for the diagnosis codes and CMS has lead responsibility for the procedure codes.

Both the HCPCS (including CPT) and ICD-9-CM coding systems serve as the basis for payment under Medicare. Often, these Medicare coding systems also are adopted by private payers, underscoring the significant uptake and impact of decisions made for the Medicare program.

b. CPT Coding Updates

The processes for updating CPT codes have undergone certain improvements in recent years. However, the timelines for updating codes remain lengthy, affecting the adoption and initial use of some tests. Also, the process for developing and implementing new coding for diagnostics would benefit from greater transparency and stakeholder input, more along the lines of coding for the MPFS. Any means for gaining such further input should not lengthen the timeline from submission of new coding applications to the effective date of new coding.

Obtaining appropriate new or revised codes for diagnostics can be complex and lengthy, requiring significant time and resources on the part of manufacturers or other sponsors. Applications for new CPT codes must be submitted by specific submission deadlines each year and are reviewed by the AMA CPT Editorial Panel, which includes 17 providers nominated by the AMA, Blue Cross and Blue Shield Association, CMS, the American Hospital Association and the Health Care Professionals Advisory Committee (which represents non-physician health care professionals), among others. The Editorial Panel also is supported by the CPT Advisory Committee, which consists of physicians nominated by national medical specialty groups.²⁶⁴

For Category I CPT codes, assignment of new or revised coding is generally based on whether a procedure is consistent with contemporary medical practice and performed often in multiple locations. Among the requirements of the Editorial Panel for Category I codes are that the test has received FDA approval for the specified use, is a distinct test in widespread use among multiple laboratories, has well-established clinical efficacy documented in the US peer-reviewed literature, is not a fragmentation of an existing procedure and has the support of a relevant medical professional association.²⁶⁵

Decisions to establish Category II (performance measurement) codes consider whether measurements have been developed and tested by a national organization; are evidence-based with established ties to outcomes; address clinical conditions of high prevalence, high risk or high cost; and are well-established and currently used by large segments of the health care industry. As Category III (emerging technology) codes are intended for data collection toward FDA approval or to document widespread use (i.e., toward subsequent designation of a Category I code), they need not conform to the same requirements for Category I codes. Any of the following may be sufficient for considering a new Category III code: a) a protocol for a study of procedures being performed; b) support from the specialties who would use the

²⁶⁴ Updates and changes to ICD-9-CM codes are the responsibility of the federal interdepartmental ICD-9-CM Coordination and Maintenance Committee, which is co-chaired by representatives of the National Center for Health Statistics (NCHS, part of the CDC) and CMS. NCHS has lead responsibility for the diagnosis codes and CMS has lead responsibility for the procedure codes.

²⁶⁵ CPT process – how a code becomes a code. Chicago, IL: American Medical Association, 2004. Accessed February 20, 2005. <http://www.ama-assn.org/ama/pub/category/3882.html>.

procedure; c) availability of US peer-reviewed literature; and d) descriptions of current US trials of the efficacy of the procedure.²⁶⁶

The length of time to make coding changes effective is subject to scheduling requirements of the coding application submissions, the review process and the processing and publishing of coding updates. Depending on the date that a coding application is submitted, and barring other sources of delay, it can take 14-26 months for a Category I CPT code to become effective and 10-16 months for a Category II or III code to become effective. Further delays can occur if the participating medical specialty societies and reviewers do not arrive at consensus regarding coding decisions (e.g., when a test is controversial or anticipated to have significant national health or economic impact) or if reviewers conclude that a technology has not met CPT requirements for widespread use or for efficacy and clinical utility at the time of review.²⁶⁷

The Editorial Panel meets three times per year (February, June and October) to review new coding requests. For Category I CPT codes, coding changes typically are decided by the Editorial Panel no later than their June meeting,²⁶⁸ released in electronic form to CPT licensees and others in September,²⁶⁹ published in the new code book in October (enabling providers and carriers to prepare to use them) and made effective in January.²⁷⁰ Subject to recent changes, Category II and III codes are now pre-released twice per year in January and July and made effective six months later, enabling time for implementation during that span.^{271,272}

The AMA recently made the coding process more open by considering recommendations of the Pathology Coding Caucus (PCC), which was established by the College of American Pathologists and met initially in 2003. Consisting of stakeholders from eight organizations, including physician, laboratory and diagnostics industry representatives and representatives from the AMA, the PCC reviews proposed revisions in clinical lab CPT codes (though not pricing for these) and provides recommendations for consideration by the AMA CPT Editorial

²⁶⁶ CPT process – how a code becomes a code. Chicago, IL: American Medical Association, 2004. Accessed February 20, 2005. <http://www.ama-assn.org/ama/pub/category/3882.html>.

²⁶⁷ Informed by interviews with staff of CMS and AMA CPT and Editorial Information Services, March 2005.

²⁶⁸ The Editorial Panel also may receive input on wording used to describe codes from the AMA Specialty Society Relative Value Update Committee (RUC), which typically meets in May each year to make relative value recommendations used in pricing new or revised codes. While not affecting decisions to establish a new code or revise an existing one, the RUC may make suggestions for clarifying wording associated with a code that will help ensure that it is used properly by providers and handled appropriately in claims processing.

²⁶⁹ This electronic release does not include the extensive annotation provided in the published version. This release is for major licensed systems developers and for providers to update their claims and other administrative systems in preparation for the coming calendar year.

²⁷⁰ New or revised coding application submission deadlines are in March, July, and November. Given the time required to organize the necessary documentation for review during the Editorial Panel meetings, the November submission deadline is the last one for which a resulting Category I CPT coding change typically can be made effective for the January update 14 months later. An application that just misses the November deadline could not result in a coding change made effective until the following January, i.e., nearly 26 months later. These timelines are effectively one month less than had been the case before 2004, when the last submission deadline was in October rather than November.

²⁷¹ Beebe M. CPT Category III codes cover new, emerging technologies. New codes developed to address issues in light of HIPAA. JAHIMA 2003;74(9):82-84,86,88.

²⁷² For Category II and III codes, an application submitted by the March deadline can result in a pre-released coding change in July, made effective the following January, i.e., 10 months after the submission. An application that just misses the March deadline could not result in a pre-released coding change until January, made effective the following July, i.e., 16 months after submission.

Panel. Certain findings of the Editorial Panel in the last few years have been consistent with PCC recommendations on clinical laboratory coding proposals.^{273,274} Also, Editorial Panel meetings are no longer closed, and their meeting agendas are made public. Still, greater opportunities for access to working documents beyond the publicly posted meeting agendas and for direct input from clinical laboratories and diagnostics manufacturers would improve the accuracy and efficiency of complex coding determinations for diagnostics, particularly in light of the growth in volume and diversity of diagnostic tests in recent years.

3. Coverage

Coverage refers to decisions by third-party payers to include a service in the package of benefits available to beneficiaries.²⁷⁵ Congress sets forth the legislative mandate for authorized services under Medicare, allowing payment for “expenses incurred for items and services” that are “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”²⁷⁶ Unless otherwise specified by Congress, the Medicare statute generally excludes coverage for other health care services, including technologies subject to FDA regulation that have not been approved by FDA as well as most preventive and screening services.²⁷⁷ In recent years, Congress has mandated Medicare coverage for certain preventive and screening services, such as bone densitometry screening for osteoporosis, prostate specific antigen (PSA) tests for identifying prostate cancer and colorectal cancer screening.

Coverage decisions influence payment determinations and affect patient access to new technologies. Almost 90% of all coverage decisions are made at the local or regional level by Medicare contractors (fiscal intermediaries, carriers and DMERCs).²⁷⁸ When coverage issues cannot be resolved locally, are subject to wide variations in local coverage policy or are otherwise considered to be of national importance, they can be raised to the national level for a coverage determination. To date, national coverage determinations rarely apply to diagnostics.

At the national level, the Medicare Coverage Advisory Committee (MCAC) advises CMS regarding the quality and relevance of evidence pertaining to specific medical items and services under consideration by CMS for Medicare coverage.²⁷⁹ When asked to evaluate diagnostic tests, MCAC panels are tasked with determining whether available evidence is

²⁷³ Coding. Washington, DC: American Clinical Laboratory Association. Accessed December 9, 2004. <http://www.clinical-labs.org/issues/coding/index.shtml>.

²⁷⁴ College of American Pathologists. CAP leads efforts for pathology in CPT process. Statline 2003;19(23). Accessed May 1, 2005. <http://www.cap.org/apps/docs/statline/stat111203.html>.

²⁷⁵ Under the Medicare program, this first involves a determination of whether the service falls under a covered benefit category.

²⁷⁶ Coverage and reimbursement of genetic tests and services. Draft report. Public comment draft. Washington, DC: US Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, April 2005.

²⁷⁷ Wolman DM, Kalfoglou AL, LeRoy L (eds). Medicare Laboratory Payment Policy: Now and in the Future. Washington, DC: Institute of Medicine, Division of Health Care Services, Committee on Medicare Payment Methodology for Clinical Laboratory Services, 2000. Accessed December 10, 2004. <http://books.nap.edu/html/mlpp/>.

²⁷⁸ The Lewin Group. Report 2: Medicare Payment Process and Patient Access to Technology. 2000.

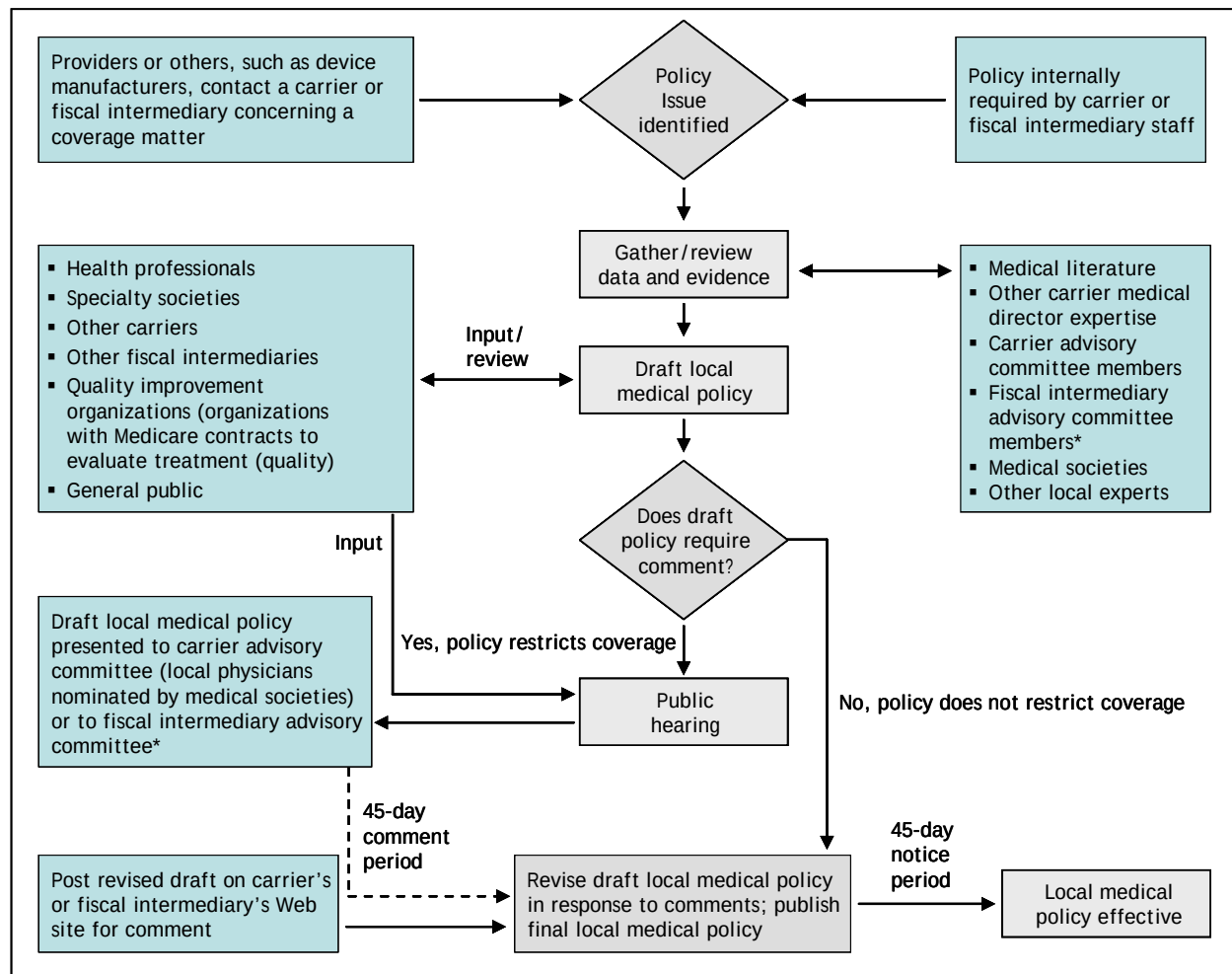
²⁷⁹ Medicare coverage: MCAC background. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 1, 2004. <http://www.cms.hhs.gov/mcac/background.asp>.

adequate to conclude that a diagnostic test improves outcomes and to classify the magnitude of the health benefit when a test is used for a specific purpose.

a. Overview of the Local Coverage Process

While national coverage decisions take precedence over local decisions, the great majority of coverage decisions for new technologies are reviewed at the local level.²⁸⁰ Figure 5.1 portrays the process that local Medicare contractors use to develop coverage policies.

Figure 5.1
Local Medicare Contractor Process for Developing Local Coverage Policies



Reproduced from: Medicare: Divided authority for policies on coverage of procedures and devices results in inequities. Washington, DC: United States General Accounting Office. April, 2003. (Publication no. GAO-03-175).

²⁸⁰ Carriers establish local coverage in the form of LMRPs or LCDs. Certain distinctions exist between LMRPs and LCDs. LMRPs may contain provisions related to coding, benefit categories, statutory exclusions, utilization controls and/or definitions of reasonable and necessary services. In contrast, LCDs only contain information regarding whether an item or service is reasonable and necessary under Medicare.

Coverage, particularly for diagnostics, is largely decentralized, presenting potential advantages and disadvantages for health care access and quality (see **Figure 5.2**). On one hand, different coverage policies among local contractors may raise concern about inequitable access for beneficiaries. In addition, when these carriers apply different thresholds of evidence or varying criteria for making coverage decisions, quality of care also can be compromised—including overuse, underuse or misuse—with attendant impacts on health and costs.^{281,282} On the other hand, if a national coverage decision is flawed, it applies across the US, with all-or-none implications for Medicare payment for potentially worthy technologies.

Figure 5.2
Primary Advantages and Disadvantages of Local Medicare Coverage Processes

Advantages	Disadvantages
• Allows Medicare the flexibility to respond to unique regional health care needs and challenges • Allows contractors flexibility to manage utilization differences, ensure appropriate billing and address instances of abusive billing swiftly • Greater opportunities for provider, manufacturer and other stakeholder input on coverage policies • Means to offer patients and practitioners access to new technologies that may not otherwise exist if all Medicare coverage decisions were made at the national level • Opportunities to accrue evidence base on the safety, effectiveness and costs associated with technologies • Opportunities to characterize circumstances of use for technologies • Early revenue generation opportunities for manufacturers to support ongoing product development that may not otherwise exist	• Significant potential for establishing variable and sometimes inappropriate coverage policies that affect patient access and quality • Significant variations in the criteria and methods used to make coverage decisions • Less than 50% of the LCDs made by the 46 Medicare carriers and fiscal intermediaries cited peer-reviewed clinical evidence (Foote 2004) • Differing availability of resources to conduct or purchase technology assessment services • Creation of coverage policies that limit or expand coverage of certain tests beyond the number per patient recommended for clinical practice (can be precipitated by a spike in claims) • Decentralized system that often results in redundant coverage efforts • Often criticized for untimely and uncoordinated mechanisms to raise eligible coverage policies for national consideration

Sources:

1. *Medicare: Divided authority for policies on coverage of procedures and devices results in inequities.* Washington, DC: US General Accounting Office 2003. (Publication no. GAO-03-175).
2. Foote SB, et al. *Resolving the tug-of-war between Medicare's national and local coverage.* *Health Affairs* 2004;23(4): 108-23.

The decentralized local coverage process provides opportunities for coverage, patient access, increased clinical experience with diagnostics and limited revenue to support ongoing diagnostics development that might not otherwise exist if most coverage determinations were

²⁸¹ Carriers establish local coverage in the form of LMRPs or LCDs. Certain distinctions exist between LMRPs and LCDs. LMRPs may contain provisions related to coding, benefit categories, statutory exclusions, utilization controls and/or definitions of reasonable and necessary services. In contrast, LCDs only contain information regarding whether an item or service is reasonable and necessary under Medicare.

²⁸² Baker L, Birnbaum H, Geppert J, et al. The relationship between technology availability and health care spending. *Health Affairs* 2003; Web Exclusive, 5 November. Accessed November 2, 2004. <http://content.healthaffairs.org/cgi/content/abstract/hlthaff.w3.537>.

made at the national level.²⁸³ Greater standardization of local coverage determination processes, however, could minimize risks for inequitable access and quality of care, while at the same time enhancing a system that fosters innovation and access.

b. Overview of the National Coverage Process

Currently, the vast majority of diagnostics are not reviewed for coverage at the national level. However, if the governance of Medicare coverage decisions for preventive and screening applications were to shift from Congress to another entity, a possibility raised in the Medicare Preventive Services Coverage Act of 2004, greater numbers of diagnostics could be considered more promptly for national coverage in the future. General aspects of the existing national coverage process and considerations specific to diagnostics are reviewed below.

Coverage issues can arise in Medicare's national coverage process in various ways. This could arise after a number of local carriers have made coverage determinations, the AMA has issued the test a CPT code or stakeholders (e.g., members of the diagnostics industry, individual clinicians) have requested a national coverage determination (NCD).²⁸⁴ Whereas local coverage policies may differ among local carriers, NCDs are binding on all Medicare contractors.²⁸⁵

Due to concerns expressed in 1998 regarding the lack of openness and transparency in national coverage decisions, the coverage process was subjected to scrutiny by Congress. As a result, CMS embarked on a new national coverage process that would be more accessible, clear and timely. In 2001, the Medicare Payment Advisory Commission (MedPAC) called for local policies to be eliminated in order to reduce "complexity, inconsistency, and uncertainty."²⁸⁶ In a 2003 memo, DHHS responded to recommendations of the GAO and others to eliminate local coverage and expand the national coverage system. This response emphasized that the lack of a local coverage presence would result in shifting sites of service and net increases in spending.²⁸⁷

The implications of the elimination of local coverage decisions for total program expenditures would be significant. There would be significant distributional effects between services within payment systems and (e.g., outpatient prospective payment system, physician fee schedule) due to unrestricted payment for certain services. There would also be increased aggregate payments for certain items and services (e.g., drugs, durable medical equipment). We specifically note that there is significant potential for aggregate payments under the physician fee schedule to increase, thereby causing negative updates in future years to adjust for additional payments. In addition, because all other payment systems (e.g., inpatient/outpatient prospective payment system) do not have a volume adjustment, total Medicare spending would also increase significantly.

To address some of the variations among local coverage decisions for diagnostics, CMS published a proposed rule on negotiated rulemaking in 2001 establishing national coverage

²⁸³ Coverage and reimbursement of genetic tests and services, 2005.

²⁸⁴ A national coverage policy for a laboratory test documents CMS policy with respect to circumstances under which the test is considered reasonable and necessary and is not used for screening under Medicare.

²⁸⁵ Wolman DM, Kalfoglou AL, LeRoy L (eds) 2000.

²⁸⁶ Medicare Payment Advisory Commission. Reducing Medicare Complexity and Regulatory Burden. Washington, DC: MedPAC, 2001.

²⁸⁷ Ibid.

policies to alleviate administrative inconsistencies in local policies for 23 widely used tests.²⁸⁸ This negotiated rulemaking process involved multiple stakeholders, including opportunities for diagnostics industry representatives to provide feedback on coding, coverage and payment refinements. Aside from this highly coordinated effort, NCDs for diagnostics have not been as transparent and open to stakeholder comment compared to local coverage decisions.

The NCDs for the 23 tests reflect coverage of approximately 60% of laboratory tests currently billed to the Medicare program. As a result, inconsistencies such as use of various ICD-9 codes (used to establish medical necessity of claims) for the same intervention were standardized, creating greater program efficiencies and clarity for stakeholders. Resulting policies describe the circumstances under which a test is covered, how often a test may be used and other coverage limitations.²⁸⁹

CMS has continued to post decisions for tests that merit national coverage consideration in subsequent years. The ability of diagnostics makers, clinical laboratories and other stakeholders to respond to coding assignments and payment issues has ensured more consistent and informed decision-making regarding new and existing diagnostics. Continuation of this process also may help reduce unnecessary spending resulting from current inconsistencies or weaknesses of the national system.

c. Coverage of Clinical Trials

While most diagnostics are submitted to the FDA as 510(k)s, certain investigational diagnostics are submitted as PMAs and often classified as Category B investigational devices. These diagnostics are eligible for (though not guaranteed) Medicare coverage of costs during clinical trials (see **Appendix B** for a more complete discussion of the criteria for Medicare's coverage of costs during clinical trials). Currently, PMAs are required most often for gene-based, molecular tests or those of like complexity or that lack a predicate test.

To the extent that PMAs are required for increasing numbers of new diagnostic tests in the future, Medicare coverage of clinical trial costs may become more significant to the diagnostics industry. Coverage of costs during clinical trials may help encourage diagnostic innovation and utilization by reducing costs to manufacturers, improving patient recruitment for trials and allowing more timely assessment of the clinical and economic value of diagnostics.

d. Health Outcomes for Diagnostics

Impacts of diagnostic tests on health outcomes often are confounded by variable effects of treatments or interventions initiated following diagnostic use. Collecting direct evidence to substantiate a link between diagnostic use and resulting health outcomes is, at least, challenging

²⁸⁸ As published in the November 23, 2001 *Federal Register*, the 23 tests included in this negotiated rulemaking were urine culture, bacterial; human immunodeficiency virus testing (prognosis including monitoring); human immunodeficiency virus testing (diagnosis); blood counts; partial thromboplastin time; prothrombin time; serum iron studies; collagen crosslinks, any method; blood glucose testing; glycated hemoglobin/glycated protein; thyroid testing; lipid testing; digoxin therapeutic drug assay; alpha-fetoprotein; carcinoembryonic antigen; human chorionic gonadotropin; tumor antigen by immunoassay CA 125; tumor antigen by immunoassay CA 15-3/CA 27.29; tumor antigen by immunoassay CA 19-9; prostate specific antigen; gamma glutamyl transferase; hepatitis panel/acute hepatitis panel; and fecal occult blood test.

²⁸⁹ Young D. Reforming laboratory reimbursement: issues, impact and innovations. A summary of the Clinical Chemistry Forum held on November 15, 2001. *Clinical Chemistry* 2002;48(5):792-5.

and is sometimes infeasible, particularly when multiple confounding effects are relevant. Direct evidence of effectiveness on health care outcomes is even less common for screening applications.²⁹⁰ Studies of diagnostic tests often focus on test specificity, sensitivity and/or utility in ruling in/out disease and less often on their impact on downstream health outcomes, which can be confounded by intervening factors.²⁹¹

e. Diagnostics for Screening

The core provision of Medicare affecting coverage of diagnostics is the limitation of payment to those items or services that are “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”^{292,293} As noted above, laboratory tests for screening purposes (i.e., performed in the absence of signs, symptoms, complaints or personal history of disease or injury) are not covered under Medicare unless Congress authorizes specific coverage for screening applications. For instance, while predictive/susceptibility tests may be used for screening, the statute generally rules out coverage of these tests under Medicare.^{294,295} Hence, most diagnostic tests are eligible for coverage under Medicare only when they are performed for symptomatic patients. In this manner, tests that identify treatment-responsive subpopulations (e.g., using pharmacogenomics) are diagnostic in nature and can be covered under Medicare.²⁹⁶

Through amendments to the Medicare statute in recent years, including via MMA 2003, Congress has become more active in providing Medicare coverage of screening and other prevention related services. Several ongoing demonstration projects within CMS also may include preventive and diagnostic tests in the context of disease management.²⁹⁷

The majority of current diagnostics are developed for detection of specific disease states to inform treatment decisions, rather than solely for screening applications. That is, diagnostics usually are not used primarily for mass or universal screening, but instead are used in targeted ways in symptomatic (or high risk) patients. Certainly, some diagnostics also are suitable for large-scale or targeted screening applications, many of which are not recognized as being medically necessary by payers.

Some emerging diagnostics may not fit neatly within Medicare’s coverage criteria, since they may provide more information than is necessary to inform patient treatment decisions and may be more suitable for screening applications. An example is pharmacogenetic testing using microarray or multiplex formats to detect genetic variations in numerous genes known to affect drug metabolism. These genetic variations result in different safety and efficacy risks among patients taking the same medication. Decisions to cover such tests may be challenging, because

²⁹⁰ Examples include certain studies of Pap smears for cervical cancer and occult blood testing for colon cancer.

²⁹¹ Recommendations for evaluating effectiveness: MCAC Executive Committee Working Group, 2004.

²⁹² 42 U.S.C. §1395y.

²⁹³ Coverage and reimbursement of genetic tests and services, 2005.

²⁹⁴ Ibid.

²⁹⁵ Medicare national coverage determinations (NCD) coding policy manual and change report. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 8, 2004. <http://www.cms.hhs.gov/coverage/manual7.pdf>.

²⁹⁶ Ibid.

²⁹⁷ Demonstration projects and evaluation reports. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 10, 2004. <http://www.cms.hhs.gov/researchers/demos/>.

they often provide broader metabolic profiles and generally are not covered for screening applications under Medicare.^{298,299} The extent to which more limited arrays, targeted to known treatment response-related biomarkers, meet existing medical necessity criteria remains controversial and may limit more rapid development and diffusion of such technologies.

4. Payment Level Determination

Payment levels affect the adoption and use of a diagnostics by providers and patient access to them.³⁰⁰ Medicare uses various payment systems to determine how much the program pays for covered services, procedures and technologies in certain health care settings. Payers increasingly focus on containing costs, placing greater cost pressures on providers. As a result, clinical laboratories, physicians, hospitals, skilled nursing facilities and other providers are more cost-sensitive, including being less willing in some instances to use diagnostics that are not adequately reimbursed.

Aside from the system for durable medical equipment, prosthetics, orthotics and supplies (DMEPOS), the provider site or type of service (hospital inpatient, hospital outpatient, skilled nursing facility, etc.) determines which payment system is used. Two predominant Medicare payment systems are retrospective fee schedules and prospective payment systems (PPS).

a. Fee Schedules

Through fee schedules, Medicare provides a fixed payment for a given procedure or item. The vast majority of diagnostics fall under the CLFS. Via a code describing a specific service, fee schedules link each service to a predetermined payment amount. Medical devices and diagnostics paid under fee schedules fall into three main categories: a) those provided by physicians and other licensed practitioners;³⁰¹ b) clinical laboratory tests; and c) DMEPOS.

- **Physician/other licensed health care practitioner services.** For diagnostic tests, the MPFS applies to clinical laboratory services that require professional interpretation, such as pathology tests and certain emerging gene-based, molecular or similarly complex tests. The three main resource categories for physician services are physician work, practice expense (all costs other than physician time required for the physician to provide the service) and malpractice expense.³⁰²

²⁹⁸ Coverage and reimbursement of genetic tests and services, 2005.

²⁹⁹ Virtually all current coverage for such gene-based tests currently occurs at the local level. The exception is a national coverage determination on cytogenetic testing, which is covered when such testing is reasonable and necessary for the diagnosis or treatment of genetic disorders in a fetus, failure of sexual development, chronic myelogenous leukemia, acute leukemias or myelodysplasia. NCD for cytogenetic studies (190.3). Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 1, 2004.
http://www.cms.hhs.gov/mcd/viewncl.asp?ncd_id=190.3&ncd_version=1&basket=ncd%3A190%2E3%3A1%3ACytogenetic+Studies.

³⁰⁰ Raab GG, Logue LJ. Medicare coverage of new clinical diagnostic laboratory tests: the need for coding and payment reforms. Clin Leaders Manag Rev 2001;15(6):376-87.

³⁰¹ Certain non-physician providers are eligible for Medicare payment under the MPFS. These providers include advanced practice nurses, clinical psychologists and occupational and physical therapists, among others.

³⁰² CMS sets payment rates for physician services according to the MPFS, which is based on the Resource-Based Relative Value Scale (RBRVS). Physician payments in the fee schedule are calculated by ranking medical services (as defined by CPT and other HCPCS codes) according to the relative costs of resources required to provide them.

- **Clinical laboratory services.** Most diagnostics are reimbursed according to the CLFS, as represented by CPT or other HCPCS codes. Under the CLFS, laboratories bill Medicare directly for tests performed. Thus, although physicians order tests, they do not receive payment unless they or their staff perform a test in their office. Technologies covered under the CLFS include diagnostic test kits and reagents, devices that analyze test results and other laboratory equipment essential to testing.
- **Durable medical equipment, prosthetics, orthotics and supplies (DMEPOS).** Medicare pays for non-implantable DMEPOS through the DMEPOS fee schedule, although some types of durable medical equipment are paid on a reasonable cost basis (e.g., dialysis supplies and equipment). This fee schedule typically does not pertain to diagnostic testing.

b. Prospective Payment System

In both the inpatient and outpatient settings, Medicare has moved toward PPS for facility payment. These systems provide a single, fixed payment per episode of care (e.g., admission, day or visit). Unlike fee schedules, each service is not assigned a specific payment amount. Rather, services are assigned to payment groups, and all services within a single group receive the same level of payment. Diagnosis-related groups (DRGs) are used in the hospital inpatient setting. Ambulatory payment classifications (APCs) are used in the hospital outpatient setting.

When diagnostics are used during inpatient stays by Medicare patients, their payment is not allocated separately as in a fee-for-service arrangement. Instead, payment for inpatient diagnostic tests is assumed to be included in the payment level for that patient's hospital stay (discharge) and is intended to account for the items, services and other resources required for that type of stay.

Clinical laboratory tests on the fee schedule are excluded from the outpatient PPS. In these circumstances, when a hospital outpatient department or other provider sends tests to a reference laboratory, prior contractual arrangements typically enable the testing facility to bill these providers for testing services.

5. Medicare Payment for Diagnostics

The Medicare payment system for diagnostic tests has changed considerably since the early 1980s. Previously, tests were paid for on a "reasonable charge" basis, physicians billed Medicare directly for diagnostic tests and beneficiaries were obligated to pay a co-payment for laboratory services. After implementation of the Deficit Reduction Act of 1984, diagnostic tests were paid based on a capped fee schedule (i.e., the CLFS). Laboratories billed Medicare for diagnostic tests, and beneficiaries were relieved of co-payments for laboratory tests. This last provision was made because charging these co-payments became less practical when laboratories, rather than physicians, assumed the responsibility for billing Medicare.³⁰³

Medicare pays for outpatient laboratory tests according to fee schedules for each of 56 geographic jurisdictions, as limited by the NLA. The payment for covered laboratory tests is the lowest of the actual charge for the service, the Medicare carrier fee schedule amount or the

³⁰³ Medicare reimbursement for clinical laboratory services. Washington, DC: American Clinical Laboratory Association, 2004. Accessed December 10, 2004. <http://www.clinical-labs.org/issues/reimbursement/index.shtml>.

NLA.³⁰⁴ By November 1 of each year, Medicare updates payment as appropriate and incorporates new codes into the fee schedule, assigns a payment rate to the new codes and distributes the fee schedule to carriers and intermediaries with an effective date of January 1.

6. Updating Medicare Payment for Diagnostics

While most diagnostic tests are reimbursed under the CLFS, CMS and the IOM have observed that there is currently “no practical method for adjusting payments to existing tests.” Existing methods of incorporating new technologies into the CLFS have been characterized by stakeholders as archaic, flawed and ineffective. The IOM has cited the following reasons:

- The current fee schedule is based on laboratory charges used in 1983.
- Many new tests, methods and equipment developed since 1983 are not in the Medicare base year charge data.
- The rate of development of new testing technologies is growing.
- Methods for cross-walking and gap-filling of tests are non-transparent and duplicative.
- Methodologies for calculating payment levels are likely to result in unreasonably low payments for diagnostics.^{305,306}

Five years after the IOM report identified these deficiencies, there still is no reasonable mechanism for updating payment for clinical laboratory services. While processes for updating the physician and ambulatory surgical center fee schedules also have come under intense scrutiny in the past few years, initiatives are underway to correct or refine processes for these schedules.^{307,308}

The process of assigning relative value to CPT pathology codes under the MPFS, including for certain emerging gene-based, molecular and other diagnostics, is a model that could be applied to other clinical laboratory coding changes. This process occurs each year through the joint actions of the AMA CPT Editorial Panel, which makes recommendations for new and revised CPT coding, and the AMA Specialty Society Relative Value Update Committee (RUC), which makes relative value recommendations used in pricing these new or revised codes.³⁰⁹

Consisting mostly of members appointed by medical specialty societies, the role of the RUC is to engage stakeholders from specialty societies in the process of recommending values for new or revised CPT codes. Prior to recommending these values, the RUC considers data to determine the level of physician effort required to perform medical services. Estimates of the time and effort required to perform the service and level of technical skill necessary by a

³⁰⁴ Raab GG 2001.

³⁰⁵ Gustafson, TA. Medicare payment for clinical laboratory services. Health Care Financing Administration. Accessed March 10, 2005: <http://www.himanet.com/publicdocs/labtalk2.ppt>. The Health Care Financing Administration was officially renamed the Centers for Medicare & Medicaid Services on July 14, 2001.

³⁰⁶ Medicare laboratory payment policy: now and in the future 2000.

³⁰⁷ Medicare Physician Fee Schedule: CMS needs a plan for updating practice expense component. Washington, DC: United States Government Accountability Office. December, 2004. (Publication no. GAO-05-60).

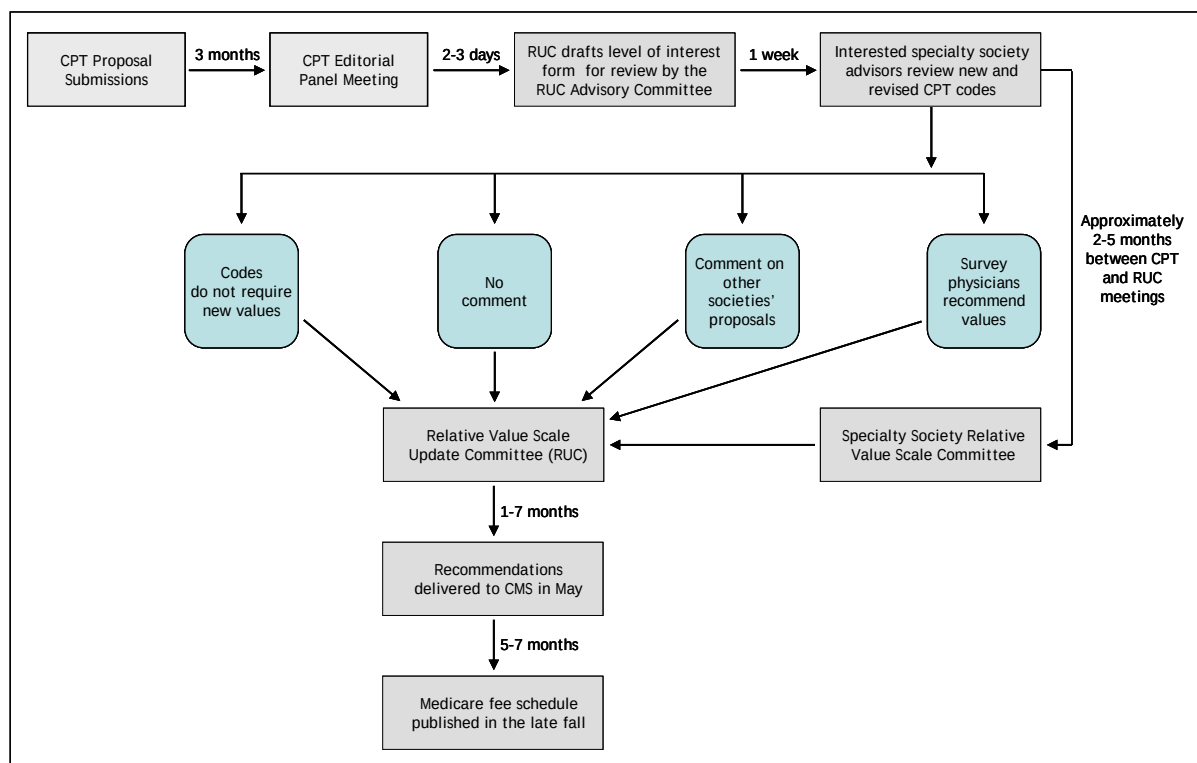
³⁰⁸ Assessing payment adequacy and updating payments for ambulatory surgical center services. Washington, DC: Medicare Payment Advisory Commission. March, 2003.

³⁰⁹ AMA/Specialty Society RVS Update Process. Chicago, IL: American Medical Association, 2003. Accessed December 16, 2004. http://www.ama-assn.org/ama1/pub/upload/mm/380/update_booklet_03.pdf.

physician are all taken into consideration and converted into relative value units (RVUs). These RVUs then are applied in Medicare or other third-party payer formulas to derive payment levels for physician services involved in a particular health intervention.

Clinical laboratory codes listed under the CLFS currently are not brought before the RUC, although certain diagnostic codes listed under the physician fee schedule are subject to RUC review. When establishing payment levels for clinical laboratory tests, increased representation and participation from the diagnostic and clinical laboratory industries through some form of payment advisory body would enhance informed and equitable decision-making reflecting the value and utility of diagnostics. More than 90% of RUC recommendations are adopted by CMS each year and incorporated into the Medicare physician payment schedule.³¹⁰ The RUC process timeline, as applied to physician payment, is depicted in **Figure 5.3**.

Figure 5.3
Timeline for the Relative Value Update Committee (RUC) Process



Adapted from: AMA/Specialty Society RVS Update Process. Chicago, IL: American Medical Association, 2003. CPT®/RUC calendar. CPT Editorial Panel process, AMA/Specialty Society RVS Update process tentative schedule. Chicago, IL: American Medical Association, 2004.

a. Other Trends that Affect Medicare Payment for Diagnostics

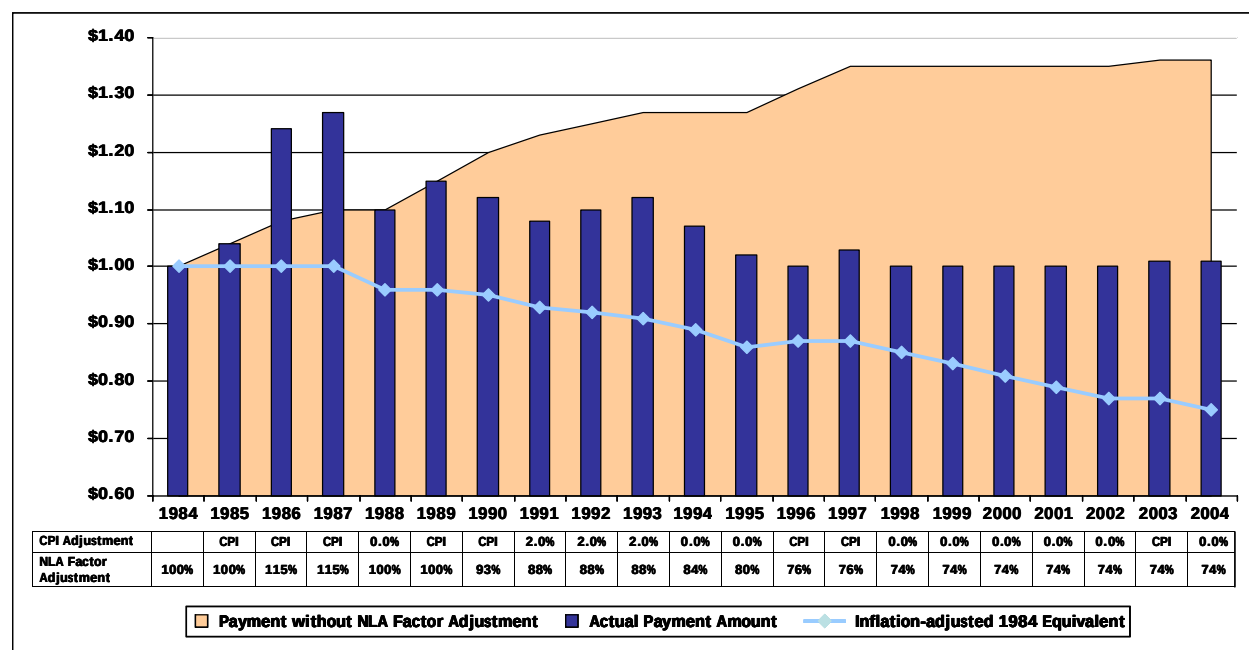
In addition to lack of practical methodologies for updating the CLFS, failure to update diagnostics to account for inflation and pay for tests at the NLA results in underpayment for many diagnostics and hurdles to innovation and adoption of tests. In the time since enactment

³¹⁰ Pathology tests included under the physician fee schedule are subject to RUC review and the Pathology Coding Caucus operates as a successful example of industry input into these tests, which represent a fraction of the number of tests listed on the CLFS.

of the Deficit Reduction Act of 1984, payment for diagnostic tests has not kept pace with inflation and has, instead, decreased over time.

While NLAs for laboratory tests were 115% of carrier median fee schedule amounts some 20 years ago, NLAs today are set at just 74% of carrier median fee schedule amounts. Further, although the CPI was intended to guide increases in payments for laboratory services to account for inflation, scheduled updates either have not occurred or have been reduced in 11 of the past 15 years (**Figure 5.4**). Consequently, adjusted for inflation, laboratory testing is paid at lower levels today than when the NLA amounts were first established.³¹¹

Figure 5.4
Impact of Clinical Laboratory Fee Schedule Updates and Reductions (1984-2003)



Base fee: \$1.00

Note: Rates reflect annual CPI US City Average (as stipulated in the Social Security Act Section 1833(h)(2)(A)(i) from previous year, but may not reflect actual rate used by HCFA/CMS, except for 2003 rate, which was the exact figure used by CMS.

Sources:

1. Consumer price indices. Washington, DC: Bureau of Labor Statistics, 2004.
2. Laboratory services. Baltimore, MD: Centers for Medicare and Medicaid Services, 2004.

Discrepancies among state fee schedules add to the challenges of setting appropriate payment levels for diagnostics. While some diagnostics are overpaid in some states, decisions resulting in underpayment are more likely and compounded by national decisions to withhold CLFS updates for inflation. For example, HCV genotyping (CPT code 87902) has an NLA set at \$359.69 for 2004; however, actual payment amounts vary widely, with some set far below the NLA in 14 of the 56 state fee schedules (**Figure 5.5**). Such payment variations are arbitrary, and payment disparities for new tests that are integrated into the existing system often are compounded by other pre-existing variations in payment levels.

³¹¹ Medicare reimbursement for clinical laboratory services, 2004.

Figure 5.5
Low-end Variation in Fee Schedules for
HCV Genotyping: Selected States

Carrier Area	Fee Schedule Amount	% Difference from NLA
AL	\$146.49	-59
GA	\$121.85	-66
MS	\$329.57	-8
TX	\$256.05	-29
MD	\$228.34	-37
VA	\$321.68	-11
UT	\$308.80	-14
ID	\$194.37	-46
TN	\$251.27	-30
NC	\$109.05	-70
ME	\$114.95	-68
MA	\$114.95	-68
NH	\$114.95	-68
VT	\$114.95	-68

Source: 2004 Clinical diagnostic laboratory fee schedule.
 Baltimore, MD: Centers for Medicare & Medicaid Services, 2003.

Further, in the Balanced Budget Act of 1997, CMS was given authority to adjust payment levels that it considered to be “inherently unreasonable” under the Medicare fee schedules. Although rarely applied to date, this authority allows CMS to reduce or increase payments for services (including laboratory services) by as much as 15% annually without using public notice and comment procedures. There also is no restriction on the number of times that a particular payment rate can be adjusted over the course of several years. Although additional clarification by CMS of the circumstances of use regarding this authority are still pending, a 2000 GAO report entitled *Medicare Payments: Use of Revised Inherent Reasonableness Generally Appropriate*, outlined the following potential risk of proposed payment reductions to Medicare beneficiary access to medical equipment and supplies (including diagnostics):

The effect of the proposed payment reductions [via exercise of inherent reasonableness authority] on beneficiary access depends on whether Medicare payment amounts fall below the point at which sufficient numbers of suppliers are willing to provide the items. If the payment amount drops so far that it no longer covers suppliers’ legitimate costs – including the cost of doing business with Medicare – then suppliers may be unwilling to provide the item for the Medicare payment amount and beneficiaries may experience access problems.³¹²

While the effects of exercising inherent reasonableness authority for “grossly excessive” or “grossly deficient” payment amounts on patient access is uncertain, this GAO study recommended that CMS establish procedures for monitoring impacts on patient access. In

³¹² Medicare payments: use of revised inherent reasonableness generally appropriate. US General Accounting Office 2000. Washington, DC: GAO/HEHS-00-79. <http://www.gao.gov/archive/2000/he00079.pdf>

instances where inherent reasonableness reductions were applied repetitively to a particular diagnostic test or test type, it is conceivable that adverse effects on access could occur.

b. Challenges to Assigning Payment Levels to Individual Tests

CMS uses two basic methods to incorporate new CPT codes for laboratory technologies into the CLFS and establish payment levels for them.³¹³ “Cross-walking” is intended for new tests that are deemed clinically similar to existing tests. “Gap-filling” is intended for novel (including breakthrough) technologies.

- **Cross-walking** is used when CMS determines that a new test is clinically similar to one or more tests with existing codes.³¹⁴ When a new test is cross-walked to an existing code, it is assigned payment based on the associated existing local fee schedule amounts and corresponding NLA. The Medicare payment is the lowest of the actual charge for the test, the carrier-set rate for the test or the NLA.³¹⁵ CMS is guided in cross-walk determinations by holding open meetings for public comment on the coding and payment determinations it should make on new codes assigned by the CPT Editorial Panel. Despite this guidance, cross-walking determinations can be subjective, as CMS can map new tests to coding that may appear to be similar, but whose features or applications may vary.
- **Gap-filling** is used to assign codes to tests that are not clinically similar to existing tests. In this instance, CMS instructs local carriers to establish a payment rate for a new test within the first quarter of the year. CMS then uses these local payment rates to assign an NLA for the new test code to guide payment after the first year. The NLA is a national cap amount. NLAs were initiated to remedy unusually high payments in certain carrier areas; however, it does not address situations in which local carriers may have set payments too low.³¹⁶

Gap-filling, which is not a standardized process, is rarely used as a payment technique. While manufacturers know that the likelihood of a test being cross-walked to an inappropriate code with a low payment level is significant, the poorly delineated pathway for gap-filling may pose even more uncertainty for marketed tests.

Novel diagnostics may present challenges to CMS in determining whether to apply cross-walking or gap-filling, and which existing tests to use as a basis for cross-walking when that approach is used. This may complicate obtaining appropriate payment for novel diagnostics. **Figure 5.6** portrays alternate routes for determining payment for a new diagnostic.

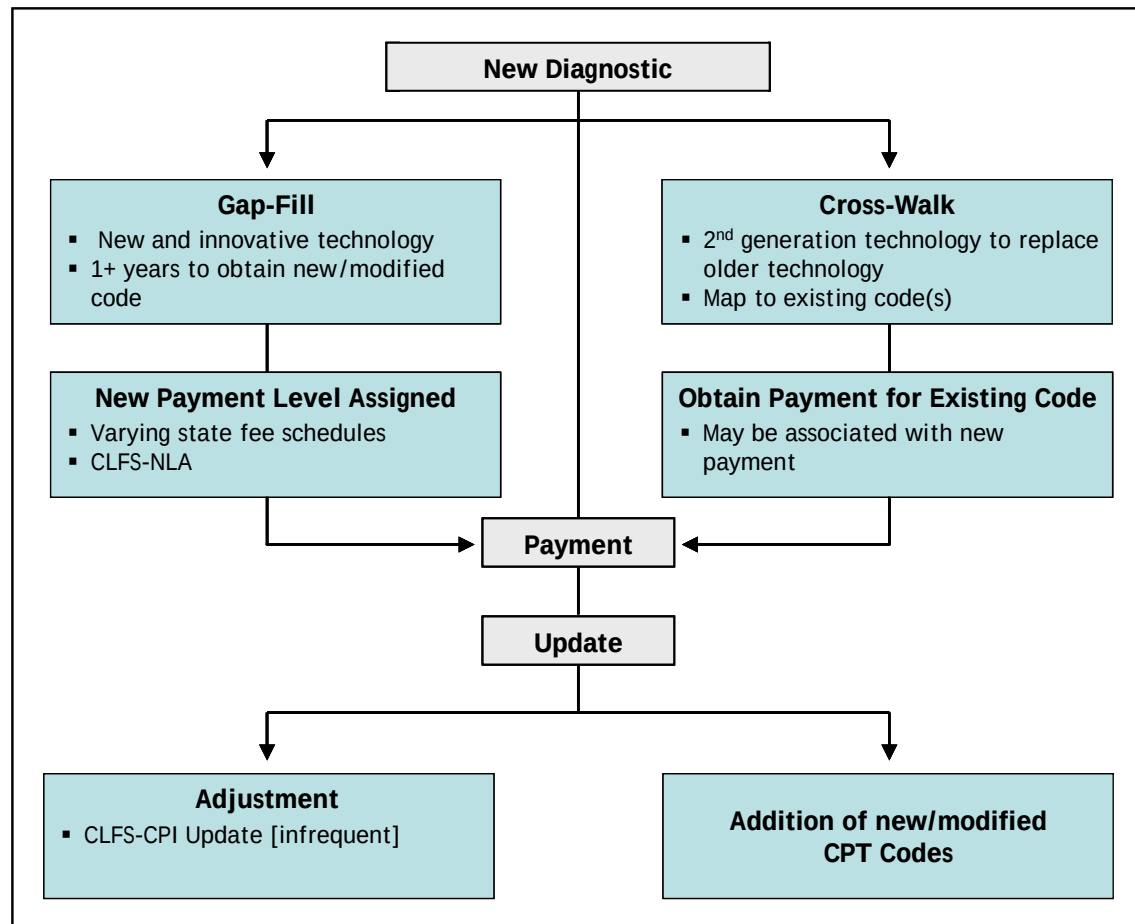
³¹³ Raab GG 2001.

³¹⁴ Coding and payment for clinical laboratory tests. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 5, 2004. <http://www.cms.hhs.gov/medicare/hcpcs/codpayproc.asp#clab>.

³¹⁵ Raab GG 2001.

³¹⁶ Ibid.

Figure 5.6
Gap-fill and Cross-walk Payment Pathways



Adapted from: The Lewin Group, Inc. Outlook for medical technology innovation: Will patients get the care they need? Report 2: The Medicare payment process and patient access to technology. Washington, DC: AdvaMed, 2000.

An analysis conducted on CMS coding determinations for 57 new CPT codes for 2001 revealed inconsistencies in the mapping process. Only one of the 57 codes was cross-walked. Of the 56 cross-walked codes, only 34 (61%) appear to have been mapped to clinically similar codes and 22 (39%) were not.³¹⁷ **Figure 5.7** identifies 9 of the 34 codes for which some carriers were paying less than half of the NLA.

³¹⁷ Raab GG 2001.

Figure 5.7
Cross-walks to Clinically Similar Codes with Carrier Payment Rates (2001)

New Code	Description	Existing Code	NLA	% Carrier Areas Paying Below NLA	% Carrier Areas Paying <50% NLA
83090	Homocysteine	82131	\$23.31	41	16
85536	Iron stain, peripheral blood	85535	8.95	11	2
86146	Beta 2 glycoprotein I antibody, each	86147	35.16	48	13
86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)	86316	28.76	13	2
86301	Immunoassay for tumor antigen, quantitative; CA 19-9	86316	28.76	13	2
86304	Immunoassay for tumor antigen, quantitative; CA 125	86316	28.76	13	2
87107	Culture, fungi, definitive identification, each organism; mold	87106	14.27	14	4
87185	Susceptibility studies, antimicrobial agent; enzyme detection (e.g., beta lactamase), per enzyme	87181	6.56	34	23
87901	Infectious agent genotype analysis by nucleic acid (DNA or RNA), HIV 1, reverse transcriptase and protease	Multiple codes	355.78	25	13

Adapted from: Raab 2001.

Of the 56 cross-walked codes, 10 (17.8%) received lower payment rates than the rates for the tests to which they were mapped. **Figure 5.8** illustrates the payment discrepancies for each of these 10 test codes. In addition, the clinical or technological appropriateness of the cross-walks made by CMS may have been questionable for four of the tests listed in this table (i.e., codes 80157, 83663, 83664 and 87254).³¹⁸

³¹⁸ Raab GG 2001.

Figure 5.8
Cross-walks Assigned Payment Levels Lower than Mapped Codes (2001)

New Code	Description	Existing Code	Description	NLA	Medicare Payment
80157	Carbamazepine; free	80185	Phenytoin; total	\$18.32	\$13.74
83663	Fetal lung maturity assessment; fluorescence polarization	83662	Fetal lung maturity assessment; foam stability test	26.14	13.07
83664	Fetal lung maturity assessment; fluorescence polarization	83662	Fetal lung maturity assessment; foam stability test	26.14	6.53
87046	Culture, bacterial; stool, additional pathogens, isolation and preliminary examination (e.g., <i>Campylobacter</i> , <i>Yersinia</i> , <i>Vibro</i> , <i>E.coli</i> 0157), each plate	87045	Culture, bacterial; stool, with isolation and preliminary examination (e.g., KIA, LIA), <i>Salmonella</i> and <i>Shigella</i> species	13.04	3.26
87071	Culture, bacterial; quantitative, aerobic with isolation and presumptive identification of isolates, any source except urine, blood, or stool	87045	Culture, bacterial; stool, with isolation and preliminary examination (e.g., KIA, LIA), <i>Salmonella</i> and <i>Shigella</i> species	13.04	6.52
87073	Culture, bacterial; quantitative, anaerobic with isolation and presumptive identification of isolates, any source except urine, blood, or stool	87045	Culture, bacterial; stool, with isolation and preliminary examination (e.g., KIA, LIA), <i>Salmonella</i> and <i>Shigella</i> species	13.04	6.52
87254	Virus isolation; shell vial, includes identification with immunofluorescence stain, each virus	87250	Virus isolation; inoculation of embryonated eggs, or small animals, includes observation and dissection	27.02	6.76
87300	Infectious agent antigen detection by immunofluorescent technique, polyvalent for multiple organism, each polyvalent antiserum	87301	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; adenovirus enteric types 40/41	16.58	8.29
87400	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; Influenza A or B, each	87301	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; adenovirus enteric types 40/41	16.58	8.29
88400	Bilirubin, total, transcutaneous	82247	Bilirubin; total	6.94	3.47

Adapted from: Raab 2001.

Another 12 (21%) codes appear to have been cross-walked to tests that are not similar. In these cases, there was no opportunity for the public to comment on the codes prior to their implementation, and CMS did not explain the reasoning behind the cross-walk determinations.³¹⁹ **Figure 5.9** presents seven of the 12 codes for which some carriers were paying less than half of the NLA.

³¹⁹ Raab GG 2001.

Figure 5.9
Cross-walks to Clinically Dissimilar Codes with Carrier Payment Rates (2001)

New Code	Description	Existing Code	Description	\$ NLA	% of Carrier Areas Paying Below NLA	% of Carrier Areas Paying <50% NLA
86611	Antibody; Bartonella	86602	Antibody; actinomyces	14.06	34	2
86666	Antibody; Ehrlichia	86602	Antibody; actinomyces	14.06	34	2
86696	Antibody; herpes simplex, type 2	86689	Antibody, HLTV or HIV antibody, confirmatory test (e.g., Western blot)	26.75	4	4
86757	Antibody; Rickettsia	86689	Antibody, HLTV or HIV antibody, confirmatory test (e.g., Western blot)	26.75	4	4
87152	Culture, typing; identification by pulse field gel typing	87158	Culture, typing; other method	7.23	4	4
87451	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative; multiple step method, polyvalent for multiple organisms, each polyvalent antiserum	87450	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative; single step method, not otherwise specified, each organism	13.25	23	5
89321	Semen analysis, presence and/or motility of sperm	89320	Semen analysis; complete (volume count, motility, and differential)	16.66	13	2

Adapted from: Raab 2001.

While the open process for public review and comment on proposed codes and payment levels has improved decision-making to a certain extent, this analysis points to important implications for assignment of payment levels to diagnostic tests. These implications are as follows.

- **Lack of an appropriately standardized and open process for paying for new diagnostics results in inefficient and flawed coding assignments.**

While Medicare makes organized changes to other fee schedules, there is no cohesive and practical method of updating the clinical laboratory fee schedule. Despite feedback from stakeholders during the public comment period, significant gaps in mapping and payment outcomes persist. A more open mechanism for mapping and payment determinations may be warranted, perhaps similar to the negotiated rulemaking process increasingly used for national coverage determinations.

- **Low payment levels, resulting from inappropriate mapping and pricing decisions, increase the financial risks to diagnostics manufacturers.**

Heightened development risks may reduce willingness to invest in development of these technologies, discouraging innovation and reducing patient access to new diagnostics.

c. Considerations for Modernizing the Clinical Laboratory Fee Schedule

The current system for updating the CLFS presents a critical issue for the role of diagnostics in health care. The system remains lengthy, confusing and often inconsistent. Unlike other Medicare payment systems, the CLFS does not have an established annual updating process to enable correcting errors and refining coding and payment. These well-established weaknesses have prompted various calls for alternative approaches. These include recommendations of the 2000 report by the IOM, *Medicare Laboratory Payment Policy: Now and in the Future*.³²⁰

Among the potential alternatives proposed by IOM and others are a charge-based relative value fee schedule, micro-costing studies to inform a new fee schedule, updating the laboratory fee schedule using negotiated rulemaking and creating a single national fee schedule for payment of clinical laboratory services. Of these, the negotiated rulemaking approach has proven to be a particularly successful model for updating the physician and ambulance fee schedules for Medicare. Each alternative offers certain advantages and disadvantages and may have different implications for the diagnostics industry, as discussed below.

CMS has considered and sponsored studies of a **charge-based relative value fee schedule** for laboratory procedures. Although considered an incomplete effort, a 2002 report commissioned by CMS evaluated a charge-based relative value fee schedule for laboratory procedures and calculated an initial set of relative values.³²¹ This type of fee schedule would use submitted charge data as a proxy for relative costs of laboratory services to establish a scale of relative values for laboratory tests. Compared with the current fee schedule, this analysis found that payments for many tests would change under a charge-based relative value fee schedule and that payments for some tests would increase or decrease substantially. Proponents of this strategy note that charge data is easily accessible and contend that the correlation between charge data and costs is valid. Certainly, using charge data as the basis for a new fee schedule would help update the current fee schedule, which was developed based on 1984 prices.

Although it is possible that a relative value updating process for diagnostics would enhance the ability to set payment levels, this strategy may not include adequate measures to control overcharging. For instance, if charges are used to establish payment amounts for diagnostic tests, this may encourage laboratories to inflate associated charge levels. This sort of inflation could undermine the basis of using charges to approximate costs. If implemented, this type of fee schedule may require substantial adjustment on the part of the diagnostics industry to accommodate altered payment rates, and the integrity of the system may suffer if overcharging becomes common. The preliminary 2002 CMS analysis reports that it may be difficult to calculate appropriate payment for automated test panels under this type of fee schedule, as such panels currently are reimbursed in bundled payments.³²²

³²⁰ Wolman DM, Kalfoglou AL, LeRoy L (eds) 2000.

³²¹ Calculation of Charge-Based Relative Values for Laboratory Procedures. Final Report CMS Contract No. 500-95-0061/T.O. #2. Baltimore, MD: Centers for Medicare & Medicaid Services, 2002 (prepared by the University of Wisconsin-Madison Center for Health Systems Research and Analysis, RTI Division of Health Economics Research and Northwestern University). Accessed December 15, 2004. <http://www.cms.hhs.gov/healthplans/research/2002LabAnalysRpt.pdf>.

³²² Ibid.

Fee schedules based on micro-costing studies would use actual cost data for laboratory services to establish relative payment values. While it would be more realistic to use actual cost data rather than charges to determine payments for laboratory services, laboratory cost information is not as readily available as charge information. This strategy would require resource-intensive studies of costs (direct and indirect) associated with laboratory services. This may be particularly challenging, given that there currently is no standard means of assessing laboratory costs and may result in significant variability across laboratories, hindering the goal of compiling standard cost data toward a more accurate fee schedule. In limited historical use of this method, response from laboratories to inquiries regarding costs was poor. Until these challenges are addressed, micro-costing approaches may not be the ideal basis of a new fee schedule. However, this strategy does hold potential for helping to set accurate payment levels in a new fee schedule, for periodic revision of payment levels and possibly for periodic “spot checks” on payment levels to confirm their appropriateness.³²³

Negotiated rulemaking may have an increasing role in reshaping the fee schedule for laboratory services. Involving multiple stakeholders in discussions to reach consensus on coding and payment issues has shown promise when applied to the Medicare ambulance and physician fee schedules and may be the least resource-intensive of these strategies. Collaborative sessions regarding these fee schedules have resulted in new codes and payment levels acceptable across stakeholders, are sensitive to geographic cost differences in the provision of laboratory services and allow correction of both over- and under-payment.³²⁴ Currently, the fee schedule for laboratory tests often fails to account for important cost differences across regions (e.g., an urban versus a rural area). An expanded role for negotiated rulemaking may provide a forum for stakeholders to express concerns regarding differential impacts of coding and other important issues, providing more interactive perspective for payment determinations.

In its 2000 report, the IOM also recommended creating a “**single, rational, national fee schedule**” for outpatient clinical laboratory services. This approach could improve payment efficiencies, reduce unnecessary resource expenditures by multiple stakeholders and improve patient access to beneficial technologies. This national system could take into account regional cost variations by employing a weighted payment schedule, which would offer the benefits of a relative value approach or micro-costing alternatives, but with reduced bureaucratic, financial and operational constraints.

A blend of these approaches may be the least resource-intensive and incorporate benefits of various proposed alternatives. This could entail the following elements.

- **Transition of the CLFS to a single national payment schedule**, instead of the 56 geographically maintained payment schedules. This would help to minimize variation

³²³ Calculation of Charge-Based Relative Values for Laboratory Procedures. Final Report CMS Contract No. 500-95-0061/T.O. #2. Baltimore, MD: Centers for Medicare & Medicaid Services, 2002 (prepared by the University of Wisconsin-Madison Center for Health Systems Research and Analysis, RTI Division of Health Economics Research and Northwestern University). Accessed December 15, 2004. <http://www.cms.hhs.gov/healthplans/research/2002LabAnalysRpt.pdf>.

³²⁴ The Negotiated Rulemaking Committee on the Medicare Ambulance Fee Schedule. Committee statement. Baltimore, MD: Centers for Medicare & Medicaid Services, 2000. Accessed December 15, 2004. <http://www.cms.hhs.gov/suppliers/afs/comstate.asp>.

and redundancy of payment determinations. Maintaining coverage as a local process would ensure the ability of Medicare to respond to regional needs and ensure opportunities for access to new diagnostics, with a national set of standardized core criteria applicable to local coverage decisions. This would include establishing a more coordinated procedure for raising priority coverage decisions to CMS for NCD rulings. Toward a single national payment schedule, CMS would:

- Establish a workable mechanism to identify and correct current gross under- and over-payment of diagnostics. This mechanism should be transparent and more effectively applied than the existing “inherent reasonableness” authority, which has been used only infrequently.
 - Publish and implement a methodology for gap-filling existing tests. Over a period of years, payment would shift from existing laboratory codes to a new schedule with a value base that better distinguishes the clinical, economic and/or other advantages of new versus existing technologies.
 - Develop a value-based payment schedule for incorporating new tests into the relevant fee schedules that overcomes current limitations of the existing cross-walk and gap-fill processes.
- **Use focused, “micro-costing” studies to periodically spot-check national payment level determinations.** Targeting of particularly high volume, costly or controversial tests for this analysis would help to determine the appropriateness of payment for certain tests and make adjustments accordingly.
 - **Create a clinical laboratory test payment advisory committee to be responsible for review of fee schedule submissions and development of recommendations to CMS regarding payment level updates/changes and other payment system refinements.** This body would include diagnostics, clinical laboratory and other relevant health services industry representatives. This would build upon successful collaborative initiatives, such as recent negotiated rulemaking for clinical laboratory tests and the activities of the Pathology Coding Caucus.
 - **Continue negotiated rulemaking processes for establishing payment for high-priority or controversial tests.** While negotiated rulemaking for every test integrated into the CLFS would be impractical, negotiated rulemaking for a limited set of eligible tests has resulted in informed and balanced decisions for such high-priority tests to date.

C. Medicaid

1. Overview

More than 50 million Americans rely on Medicaid for their health insurance. Administered jointly by the federal and state governments, Medicaid provides coverage for individuals earning less than a specified income level and for those with certain disabilities. Further, Medicaid is a substantial payer for nursing home care. While the federal government is responsible for setting the minimum level of benefits to be covered under Medicaid, states have

the ability to expand the scope of covered services and eligibility for the program.³²⁵ Because Medicaid is a state administered program, clarification of coding, coverage and payment decisions can be difficult and resource intensive.

2. Coding

The national coding systems used by Medicare often are adopted by other payers, including state Medicaid programs. In cases where existing HCPCS codes do not reflect the services or items provided under Medicaid adequately, there is a HCPCS code modification process that state Medicaid programs may pursue to meet their coding needs.³²⁶ This modification process results in the creation of “T” codes, following a state Medicaid agency’s request for new codes from the CMS Center for Medicaid and State Operations (CMSO). While assigned for Medicaid coding purposes, private payers also may use T codes in some instances.

3. Coverage

The federal government sets the minimum scope of coverage for state Medicaid programs and includes coverage for services incurred during inpatient and outpatient hospital care, provider visits and nursing home stays or home health care visits. Among the basic services federally mandated for state Medicaid programs are laboratory and radiological services; early and periodic screening, diagnosis and treatment for children younger than 21; family planning services and pregnancy care; and health care centers such as rural health clinics.³²⁷

Many state Medicaid programs have been under extraordinary budget constraints in recent years, prompting them to experiment with various approaches of cost containment. Contractual arrangement with private managed care companies is one such method that has grown in popularity; nearly 60% of Medicaid recipients were enrolled in some form of a managed care program in 2003.³²⁸

4. Payment

While separate from Medicare, Medicaid is bound by the Medicare fee schedule for payment of clinical diagnostic laboratory tests. As such, Medicaid payment for such services may not be higher than the NLA set by Medicare. In fact, some Medicaid programs pay for services at a given percentage less than Medicare payment rates. For instance, California’s Medicaid program (Medi-Cal) pays physicians rates that are approximately two-thirds of Medicare payment rates.³²⁹ In cases where a Medicare fee is not available for a test being provided under a Medicaid plan, the payment is not bound by these limitations. Clearly, however, Medicare

³²⁵ The Medicaid program at a glance. Menlo Park, CA: The Henry J. Kaiser Family Foundation, 2004. Accessed November 8, 2004. <http://www.kff.org/medicaid/2004-04.cfm>.

³²⁶ HCPCS code modification process: Medicaid. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 5, 2004. <http://www.cms.hhs.gov/states/hcpcs.asp>.

³²⁷ Medicaid services. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 10, 2004. <http://www.cms.hhs.gov/medicaid/mservice.asp?>.

³²⁸ Managed care trends. Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed December 10, 2004. <http://www.cms.hhs.gov/medicaid/managedcare/trends03.pdf>.

³²⁹ Medi-Cal facts and figures: a look at California’s Medicaid program. Oakland, CA: California HealthCare Foundation, 2004. Accessed February 25, 2005. <http://www.chcf.org/documents/policy/MediCalFactsAndFigures.pdf>.

payment rates often serve as an important benchmark affecting Medicaid payment levels.³³⁰ This extends the effects of inadequacies of the processes used by Medicare to set payment rates for diagnostics to additional providers and millions of Medicaid beneficiaries.

D. Private Payers

1. Overview

Private payers make available a multitude of evolving health plan configurations ranging from the most managed types of closed staff model HMOs to traditional indemnity insurance plans that operate on an unrestricted fee-for-service basis. Managed care plans gained popularity during the 1970s and 1980s and were seen as a solution to the escalating health care costs during this time period. Managed care plans accounted for 95% of the health insurance market in 2003.³³¹ The defining attribute of managed care plans is their integration of the management of financing and delivery of health care for their members. Several different models of managed care plans have been developed over the years with varying degrees of utilization controls and payment structures, including HMO, point of service (POS) plans, preferred provider organizations (PPOs) and consumer-driven health plans. In practice, health plans often embody mixed models of managed care that may not be discernable to their beneficiaries.

Managed care plans insure approximately 200 million Americans, including 15 million enrolled in Medicaid managed care programs and 7 million in Medicare managed care programs. There are more than 700 HMO plans and 1,000 PPO plans. Among the largest chains or networks are Aetna, US Healthcare, Blue Cross Blue Shield, CIGNA Healthcare, Kaiser Foundation Health Plan, United Healthcare and WellPoint Health Networks.

Indemnity insurance plans differ from managed care options, because they use a fee-for-service payment structure and generally allow their beneficiaries unrestricted access to providers. Indemnity plans dominated the early years of the private health insurance market. In recent years, they have adopted management features used by managed care plans in an effort to contain costs. Indemnity plans generally cover preventive services less often than managed care plans. Because there are fewer constraints on health care utilization with indemnity plans, premiums tend to be higher than with managed care. These plans have become less prevalent as cost pressures have increased and managed care options have broadened.

In the US, access to private health insurance usually is tied to employment, making employers the largest group of direct purchasers for this commodity. For individuals not covered through employment-based health insurance or under public programs such as Medicaid and Medicare, the option to purchase health insurance directly from a private company also is available. Employers and individuals have a diverse range of health plan products from which to choose. Although they account for a relatively small portion of the market, consumer-driven health plans have been gaining attention in recent years.

³³⁰ Payment for outpatient clinical diagnostic laboratory tests. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 5, 2004. http://www.cms.hhs.gov/manuals/45_smm/sm_06_6000_to_6400.3.asp#_toc490464478.

³³¹ Trends and Indicators in the Changing Health Care Marketplace, 2004 Update. Washington, DC: Kaiser Family Foundation, 2004. Accessed December 10, 2004. <http://www.kff.org/insurance/7031/index.cfm>.

2. Coverage

Although private payers often look to and follow coverage decisions by Medicare and certain larger private health plans, most private insurers still have their own specific processes for making coverage decisions. With the introduction of new technologies to the market, health plans may consider adding or excluding services or making other adjustments to existing policies. The impetus for such changes may come from various sources, including state or federal mandates, consumer preference or financial considerations.³³²

a. Technology Assessment Processes

Used by public and private sector payers, technology assessments typically are conducted for certain new technologies. Higher profile breakthrough technologies tend to be subject to health technology assessment (HTA), particularly if they have a large potential health or economic impact. While such impacts may be direct, they also may be indirect, such as when the results of a diagnostic test or procedure have the potential to increase or decrease the use of costly downstream interventions.

Although private payers often make coverage decisions pertaining to the same technologies and use internal and/or external HTAs, there is considerable variation in the resulting coverage determinations. Many health plans do not conduct formal, comprehensive reviews of new technologies, due to insufficient internal expertise or resources. However, the larger plans and networks such as Aetna, CIGNA, Harvard Community Health Plan, HealthPartners of Minnesota, United Healthcare, WellPoint, Highmark and various Blue Cross and Blue Shield plans have extensive internal functions for this purpose. Further, they purchase assessments from HTA vendors.

An example of an influential HTA program is the joint Technology Evaluation Center (TEC) of the Blue Cross Blue Shield Association (BCBSA) and Kaiser Permanente. Assessments from BCBSA's TEC often rise to national visibility and serve as an important source of information for Blue Cross and Blue Shield plans, as well as other payers. Their purpose is to provide health care decision-makers with "timely, objective and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management and prevention of disease."^{333,334} A medical advisory panel comprising independent, nationally recognized experts in HTA, clinical research and medical specialties, has scientific accountability for all TEC assessments. TEC uses the following five criteria (**Figure 5.10**) to assess whether a technology improves health outcomes such as length of life, quality of life and functional ability.³³⁵ Similar criteria also have been adopted by other private sector payers.

³³² Coverage and reimbursement of genetic tests and services, 2005.

³³³ The Blue Cross and Blue Shield Association Technology Evaluation Center has been in place since 1985. Its collaborative relationship with Kaiser Permanente began in 1993.

³³⁴ Technology Evaluation Center. Chicago, IL: Blue Cross Blue Shield Association, 2004. Accessed November 1, 2004. <http://www.bcbs.com/tec/>.

³³⁵ What is TEC? Chicago, IL: Blue Cross Blue Shield Association, 2004. Accessed November 1, 2004. <http://www.bcbs.com/tec/teccriteria.html>.

Figure 5.10
Technology Evaluation Center (TEC) Criteria for Assessment of Health Technologies

1. The technology must have final approval from the appropriate governmental regulatory bodies.
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
3. The technology must improve the net health outcome.
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside investigational settings.

*Reproduced from the Blue Cross Blue Shield Association; Technology Evaluation Center criteria:
<http://www.bluecares.com/tec/teccriteria.html>.*

TEC reports provide findings regarding whether a technology meets these criteria, but do not generate coverage decisions or other policies and, therefore, are not binding on Blue Cross and Blue Shield plans. Still, individual Blue Cross and Blue Shield plans and other private sector payers frequently use TEC's findings in formulating their own coverage determinations.

The set of diagnostics that BCBSA TEC has assessed in recent years, listed below, is indicative of the types of technologies that are subject to HTA by payers. In general, these share at least two of the following attributes: new; potential to be used in large populations; costly on a unit or aggregate basis; and significant potential to affect downstream resource use.³³⁶

- Serial endpoint testing for the diagnosis and treatment of allergic disorders
- High-sensitivity C-reactive protein measurement for coronary heart disease risk stratification
- Immunochemical versus guaiac fecal-occult blood tests (iFOBT vs. gFOBT)
- Use of intermittent or continuous interstitial fluid glucose monitoring in patients with diabetes mellitus
- Use of epithelial cell cytology in breast cancer risk assessment and high-risk patient management
- Chemotherapy sensitivity and resistance assays

In the case of iFOBT, the BCBS Medical Advisory Panel determined that this test for colorectal cancer screening did not meet the TEC criteria. Based on the available evidence, TEC observed that the matter of whether iFOBT improves health outcomes relative to gFOBT has not been demonstrated in an investigational setting, let alone in community practice. In contrast, CMS released a decision memorandum with the intent to issue a positive NCD concluding that there is adequate evidence to determine that the iFOBT is an appropriate and effective colorectal cancer screening test for Medicare beneficiaries aged 50 and older. Although direct evidence demonstrating improvements in colorectal cancer net health outcomes were unavailable, CMS expanded coverage to "further stimulate awareness of the importance of colorectal cancer

³³⁶ TEC assessments. Chicago, IL: Blue Cross Blue Shield Association, 2004. Accessed November 1, 2004.
<http://www.bluecares.com/tec/tecassessments.html>.

screening,” anticipating that availability of this additional test will result in an overall increase in currently low colorectal cancer screening rates.³³⁷ As further evidence on the relationship between iFOBT and health outcomes emerges, it is possible that CMS will refine the circumstances of coverage of this test for screening applications.

b. Coverage Policies

Coverage decisions, and the consideration of cost in these decisions, appear to be associated with payers’ organizational type and level of financial risk sharing. Significant coverage variation indicates that a large proportion of the population covered by private payers may lack access to treatments that routinely are available to others. When making decisions about the services to be covered under a particular plan, HTA findings may be reviewed along with clinical practice guidelines, cost considerations (including cost-effectiveness compared to alternative interventions where relevant for a particular payer) and the availability of an applicable CPT code.³³⁸

With predictive diagnostics in particular, the benefit of using a test may not accrue until years later. In such cases, while a payer may cover a particular test, it may impose other limitations or conditions that mediate access (e.g., particular indications or prior authorization).

Private payer coverage policies and the processes they use to arrive at coverage determinations generally are not publicly available, making it difficult to assess the extent to which diagnostics currently are covered by private payers. When benefits or coverage criteria are not defined explicitly, decisions are made on a case-by-case basis, and such decisions can be made prospectively through prior authorization mechanisms or retrospectively through claims processing. Although the trend is toward higher evidence requirements in general, new technologies remain subject to varying and inconsistent requirements across private payers.

The lack of a uniform process for making coverage determinations can result in inconsistent access to diagnostics across beneficiary populations. Providers can be reluctant to use new technologies, given the variability and uncertainty in coverage policies pertaining to their patients. This can result in varying standards of care and inappropriate use—including underuse and overuse—of beneficial technologies.

3. Payment

Although the CLFS and MPFS are specific to Medicare, private payers often adopt similar fee schedules as a basis to pay for laboratory tests and other services. For inpatient and hospital outpatient settings, private payers typically use one of several prospective payment methodologies, including all-inclusive case rates, per diem rates and PPS using DRGs. As with the Medicare PPS, these all-inclusive rates do not provide separate payment for each resource used in delivering a health care service. Therefore, these PPS also rely on being able to capture or estimate the cost of each resource in order to account for these when determining payment rates, as is the case for the inpatient PPS regarding accounting for costs of certain medical

³³⁷ Decision memo for screening immunoassay fecal-occult blood test (CAG-00180N). Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed November 1, 2004.
<http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87>.

³³⁸ Coverage and reimbursement of genetic tests and services, 2005.

technologies. Managed care payment systems vary according to contract terms established between payers and providers.

While technology innovators and manufacturers are cognizant of the role of commercial payer coverage and payment, concerns regarding Medicare are particularly acute, reflecting the program's size and scope of influence. While its 41 million beneficiaries are affected directly by Medicare's policies, the program's effects extend to Medicaid, private payers and others influenced by its coverage policies and fee schedules. At the same time, there is diversity in coverage and payment, even among Medicare carriers, presenting a complex reimbursement environment to diagnostics makers, clinicians, provider institutions and patients.

E. Medicare Prescription Drug Improvement and Modernization Act of 2003

MMA provides the most significant reforms to the Medicare program in nearly 40 years. Included in the Act are key improvements to the processes for determining coding assignments and payment for new clinical laboratory tests and the avoidance of beneficiary co-payments.

The MMA legislation reflects at least two provisions, both the result of compromises that are particularly relevant to diagnostics: a) a requirement for a demonstration project on competitive bidding among clinical laboratories; and b) a five-year freeze on the clinical lab fee schedule.³³⁹ Other provisions that also may affect diagnostics include changes to the process for establishing new CPT codes, coverage of cardiovascular and diabetes screening, development of a new council within CMS to review innovative technologies in a timely manner and changes to the national coverage determination process. The primary policy changes and main implications of each provision are summarized in **Figure 5.11** and detailed in **Appendix E**.

Figure 5.11
MMA Provisions Pertaining to Diagnostics

MMA Provision Topic	Main Changes	Main Implications
Regulation and Coverage	Provides cross-walk versus gap-fill guidance, encourages stakeholder participation in processes	CMS is expanding stakeholder input in payment determinations; may help increase transparency and accuracy of some reimbursement determinations
CLFS Freeze	5-year freeze on the CPI update to the CLFS (through 2008)	Payment for diagnostics will continue to lag behind inflation; this will extend disincentives for innovation adoption, and patient access to diagnostics
Competitive Bidding Demonstration	Applies competitive acquisition to payment for diagnostics	Expectation that lower total payment amounts to have financial impacts on industry; if CMS views as successful, may be implemented more widely in the future
Cardiovascular and Diabetes Screening	Establishes coverage for cardiovascular and diabetes screening for at-risk individuals; allows a fast track to payment for diabetes screening tests; specifies that cardiovascular tests must be recommended by USPSTF	Fast-track option for diabetes screening-related tests may result in more timely patient access; requiring that USPSTF recommend cardiovascular screening tests sets a high evidence hurdle for diagnostics manufacturers

³³⁹ Ivor L. The Medicare Modernization Act: what's in it for IVDs? IVD Technology;2004:18.

MMA Provision Topic	Main Changes	Main Implications
CMS Council for Technology and Innovation	CTI will work to coordinate coding, coverage and payment processes for new tests through two working groups	Will promote/support evidence-based evaluation and may ease burden on diagnostics manufacturers of collecting unnecessary evidence on certain low/moderate risk tests.
NCD Process	Requires that factors used to determine NCDs are made public and guidance documents made available in a timely manner; specifies total time for completion of an NCD; allows the issuance of temporary HCPCS codes	Increases openness, standardization and timely interaction with CMS; anticipated to make NCDs a more iterative process

The Medicare Modernization Act. The Centers for Medicare & Medicaid Services.

MMA calls for improvements in establishing open, rational and interactive processes in the reimbursement of diagnostics and other technologies. These are intended to address concerns regarding coding, coverage and payment of new technologies and access for Medicare beneficiaries. While the Act conveys the intent of Congress, industry and other stakeholders in safe, effective and efficient testing, it also will be essential to monitor the implementation and real-world impact of these provisions and to evaluate the need for future refinements.

F. Diagnostics Reimbursement: Findings and Recommendations

Third-party payment influences the development and diffusion of diagnostics. In contrast to working with only one main regulatory agency (i.e., the FDA) in the US to obtain approval to market a diagnostic, the processes for obtaining coding, coverage and payment involve many more payers and other groups with often varying policies, increasing the uncertainty of investing in new product development.

In today's market, payers, including Medicare and Medicaid programs and the wide array of managed care organizations, exert pressure on providers to deliver higher quality health care while constraining costs. Providers and professionals demand improved technology from manufacturers while placing downward pressure on costs. Successfully navigating the large, diverse and complex US payer environment is daunting, often requiring extensive expertise and resources, and can delay access to beneficial technologies by months or years. These pressures may diminish the value that diagnostics add to health care, including potential improvements in health outcomes and expenditures.

1. Findings

Current coding, coverage and payment processes pose disincentives to manufacturers to develop new tests and can inappropriately influence test ordering by providers. Although the Institute of Medicine's 2000 report on Medicare laboratory payment policy provided recommendations for correcting existing flaws in the system, the reimbursement process for diagnostics remains largely unchanged.

- MMA 2003 calls for significant advances in establishing open, rational and iterative processes in the reimbursement of diagnostics and other technologies. However, these remain to be fully implemented.

The successful adoption and use of new diagnostic tests can depend directly on CPT coding, because assignment of a particular code determines the payment level for a test. Despite recent improvements, current mechanisms for securing proper codes can be complex and time-consuming and would benefit from more direct involvement of physicians, laboratories, diagnostics manufacturers and other sponsors.

- The timelines for updating codes applicable to the Medicare CLFS remain lengthy. Depending on the date of submission for new or revised coding, it can take 14-26 months for a CPT Category I code to become effective and 10-16 months for a Category II or III code to become effective. Further delays can occur if the participating medical specialty societies and reviewers do not arrive at consensus regarding coding decisions or if reviewers conclude that a technology has not met CPT requirements for widespread use or for efficacy and clinical utility.
- Recently, the AMA, which governs the coding processes, began considering certain coding recommendations of the Pathology Coding Caucus, which was established by the College of American Pathologists.

Coverage establishes the clinical indications for which a new diagnostic can be paid and describes circumstances of use. There is no uniformly applied method for making coverage decisions for diagnostics, and decisions often seem to be ambiguous, arbitrary or redundant.

- Payers increasingly require evidence linking diagnostic test use to health and economic outcomes. It is appropriate to require evidence of the health, economic and/or other valued impacts of diagnostics. However, establishing causal effects of diagnostics, particularly on health outcomes, can be challenging and sometimes impractical, as various factors (e.g., use of multiple diagnostics, physicians' desire to rule out conditions, and multiple treatment options) can confound these downstream effects.
- Coverage of emerging diagnostics that test for multiple biomarkers or provide predictive data is inhibited by current interpretations of medical necessity. While such tests may offer new paradigms for patient care, the current medical necessity hurdles may limit rapid development and diffusion of diagnostics.

Methods of setting Medicare payment levels for new diagnostics are archaic, inconsistent and severely flawed. They fail to reflect the relative value of diagnostics to health care, sending inefficient market signals to innovators, clinicians and payers.

- Payment levels often do not reflect the value of diagnostics to patient health or the health care system. A new test that confers greater benefits often is paid the same as or less than an existing one sharing the same code. As such, both incremental and breakthrough advances in diagnostics frequently are underpaid, precipitating suboptimal resource allocation and disincentives for innovation.
- The CLFS has not been updated for inflation in 11 of the past 15 years and will not be updated again until after 2008. As a result, each dollar paid in 2004 under the CLFS is equivalent to \$0.75 in 1984 dollars, after adjusting for inflation and mandated payment reductions below the NLA.

- The crosswalk and gap-fill methods used for setting initial payment levels for diagnostic tests and updating existing ones in the CLFS used by Medicare are non-standardized and inconsistently applied.
- The flaws of the CLFS used by Medicare extend beyond that program to payment for care for many millions of other patients, whose payers use or are guided in their payment of diagnostics by Medicare payment policies.
- There are great discrepancies in payment for diagnostic laboratory tests among state Medicaid programs, which are bound by the NLAs set by Medicare. While some diagnostics are overpaid in these fee schedules, decisions resulting in underpayment are more likely, including many that are significantly below the NLA, compounded by national decisions to withhold CLFS updates for inflation.

2. Recommendations

CMS should promptly modernize the Medicare CLFS into a single national payment schedule with an open, systematic and accountable process that would reduce wide pricing variations among carriers. While implementing this modernized process, CMS also should correct historic pricing and coding errors, clarify processes and criteria for incorporating new tests into the CLFS and provide for regular stakeholder input on CLFS modifications.

- CMS should publish and implement clear administrative procedures for responding to contractor and other stakeholder requests to correct historical pricing errors and inappropriate cross-walks of new test codes to “clinically similar” test codes in the CLFS. To minimize the burden on CMS of responding to these requests, clear criteria for considering requests should be established, including, e.g., substantive patient access concerns, evidence of incorrect cross-walk assignment or pricing of predicate tests and limits on the number of updates considered annually.
- CMS generally should price new test codes at no less than the NLA of the test codes to which they are cross-walked. If specific circumstances warrant payment below the NLA, CMS should publish clear rationale for such decisions.
- CMS should clarify the process and criteria for cross-walking new tests into the CLFS, including defining “clinically similar” for the purpose of identifying existing tests to which a new test might be cross-walked. CMS should eliminate flawed pricing practices such as pricing tests newly introduced to the CLFS based on fractional amounts of existing tests in the CLFS.³⁴⁰
- CMS should pursue national coordination and consistency of the CLFS. National pricing provisions would minimize instances of gross variation in test payment. At least until a better value-based system is implemented, CMS should establish a “floor” that eliminates low-priced outliers, counterbalancing existing NLA payment caps for

³⁴⁰ This is consistent with recommendations made by the Institute of Medicine in 2000.

high-priced outliers.³⁴¹ CMS should evaluate the appropriateness of lowest contractor-set fee schedule rates and their impact on access and quality.

- CMS should develop a revised process for setting payment rates for new test codes not eligible for cross-walk (i.e., not clinically similar to existing tests on the CLFS). To the extent that this process would base rates on the health, economic or other attributes of value of new tests, it would comprise an important step toward the broader value-based approach recommended below.
- CMS should use interim pricing strategies (e.g., that are subject to annual revision) for such new tests to enable later adjustments for technological change, potential initial pricing errors and impact on providers and patient access. For any approach to incorporating new tests into the CLFS, CMS should provide clear rationale and evidentiary basis for price setting.
- CMS should provide a clear and accountable process for stakeholders to appeal cross-walk and pricing decisions, with the ability to incorporate new information about a technology, how it is used or its impact on practice or access.
- The CLFS should be adjusted annually for inflation, based on the Consumer Price Index or similar means, and for reasonable costs of providing clinical laboratory services.
- The open and ongoing process for maintaining the currency of the CLFS should reflect technological advances and market conditions and assess the impact of pricing decisions on providers, patients, manufacturers and other stakeholders. It should include development of guidance, and regulations as necessary, that address and clearly explain standard criteria for updating decisions.

In parallel to the modernization into a single national payment schedule, CMS should develop and implement value-based payment for clinical laboratory tests that overcomes inherent limitations of the current cross-walk and gap-fill processes. This process should shift over a period of years from existing payment practices to a value-based resource payment approach that better recognizes the clinical, economic, and other benefits of improved diagnostic testing.

- The system should be applied initially to new tests (especially those that are not eligible for cross-walk under the current system) and gradually extended to existing tests on the CLFS.
- This value-based payment process should be open, transparent and deliberative. At a minimum, it would involve open planning meetings with stakeholders, but also may be supported by a FACA-compliant³⁴² clinical laboratory test payment advisory committee. This committee would be responsible for review of fee schedule submissions and development of recommendations to CMS regarding payment level updates/changes

³⁴¹ The NLA currently caps payments at 74% of the median contractor prices. An NLA “floor” would serve the same purpose by raising the lowest prices to a percent of the median to eliminate outlier pricing that may preclude local test availability and patient access.

³⁴² The Federal Advisory Committee Act (FACA) of 1972 sets requirements for any group established by the government for the purpose of advising the government and that includes any members that are not government employees.

and other payment system refinements.³⁴³ Represented stakeholders should include experts from industry, laboratories and clinical care.

- Negotiated rulemaking should be employed as a means of establishing payment for high national priority or controversial clinical laboratory tests.

Access to new diagnostics depends on timely, appropriate coding assignments, as well as designation of adequate payment levels. Therefore, while recognizing the practical time requirements of gaining and processing expert input, the AMA and CMS should continue to strive for greater efficiency and shorter timelines for establishing these codes.

- Of particular value would be reductions in the 14-26 month period and any associated delays entailed in establishing and making effective a new or revised Category I CPT code.
- The AMA should allow for increased transparency and stakeholder input, including from diagnostics manufacturers and clinical laboratories, to processes for assigning new and revised CPT codes. Greater transparency would entail, e.g., more sharing of relevant documentation and information about disposition of coding decisions on designated web sites.

For purposes of making Medicare coverage decisions, CMS should carefully consider evidence requirements for diagnostics, given the challenges of establishing direct evidence of the causal effects of using diagnostics on improvements in health and economic outcomes.

- Evidence requirements for diagnostics, including applicable methods and data sources, should be developed with input from various appropriate methodological experts and stakeholders, including health care providers and representatives of diagnostics manufacturers and the clinical laboratory industry.
- Implementation of standardized, evidence-based coverage decision criteria for diagnostics across local Medicare coverage processes, though retaining local coverage decisions, would reduce inefficiencies and improve health care access and quality.

Public and private payers should establish a transparent basis for determining medical necessity of clinical laboratory tests reflecting opportunities of evolving diagnostic technologies.

- Stakeholders should move to adopt the ICD-10-CM coding system for clinical laboratory services. While initially burdensome, this will offer the capacity to accommodate the increasing volume and complexity of tests entering the market. CMS should develop and implement reasonable incentives to facilitate this transition consistent with MMA reform requirements.
- Along with other payers and with input from informed stakeholders, CMS should anticipate the potential benefits of broadening interpretations of medical necessity as it

³⁴³ This role may be analogous in certain respects to that of the AMA/Specialty RVS Update Committee (RUC), which makes recommendations to CMS on the relative values to be assigned to new or revised CPT codes designated by the AMA CPT Editorial Panel. Clinical laboratory codes listed under the CLFS currently are not brought before the RUC, although certain diagnostic codes listed under the Medicare Physician Fee Schedule are subject to RUC review.

applies to many emerging diagnostics, such as those involving multiple biomarkers or gene-based predictive tests, that hold significant potential for early and effective preventive care in specific populations.

In consultation with DHHS, health professional groups and other stakeholders, Congress should consider transferring responsibility for coverage determinations for preventive services under Medicare to DHHS. This would enable more timely, evidence-based coverage for diagnostics that are demonstrated to be useful in screening and prevention.

- While most diagnostics currently are not used for screening purposes, many (including some emerging diagnostics) hold great promise as screening tests for certain high-risk populations. The Medicare statute does not provide for coverage of screening tests, except as mandated by Congress. Transfer of this responsibility likely would require a change in the Medicare statute, as has been proposed under S. 2535, the Medicare Preventive Services Act of 2004, introduced in the 108th Congress.
- Coverage determinations for diagnostics should continue to be informed by the USPSTF with input from the Medicare Coverage and Advisory Committee, as appropriate. This may include expanded technical support from AHRQ and its Evidence-based Practice Centers program, health professions groups and others with objective and well-documented evidence review processes.

VI. Additional Factors Affecting Viability and Value of Diagnostics

A. International Regulatory and Payment Requirements

The magnitude of the global diagnostics market is approximately \$28 billion and is expected to reach \$39 billion in the next four years. North America, Western Europe and Japan account for the majority of the world market. However, the rapid growth of the middle class in India, China and Latin America will lead to strong demand for diagnostics in these areas over the next several years.³⁴⁴

Though their specific requirements and oversight differ, most countries have regulatory frameworks that apply to medical devices, including diagnostics. To some extent, almost all of them use device classification to determine the category or level of oversight, an assessment of device conformity to minimal standards, registration of manufacturing firms and devices, quality management programs and postmarket surveillance and adverse event reporting.

A major step toward global harmonization of regulatory processes occurred 1997, when the US entered an umbrella agreement with the European Community (EC).³⁴⁵ Subsequent cooperation has resulted in participation in the Global Harmonization Task Force (GHTF), comprising device regulatory officials and industry representatives from the US, EU, Japan, Australia and Canada.³⁴⁶ Participation in the GHTF is voluntary, and the GHTF holds no official regulatory authority. To date, representatives of the medical device industry have played an active role in the GHTF, whereas diagnostics industry stakeholders have been less active. Activities of the GHTF include a pilot program aimed at processing premarket submissions that are prepared using GHTF guidelines.

International Health Care Markets

Health care systems and their expenditures differ among developed nations. EU nations provide coverage for the great majority of their citizens; for instance, Germany provides Statutory Health Insurance (SHI) through sickness funds to 88% of its population.³⁴⁷ The average Organization for Economic Cooperation and Development (OECD) country spends roughly 8% of its gross domestic product (GDP) on health care expenditures, compared to more than 15% of GDP in the US; only Switzerland and Germany exceed 10%.³⁴⁸ US per-capita spending is roughly twice that of other highly developed countries (**Figure 6.1**). Despite these differences, most nations share concerns about the limitations of existing systems, particularly the quality of health care and magnitude of overall health expenditures.³⁴⁹

³⁴⁴ Rosen S. Market outlook for IVDs: Advances in molecular technologies should lend a boost to the global IVD market. *IVDT* 2004;39.

³⁴⁵ Merrill RA 1994.

³⁴⁶ FDA guidance for industry and FDA staff. A pilot program to evaluate a proposed globally harmonized alternative for premarket procedures. Rockville, MD: US Food and Drug Administration, 2004. Accessed November 12, 2004. <http://www.fda.gov/cdrh/ode/guidance/1347.pdf>.

³⁴⁷ Busse R. Disease management programs in Germany's statutory health insurance system. *Health Aff* 2004;23:56-67.

³⁴⁸ Reinhardt UE, Hussey PS, Anderson GF. US health care spending in an international context. *Health Aff* 2004;23:10-25.

³⁴⁹ Barton JH. TRIPS and the global pharmaceutical market. *Health Aff* 2004;23:146-154.

Figure 6.1
Per-capita spending by Nation

Country	Per-capita Health Spending (US dollars)
United States	\$4,869
Canada	\$2,743
Germany	\$2,735
France	\$2,588
Japan	\$2,077
United Kingdom	\$2,012

Adapted from: OECD Health Data 2004. Paris, FR: Organization for Economic Co-Operation and Development, 2004., 1st ed.

In general, EU countries and Japan are similar to the US in that they continue to enact public policies that attempt to curb the growth of health care spending. However, these countries have more control over health care spending than the US, because their governments play a more dominant, central role in its financing.³⁵⁰ Despite their large share of the worldwide diagnostics market, the US, EU and Japan historically have spent less than 1% of their per-capita health care outlays on laboratory testing.³⁵¹

The UK stands as a notable exception to the trend of cost-containment; tax increases enacted in 2003 are intended to increase total health spending to more than 9% by 2008.³⁵² The UK has had a single-payer National Health Service since 1948 that has enabled tighter management of health care expenditures. This system provides universal coverage for its citizens, albeit with recognized limitations in personnel, infrastructure, technology and access. These system-wide shortfalls have prompted the UK to increase spending on health care.

B. Regulation and Reimbursement in Europe

In general, European nations have compulsory health insurance for citizens, high levels of coverage and public ownership of hospitals. Their economic systems often are characterized by protectionist policies and labor laws that govern working hours, vacation times and retirement ages inside and outside of the health care market. National governments historically have managed the funding and regulation of health care, including laboratory testing.

The EU began considering a framework for regulation of diagnostics in the early 1990s. The basis for this framework is the EU Treaty, which provides for regulations that “have as their object the establishment and functioning of the internal market.”³⁵³ Regulations across member states are aimed primarily at the free movement of products and services across national boundaries. However, given the strong role of European states in health care delivery, financing and regulation, EU-wide regulations also would be expected to consider public health and safety of medical devices.

³⁵⁰ Saltman RB, Figueras J. Analyzing the evidence on European health care reforms. *Health Aff* 1998;17:85-108.

³⁵¹ Place JF. Staying ahead of the curve. *Proceedings of Lab* 2002; 2000 Mar 23-24; New York.

³⁵² Stevens S. Reform strategies for the English NHS. *Health Aff* 2004;23:37-44.

³⁵³ EEC Treaty- Article 100a. OJ No C 313, 30. 11. (1992).

Before the 1980s, only France and Germany regulated diagnostics. Evolving differently among nations, regulation began to take shape with the emergence of HIV/AIDS.³⁵⁴ By the early 1990s, most countries had developed limited regulations and registration requirements with differing scope and standards. In December 2003, Europe implemented the In Vitro Diagnostics Directive (IVDD), requiring the CE mark on all diagnostics marketed in Europe. The IVDD also requires companies that market in the EU to have an authorized representative based in Europe.

The IVDD regulates products with the objectives of enabling the flow of diagnostics across international borders and ensuring their safety for intended uses. A central goal is to harmonize the regulation of products, though not their reimbursement. The scope of the directive includes those diagnostics used professionally, some self-testing products, accessories, controls and calibrators. Home brews and general laboratory products are excluded from the IVDD and research applications of products are not mentioned in the IVDD.³⁵⁵

The Role of Standards and Regulation

The International Organization for Standardization (ISO) was founded in 1995 to harmonize certain products and services specifications so that companies can minimize unnecessary/redundant development and compete internationally with greater ease. Within the ISO, one technical committee (TC212) has the primary responsibility for developing standards for clinical laboratory testing and diagnostics.³⁵⁶

Standards developed by the ISO and other organizations do not, by themselves, constitute regulations; however, national regulatory agencies (including the FDA) do consider such standards in their own regulatory frameworks.³⁵⁷ For instance, quality system regulations codified in US federal regulations (21 CFR Part 820) are “harmonized” to ISO 13485:1996.³⁵⁸ In general, standards may receive “recognized standard” status in the US if they are issued by a standards body that satisfies conditions such as transparency and do not conflict with regulations. The FDA officially recognizes standards by publication in the *Federal Register*. Although consideration and harmonization by various international regulatory authorities occur, diagnostics still must adhere to a variety of requirements specific to a particular EU country, involving costly multiple reviews and inspections to ensure compliance to different standards. Standards and guidance documents also change over time, requiring additional resources for tracking and compliance.

In the EU, official authority for enforcing the IVDD rests with the Competent Authorities (CA). However, the IVDD is, in some ways, upheld by manufacturers themselves, and the level of

³⁵⁴ Place JF. IVD MD directive 98/79/EC. Proceedings of the Vejlefjord Center; 2001 Feb; Denmark.

³⁵⁵ Ibid.

³⁵⁶ Powers DM. International standards for IVDs: part 1. IVDT 2004:28.

³⁵⁷ An exception to this generalization is standards drafted by the European Committee for Standardization (CEN) under contract for the IVDD. As a European-based group, CEN's standards are developed mainly with input from European experts. However, the close working relationship between the CEN and the ISO's TC212 committee has fostered an environment in which industry representatives from outside of Europe are able to comment on standards, which often are adopted by the ISO. When changes are made to a CEN standard by the ISO, these changes typically also are made in the IVDD standard as allowed under the Vienna Agreement.

³⁵⁸ ISO 9001:2000. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, 2003. Accessed March 31, 2005. <http://www.fda.gov/cdrh/devadvice/ISO9001.pdf>.

enforcement varies by nation.³⁵⁹ However, noncompliance with the IVDD constitutes a criminal violation that may carry severe penalties, but has not been a significant issue for diagnostics manufacturers to date.

Despite the regulatory agreements between EU countries, many challenges to reimbursement remain. National governments exert a high level of control over health care services, as well as the personnel and infrastructure required to deliver care. High taxation rates affect the financial viability of many devices and new costs may arise that may be prohibitive for small or start-up firms. These can include the costs associated with the creation of regulatory databases for surveillance, language and packaging requirements across nations and redundant regulatory structures in particular countries.³⁶⁰

Reimbursement in the European market differs by member nation and may be more difficult to navigate than regulatory differences. Most nations continue to be concerned about the magnitude of health care costs and play an active role in reimbursement policy, though specific controls vary by country. The DRG payment system in Germany is evolving and may significantly affect diagnostic reimbursement. Office-based payment for tests, particularly new ones, may depend on findings of a technology assessment committee before being officially placed on a price list. The French reimbursement process also requires an assessment of medical benefit by a government commission, with a separate review group responsible for establishing price as well as volume. Reimbursement in many European hospital laboratories is also limited, because of the imposition of global budget restrictions.

Although the intention of the IVDD is to help centralize the clearance process for new technologies, many country-specific systemic and procedural differences remain. As with FDA clearance in the US, while the CE mark signifies that regulatory criteria have been satisfied, it does not guarantee reimbursement. Companies that obtain CE marking must navigate some 15 different payment systems in Europe to get products reimbursed and frequently may experience delays in coverage determinations. Such disincentives may inhibit many companies, particularly small-to-medium ones with limited resources, from entering the EU and other international markets. In essence, the existing regulatory structure requires manufacturers to satisfy the requirements of the IVDD as well as any additional requirements of individual EU nations, resulting in a particularly complex environment for securing coverage and payment.³⁶¹

³⁵⁹ Spencer S, Williams D, Andrews J, Bufton A. Taking a look at the future of the European IVD market. *IVDT* 2003;50.

³⁶⁰ Place JF 001.

³⁶¹ *Ibid.*

C. Regulation and Reimbursement in Japan

Health care spending in Japan declined in 2002, a rarity among developed nations. This was achieved through intense government control of prices and utilization. Though the majority of health care services are provided by the private sector, the Japanese Ministry of Health, Labor, and Welfare (MHLW) establishes the fee schedule for reimbursement for all services, procedures, drugs and devices. Revisions to the fee schedule are negotiated between providers and the government on a biennial basis. Because the government controls all reimbursement rates, medical inflation averaged 0.46% annually from 1980 to 2000. Despite these controls, the Japanese have grown increasingly concerned about total health care outlays, in part due to the impacts of an aging population. As a result, Japan has exerted significant control over the use of health care services as well. When services or procedures show rapid increases in volume, the government tends to decrease their reimbursement.³⁶²

The Japanese classify diagnostics as pharmaceuticals under the Pharmaceutical Affairs Law (PAL). The regulatory framework for diagnostics was changed significantly by the revision of the PAL enacted by the Japanese parliament in 2002. The revised system, implemented in 2005, requires the classification of medical devices by risk category similar to the system in place in the US. Class I devices are low risk and require no approval; Class II devices carry moderate risk and are to be certified by third parties; Class III devices potentially are high risk and must be approved by the MHLW.

The MHLW is required to establish qualification requirements for third-party certification organizations, accredit outside organizations and establish procedures and requirements for device approval. This use of third parties in certification and approval is likely to be similar to the EU process; the Japanese government decided on a third-party role for approval and certification, because of its desire to adopt a system harmonized to global regulatory structure.

Japan has a history of slow approval for new diagnostics, with only 12% reaching approval decisions within the targeted review period of six months. However, decision time has improved recently, with more than 87% of applications being reviewed on schedule.³⁶³ Although there are similarities to the US system, the Japanese regulatory environment is highly complicated, uncertain and can be restrictive. Factors such as the number of test subjects and trial sites necessary to demonstrate product safety and effectiveness are not standardized and are highly subject to interpretation by MHLW officials. Less than 20% of foreign clinical data is acceptable in Japan without additional testing in Japanese subjects.³⁶⁴

The Japanese government currently is evaluating health care reimbursement strategies, piloting diagnosis-based, all-inclusive reimbursements for inpatient care at public hospitals. Reimbursement for diagnostics under the fee-for-service system continues to be determined by government-established rates that are revisited, on average, every two years. The payment environment in Japan poses risks to the diagnostics industry, as it is highly regulated and

³⁶² Ikegami N, Campbell JC. Japan's health care system: containing costs and attempting reform. *Health Aff* 2004;23:26-36.

³⁶³ Reducing the burden of regulation for companies. EU comments accessed on the Cabinet Office of the Government of Japan website. Japan: Council for Regulatory Reform, Ministry of Health. Accessed November 14, 2004. <http://www8.cao.go.jp/kisei/giji/02/009/2-1-5e.pdf>

³⁶⁴ Ibid.

subject to interpretation by the MHLW. In particular, the “by function” categorization system for reimbursement in Japan can be a barrier to development of new products, because of a higher market risk for assignment to a payment code that may not cover costs of providing a particular test adequately. In the event that a product is inappropriately classified, the Japanese system does not readily accommodate code changes for novel products with similar, but improved functions and may require substantial cost-effectiveness evidence.

This combination of stringent regulation and open interpretation makes the Japanese diagnostics market highly uncertain for product development and payment. This environment requires that industry representatives remain cognizant of the changing requirements of the MHLW and produce sufficient supporting evidence to enable market access.

D. Implications for International Access to In Vitro Diagnostics

New legislative and regulatory changes enacted in Japan and the EU present new challenges to diagnostics manufacturers. Greater harmonization of global standards may make it easier for large and established firms to extend their markets across national boundaries. Significant challenges, even for global firms, still exist and include language and labeling issues, increased postmarket surveillance and increased scrutiny on emerging classes of diagnostics. These issues may increase the difficulty for smaller diagnostic manufacturers when attempting international product launches, as they juggle limited resources and uncertain supplemental funding horizons. National language labeling comprises another hurdle for manufacturers that market to EU countries with this requirement, particularly as the EU expands to include additional nations.

Manufacturers of new devices may benefit from the classification differences in the EU and Japan. Because the US establishes risk through the use of expert panels, new devices often are placed in Class III. Classification in other rule-based systems may aid in placing new devices quickly into low- or moderate-risk categories when it is appropriate to do so. However, existing devices may be classified differently in the US than in other nations.

Postmarket surveillance requirements have changed from a procedural requirement in many markets to one that demands evidence of data collection and analysis. These postmarket requirements are becoming emphasized in the new EU environment and are echoed in ISO standards as well as the FDA Quality Systems Regulation.

As a result of such challenges, it is possible that some devices will be discontinued in Europe and other nations. Initiatives moving toward a globally harmonized set of regulations and standards for diagnostics may include simplification of marketing requirements for manufacturers operating in a global marketplace. Industry representatives have an important role to play in informing the development of standards by organizations such as the ISO. Whether the opportunities for simplification will outweigh the potential barriers to market depends, in part, on the willingness of the diagnostics industry to stay informed about and involved in regulatory developments worldwide.

Continued pressures to reduce total health care costs and demonstrate value-added benefits of new products, along with the uncertainties of international health reform efforts, increase the need for diagnostics companies to demonstrate the clinical and economic benefits associated with improved technology. This can be costly and cumbersome, since regulatory and

reimbursement evidence requirements for diagnostics often differ significantly, even within the same market. Although various standards development and harmonization efforts have improved international regulatory and reimbursement processes, the variability among countries remains significant and could inhibit product innovation and patient access. Closer alignment of appropriate development and marketing activities to evidence requirements across the total product lifecycle could enhance companies' ability to better navigate existing systems while harmonization efforts continue.

E. Societal, Ethical and Legal Considerations for Diagnostics

Technological advances can challenge, and sometimes outstrip, social, ethical and legal conventions. The collection, use and interpretation of personal diagnostic information poses such challenges today. The confidentiality of diagnostic information, the psychological effects of predictive diagnostics, decision-making following testing and unequal access to certain diagnostic and treatment modalities reflect some of the main considerations associated with existing and emerging diagnostic tests. These issues are influenced by policy at various organizational (e.g., employers, health plans), state and federal levels. This section covers key aspects of the mutual effects of the diagnostics industry and broad social, ethical and legal constructs pertaining to, e.g., patient privacy, unintended psychosocial effects of diagnostic testing and patient access.

1. Patient Privacy and Diagnostics

Contemporary Issues

- Advances in methods of diagnostic information exchange and storage within health care (including e-mail, electronic medical records and wireless transmission) raise concerns about patient privacy and improper use of patient information.
- Genetic discrimination in the form of employment termination or limiting health insurance based on diagnostic test results has only recently been addressed by specific federal legislation.

Advances of the electronic age have renewed and reframed debate on the importance of confidentiality and the protection and privacy of patient data. Prior to recent enhancements of connectivity and improvements in electronic information transfer/storage, it generally was assumed that protection of patient privacy involved locking patient files and closing the office door before discussing a patient's medical history with a colleague. With the advent of digital tools such as electronic medical records (EMRs) and e-mail communication, there is potential for accidental or intentional electronic transmission of diagnostic or other health information to unauthorized parties.³⁶⁵ Of course, this potential, including various current and evolving safeguards against it, must be weighed against the security weaknesses associated with paper record systems. Such weaknesses may include barriers to information dissemination, potential

³⁶⁵ While protected to some extent by the Health Insurance Portability and Accountability Act, electronic medical records and other electronic health information/communications systems that contain confidential patient specific information may not provide sufficient safeguards ensuring that such information cannot be obtained or inappropriately used by employers, health plans and unauthorized others. The Genetic Nondiscrimination Act of 2005, passed in February 2005, bolsters established patient protections and reduces the risks of misuse of genetic and other health information in determining eligibility for employment, scope of health insurance coverage, etc.

risks to patient safety (e.g., when handwriting is not legible) and limited capacity for expansion to accommodate changing information needs).

a. Patient Privacy Protections and Diagnostics

Approximately 60% of the information contained in EMRs is reported to be personal diagnostic test information.³⁶⁶ Diagnoses of chronic, life-threatening or treatment-intensive diseases such as HIV/AIDS, multiple sclerosis and certain genetic disorders (e.g., Huntington's disease and sickle cell anemia) are of particular concern in patient privacy debates, not only for the societal stigma associated with some of them, but because of the high costs of their management. The extensive data exchange among health insurers, providers and employers, along with the escalating cost of insurance premiums, raise concerns over the potential for employment termination or denial or other limitation of insurance coverage due to unauthorized disclosures of diagnostic information.³⁶⁷

Congress has addressed concerns over the privacy and confidentiality of health information through legislation such as HIPAA, which mandates that health plans and health care providers present patients with a clear written explanation of patients' rights and the allowable uses of their personal health information. While the diagnostics industry cannot control the ways in which test results are used or dispersed in health care directly, it can ensure that diagnostic products themselves comply with HIPAA and other privacy regulations. For instance, with POCT, diagnostic information often is digitally transmitted to central labs and EMRs. By creating diagnostic devices that meet and exceed HIPAA's information security and encryption standards, the industry is playing a substantial role in the protection of patient information.

b. Protection of Genetic Information

Protection of genetic information and prevention of potential discriminatory practices based on knowledge of genetic disorders is of increasing concern. The regulatory provisions applied to genetic discrimination include a variety of policies, most of which were written prior to the need for genetic privacy, such as the Americans with Disabilities Act of 1990 and Title VII of the Civil Rights Act of 1964. As such, these policies are not adequate for addressing the challenges related to genetic discrimination. Furthermore, state policies often are contradictory or nonspecific to these issues, making protection against genetic discrimination difficult.

The Genetic Information Nondiscrimination Act of 2005 was approved by the House and Senate with the goal of establishing legal protections for patients to encourage use of genetic screening and testing.³⁶⁸ While the health insurance industry contends that the nondiscriminatory provisions of this act already are mandated under HIPAA, this act creates national standards for the specific protection of genetic information.³⁶⁹ With federal regulation of genetic privacy,

³⁶⁶ Bufton A. Business briefing: information management trends in in vitro diagnostics. *Medical Device Manufacturing and Technology* 2002:84-8.

³⁶⁷ Gostin LO. National health information privacy regulations under the health insurance portability and accountability act. *JAMA* 2001;285:3015-21.

³⁶⁸ Genetic information nondiscrimination act of 2003. S.1053, 108th Congress. (2003).

³⁶⁹ Genetic nondiscrimination issue in brief. Washington, DC: America's Health Insurance Plans, 2003. Accessed November 12, 2004.

there is now a uniform, basic standard for protection of patients from discriminatory practices, such as health insurance premium increases or unlawful termination of employment, due to genetic predisposition to chronic, expensive or terminal illness.

Proponents of this legislation argued that, without such legislation, providers, payers and employers could be placed at greater risk for litigation (and associated costs) if actions based on knowledge of genetic predisposition or health status were deemed inappropriate by patients. Others argued that special protection could precipitate many of the problems of concern to supporters of such legislation. Legal experts in this area summarize these concerns as follows.

Providing special protection to genetic information will often be unfair because it treats people facing the same social risks differently based on the biological cause of their otherwise identical health conditions. Why, for example, should a woman who has developed breast cancer of genetic origin (e.g., BRCA 1 or 2) be given greater protection than a woman who has developed breast cancer because of environmental or behavioral factors (e.g., smoking)? Even diseases that are solely genetic are not inherently special so as to give rise to unusual claims to legal protection. A debilitating, ultimately fatal condition exposes those who have it to pain, emotional distress and social risk with substantially equal severity whether it is caused by a gene, like Huntington's, or a virus, like HIV. Indeed, it is conceivable that genetic illnesses are less in need of legal protection than sexually transmitted diseases, which often carry a stigma arising from the perception that they are just desserts for voluntary behavior.

On a practical level, we must be cautious that the very people whom policy makers hope to encourage to take advantage of genetic testing may become more reluctant because of the heightened focus on its exceptional nature. Treating genetics as distinct from the rest of medicine may enhance the stigma of genetics testing, even as legislators attempt to remove its stigmatizing effects. This can create public fears and misapprehensions about genetics that could discourage individuals from seeking testing and treatment, and thwart future scientific progress. Conversely, by focusing only on genetics information, legislators may convey the perception that the public need not worry about the confidentiality of other kinds of medical information, fostering complacency in an area where insufficient protections may exist.³⁷⁰

This federal legislation standardizes more than 40 state-level policies addressing genetic discrimination that often were found to be contradictory and inadequate in providing adequate patient protection.³⁷¹ The uniform and basic standard for the prevention of genetic discrimination provided by the Genetic Information Nondiscrimination Act should support continued innovation of diagnostics based on genetic information. The National Council on Disability, an independent federal agency reporting directly to the President and Congress on

<http://www.aahp.org/DocTemplate.cfm?Section=Genetics&template=/ContentManagement/ContentDisplay.cfm&ContentID=12750>.

³⁷⁰ Burris S, Gostin LO, Tress D. Public health surveillance of genetic information: ethical and legal responses to social risk. In: Khoury M., Burke W, Thompson E (eds). *Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease*. Oxford, UK: Oxford University Press; 2000. <http://www.cdc.gov/genomics/info/books/21stcentury.htm>.

³⁷¹ Ciarleglio LJ, Bennett RL, Williamson J, et al. Genetic counseling throughout the life cycle. *J Clin Invest* 2003;112(9):1280-6.

matters affecting Americans with disabilities, has addressed the effects of genetic discrimination, as follows.

*The misuse of genetic information not only excludes qualified individuals from employment and denies insurance coverage to individuals without justification, but also undercuts the fundamental purposes of genetic research. Such research has been undertaken with the goals of early identification, prevention and effective treatment of disease. These goals will be undermined if fear of discrimination deters people from genetic diagnosis and prognosis, makes them fearful of confiding in physicians and genetic counselors, and makes them more concerned with loss of a job or insurance than with care and treatment.*³⁷²

Because of fears about genetic discrimination from employers and insurers, some individuals may refrain from using diagnostics that can identify diseases or predispositions or risk factors for these, inform preventive or treatment interventions and reduce adverse health outcomes. Diagnostics companies could be reluctant to invest in R&D for these products due to subdued levels of demand, even if they have potential for societal benefit. As gene-based and other diagnostics emerge, further debate of their utility and implications will inform their incorporation into practice and related regulatory, payment, and legal policies.

2. Psychosocial Effects of Diagnostic Testing

Contemporary Issues

- Interpretation of diagnostic test results pertaining to health status and health risks requires appropriately trained clinicians and may require consultation with genetic counselors or other specially trained individuals.
- The potential psychosocial effects of diagnostic testing often are not explained to patients prior to testing. In some cases, the knowledge of disease risks or health status can have significant psychosocial impacts on patients and their families.

As diagnostic tests that identify individual risk of developing disease become more sophisticated and accessible, the societal impact of predictive testing merits close attention. There are benefits and risks associated with testing for health risks of eventual undesirable health outcomes in currently healthy individuals. Advance knowledge provided by diagnostic tests can allow patients and their families to plan long-term adjustments if a serious and debilitating disease such as Lou Gehrig's disease (ALS) or Huntington's disease is detected. Drawbacks to the information provided by predictive diagnostics may include psychological distress and behavioral changes for patients and their families and discrimination based on knowledge of disease risk and potential related psychosocial ramifications. Diagnostic testing causes anxiety, distress and concern in some patients, especially in cases where they do not clearly understand the meaning of test results or are inadequately informed about them.³⁷³ One study of use and interpretation of genetic testing indicated that physicians misinterpreted

³⁷² Position paper on genetic discrimination legislation. Washington, DC: National Council on Disability, 2002. Accessed November 15, 2004.

http://www.ncd.gov/newsroom/publications/2002/geneticdiscrimination_positionpaper.htm.

³⁷³ Maissi E, Marteau TM, Hankins M, et al. Psychological impact of human papillomavirus testing in women with borderline dyskaryotic cervical smear test results: cross sectional questionnaire study. *BMJ* 2004;328(7451):1293.

genetic test results for a predictive colon cancer test in 31.6% of studied cases and only 18.6% of patients received genetic counseling.³⁷⁴ To the extent applicable in other predictive tests, such misinterpretation and lack of appropriate counseling could result in detrimental or inappropriate downstream health decision-making and potential adverse health effects.

a. Psychological Effects

The psychological effects on individuals who currently are healthy but learn of a predisposition to developing a disorder can be profound. Even when a diagnostic test reveals that a patient is not predisposed to a disease, these individuals can experience a form of “survivor’s guilt” when siblings or other family members are found to be susceptible.³⁷⁵ The psychological effects of undergoing diagnostic testing, especially for diseases for which there are few or no treatment options, cannot be underestimated and must be discussed by health care providers and patients prior to the test. Yet, despite the potential for these serious psychological effects, many patients do not receive such counseling prior to diagnostic testing for a serious or debilitating illness. It is reported that only 16% of individuals who undergo cancer susceptibility testing receive this type of information prior to testing.³⁷⁶

Detection of certain chronic and/or life threatening diseases, such as sexually transmitted diseases, autism, Parkinson’s disease or lupus erythematosus, also can cause psychological trauma. Individuals may experience discrimination and feel isolated or alone as the behaviors and perceptions of others, even close family members, sometimes change following knowledge of diagnosis. Stigma and misunderstanding can lead to downstream effects, such as loss of marriage, reduced productivity and decreased quality of life, among others. As mentioned above, insufficient access to counseling services also inhibits patients and family from receiving valuable input for addressing the non-medical challenges that certain diseases can pose.

b. Behavioral Effects

In addition to psychological impacts, there may be behavior effects associated with diagnostic testing. For some, the behavioral effects resulting from a positive susceptibility test are beneficial, as individuals may make lifestyle changes to improve their health and potentially lower the severity of disease, and perhaps the risk of developing it. In other cases, predictive diagnostics may lead to difficult or insufficiently informed decisions about the best course of action to pursue. For example, a woman who discovers a genetic predisposition to breast cancer may opt for a mastectomy to reduce risk without full consideration of other mitigating risk factors or impact on her quality of life.

The use of diagnostics in reproductive medicine exemplifies the beneficial capabilities of diagnostics, as well as the difficult choices resulting from knowledge of this information. For example, individuals who do not want to pass a genetic condition to a child may consider options such as embryo selection. With the use of diagnostics, devastating hereditary

³⁷⁴ Giardiello FM, Brensinger JD, Peterson GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *N Engl J Med* 1997;336(12):823-7.

³⁷⁵ Bennett RL, Hampel HL, Mandell JB, Marks JH. Genetic counselors: translating genomic science into clinical practice. *J Clin Invest* 2003;112(9):1274-9.

³⁷⁶ McGee G. Ethical issues in genetics in the next 100 years. *Am J Bioeth* 2002. Accessed November 1, 2004. <http://www.bioethics.net/articles.php?viewCat=6&articleId=59>.

conditions such as Tay-Sachs disease can be identified in the embryonic stage. Some parents may use this diagnostic information and choose only those embryos that are free of the condition prior to implantation. For individuals who undergo prenatal diagnostic testing following conception, test results may raise decisions about whether to proceed with a pregnancy when a potential disorder such as Down's syndrome is identified. Such prenatal testing can provide families with time to prepare medically, financially and emotionally for a child who will have special needs. Others would interpret such interventions as morally or ethically inappropriate. Ethical debates over preconception and prenatal diagnostic testing continue, particularly regarding testing for conditions for which there is no definitive or effective treatment or conditions that are not life-threatening.³⁷⁷

3. Implications of Diagnostic Information for Access to Health Services

Contemporary Issues

- Advances in diagnostic testing may result in expanded services for some patients and reduced access for others, as tests increasingly help health practitioners to assess individual risks and benefits of downstream health interventions.
- Use of emerging gene-based diagnostics will continue to alter health care delivery paradigms by shifting health resources toward preventive and early-stage health interventions.
- The volume and complexity of health information potentially available from evolving gene-based and other diagnostics may necessitate additional investment in health information systems, decision support systems and health practitioner education and training.

The availability and use of diagnostics pose unique considerations for allocation of health services. Diagnostic information is essential for accurate assessment of health status and informed treatment decisions. This information can narrow or broaden the potential target population that stands to benefit from particular health care interventions. As evolving diagnostics improve identification of patients at risk, and evidence accrues to support indicated health interventions, access to some health services may change.

Emerging susceptibility/predictive tests provide one example of this relationship. Predictive tests such as BRCA I and II, which can provide insight into a woman's risk of developing breast or ovarian cancer, only are covered by a small percentage of health providers, and then only for patients with strong family histories of breast cancer. This is primarily because the likelihood of developing breast cancer, even for those with certain BRCA I and II mutations, is uncertain. While the lifetime risk of developing breast cancer for these women is high (approximately 45-85%), BRCA I and II testing cannot predict with full certainty which individuals ultimately will develop the disease.³⁷⁸ In scenarios where benefits to an at-risk population may be limited, payers may opt to cover some predictive tests, but require higher co-pays or supplemental co-insurance. This could, in turn, discourage patients with insufficient financial resources from undertaking diagnostic testing.

Such possibilities raise resource allocation challenges for third-party payers, health care providers and policymakers. Predictive diagnostics will shift the use of health care resources

³⁷⁷ Khoury MJ. Relationship between medical genetics and public health: changing the paradigm of disease prevention and the definition of a genetic disease. *Am J Med Genet* 1997;71:289-91.

³⁷⁸ Bennett RL 2003.

along the health care continuum. Changes may include increased demand for preventive interventions and more frequent follow-ups with patients at higher risk for disease.

Emerging modalities, such as pharmacokinetic tests, should help clinicians select among alternative treatments and presumably improve immediate and longer-term health outcomes and cost savings.³⁷⁹ For instance, diagnostic information may allow a health practitioner to determine that medical management is a better course of action for a particular patient because of underlying health risks detected during testing. Or, a test may indicate that one type or class of medication poses a higher risk than others, based on a patient's genetic makeup, allowing the clinician to select among alternatives.

While there are obvious advantages to the value of diagnostics in identifying patient-specific risks and benefits, information regarding differential risks and benefits may be associated with greater health disparities and unequal access to care. A 2004 report released by the DHHS Secretary's Advisory Committee on Genetics, Health and Society highlights broader access implications of personalized medicine, as follows:

*As more pharmacogenomic drugs are developed, [health] disparities may increase. Health plans and insurance programs will need to strike a balance between providing access to the most effective drug based on genotype and providing access to drugs for the largest number of people. Traditional formularies could limit access to the most effective drug with respect to genotype. Currently, however, there are very few drugs for which a solid scientific evidence base exists demonstrating a clear correlation between genotype and drug efficacy (one exception is 6-mercaptopurine, used to treat leukemia). In the future, it may be necessary to fundamentally redesign the concept of formularies in response to genetic medicine, and specifically pharmacogenomics.*³⁸⁰

Payer coverage decisions increasingly are based on available clinical evidence. As is the case for other interventions, flaws in available evidence can mask the direct and indirect benefits and risks of emerging diagnostic technologies, including limited study populations, data that is not sufficiently representative of beneficiary populations and unrealistic data on compliance with testing or indicated interventions. Such factors can contribute to suboptimal payment decisions.³⁸¹ In the current payment environment, the burden of proof has shifted to technology sponsors to provide data meeting higher, more specific evidence standards of payers. At the same time, more payers are providing forms of "conditional coverage" that provide selective payment for promising technologies in exchange for agreements to generate more real-world evidence. Timely communication between technology sponsors and payers, with provisions for technology assessment involving informed evidence interpretation regarding diagnostics, will minimize instances of inappropriate coverage and disparities in access.

³⁷⁹ Melzer D, Raven A, Detmer D, et al. My Very Own Medicine: What Must I Know? Information Policy for Pharmacogenetics. Cambridge, UK: University of Cambridge; 2003.

³⁸⁰ Coverage and reimbursement of genetic technologies and services. Washington, DC: Secretary's Advisory Committee on Genetics, Health, and Society, 2004. Accessed November 14, 2004. <http://www4.od.nih.gov/oba/SACGHS/meetings/June2004/Berry.pdf>.

³⁸¹ Ibid.

4. Implications of Social, Ethical and Legal Considerations for Diagnostic Use

Like many health care tools, diagnostics have great potential to improve patient care, but responsible dissemination, interpretation and nonmedical actions based on this information must be considered carefully by all stakeholders. Physicians and patients must be able to discuss implications of diagnostic testing, especially in cases with limited or no treatment options that involve life-altering decisions. Informed patient understanding of the ramifications of diagnostic use under such scenarios can help to minimize resulting stress or trauma and allow patients to make better informed decisions.

In addition to issues such as variability in coverage and unequal access to some diagnostics, patient apprehension about potential consequences of genetic testing for diseases presents a significant barrier to use of some diagnostics services. Policies intended to protect patients from discrimination who seek genetic testing, such as the Genetic Information Nondiscrimination Act of 2005, also may improve the environment for R&D in these areas. Adequate provider and patient education related to the psychosocial and behavioral consequences of diagnostic use is essential to responsive and high quality care.

Health decision-makers must be informed and vigilant when interpreting diagnostic information and understand the inherent strengths and weaknesses of diagnostic test results and other forms of medical/health information. Reasoned evaluation of evidence limitations and implications for provision of health services will balance the spectrum of practical considerations involved in responsible health care services and policy decisions. Such precautions will minimize the risks of inappropriate payment decisions for diagnostic technologies, reduce disparities in access to care and ensure that diagnostic information is properly interpreted and applied.

F. Other Market Factors: Work Force Considerations

The diagnostics industry depends on a spectrum of professionals at all stages of the product lifecycle. These include a highly educated R&D workforce of scientists and engineers, as well as a variety of highly skilled clinical laboratory technicians and other specialized administrative, legal and product development staff. Companies must compete for business and management professionals common to several industry sectors.

Diagnostics R&D requires the efforts of doctoral and other graduate-level scientists, including chemists, biologists, microbiologists, pharmacologists and others. The diagnostics industry employs almost 30,000 people in Europe alone.³⁸² Though estimates differ by definition and time period, the US government estimates that, as of 2001, more than 40,000 were employed by manufacturers of diagnostics products.³⁸³ While some reports indicate that diagnostics manufacturers have had more qualified candidates than open positions in recent years, several “pipeline” issues remain.

³⁸² Press release: world asthma day 2004. London, UK: British In Vitro Diagnostics Association, 2004. Accessed November 2004. <http://www.bivda.co.uk/news/index.cfm?ccs=115&cs=934>.

³⁸³ In-vitro diagnostic substance manufacturing. Washington, DC: US Census Bureau, 2002. Accessed November 25, 2004. <http://www.census.gov/prod/ec02/ec0231i325413.pdf>.

According to the National Science Foundation (NSF), the number of science and engineering doctorates awarded by US universities has decreased steadily since 1993.³⁸⁴ This same NSF study found that about 30% of graduates are non-US citizens, which may affect the ability of all US sectors to attract and retain scientists. Increasing competition for well-qualified employees is likely to increase the median compensation for senior R&D employees from its current level of \$110,000.³⁸⁵

The growth of the diagnostics industry also is strongly tied to availability of end-users and the demand they are able to sustain. These include a diverse set of laboratories, researchers, clinicians and patients. The largest current consumers of diagnostics by far are hospital and clinical labs, both of which are experiencing difficulty in meeting human resource needs.³⁸⁶

Laboratory technologists generally hold a bachelor's degree in the life sciences or medical technology, while technicians usually have an associate's degree or certificate; together, they account for almost 300,000 positions in the US. Technologists usually collect and prepare specimens, train other personnel and must be able to recognize normal and abnormal lab values, as well as instrument and data problems. They may specialize in blood banking, cytotechnology or other areas and be employed in diverse settings. Laboratory technicians generally perform less complex tests and are more likely to prepare specimens for automated analysis, though they also may specialize in areas such as histology. Median salaries reflect this difference in training and occupational duties, with medical technologists earning 47% more than technicians (\$40,518 vs. \$27,539) and registered nurses (\$48,090) earning 57% more, according to recent Department of Labor statistics.³⁸⁷

Medical directors, usually MD-educated pathologists or PhD-educated and board certified technical directors³⁸⁸, dedicated to diagnostic/laboratory functions also may be challenging to recruit and retain if the proper career and reimbursement incentives are not in place for such specialists. For example, the median salary for a laboratory director is, on average, 54% lower than that of their pathologist counterparts (\$159,238 vs. \$86,698), based on a recent survey of laboratory personnel.³⁸⁹

Licensure requirements for clinical lab workers vary by state, and certification often is voluntary; however, many employers require it. Certification is available through several bodies, including the American Society of Clinical Pathologists Board of Registry, American Medical Technologists, the National Credentialing Agency for Laboratory Personnel and the Board of Registry of the American Association of Bioanalysis.³⁹⁰

³⁸⁴ National survey reveals continuing decline in science and engineering doctoral degrees. Arlington, VA: National Science Foundation, 2003. Accessed November 21, 2004. <http://www.nsf.gov/od/lpa/news/03/pr03134.htm>.

³⁸⁵ MDDI salary survey. MDDI 2003;12:71.

³⁸⁶ Ibid.

³⁸⁷ Bureau of Labor Statistics(US). Occupational Outlook Handbook. Washington, DC: US Department of Labor, Bureau of Labor Statistics, 2004-2005.

³⁸⁸ Some of the most common areas of specialization for laboratory technical directors/administrators may include clinical chemistry, microbiology, toxicology, immunology or molecular biology.

³⁸⁹ Haigh A. Survival of the fittest. *Med Lab Observ* 2005;37(3);28-30.

³⁹⁰ Grover A. Clinical laboratory workers. Proceedings of the Clinical Laboratory Improvement Advisory Committee; 2002 Sept 12; Atlanta, GA. Accessed November 24, 2004. <http://www.phppo.cdc.gov/cliac/pdf/Addenda/cliac0902/Grover0902N.pdf>

While there has been a recent expansion of technologist and technician training programs,³⁹¹ total enrollment in accredited programs has fallen in the last 20 years. Similarly, the number of new certifications of lab workers decreased during the 1980s and 1990s. Vacancy rates for clinical laboratory workers in 2002 were approximately 16% higher than the average unemployment rate, at about 7%, reflecting the inadequate supply.³⁹² The American Association of Clinical Chemistry (AACC) and the American Society of Clinical Laboratory Science (ASCLS), two of the leading professional associations representing the clinical laboratory industry, project that there will be only 4,000-5,200 of the estimated 12,000-13,000 annual graduates required to meet demand for clinical laboratory personnel from 2002 to 2012. These estimates, based on projections of the US Bureau of Labor Statistics, indicate a deficit of up to 60-69% in specialized/certified clinical laboratory personnel during this period.³⁹³

Several other factors have contributed to increasing vacancy rates and few new entrants of these workers. These include relatively low salary levels compared to occupations with similar training requirements, stressful working conditions, lack of visibility on the health care team, risk of contracting infectious diseases and limited opportunities for advancement in some cases.³⁹⁴ These problems are likely to be exacerbated by demographic factors in lab medicine. About 75% of technologists are women, and the field increasingly has been forced to compete with a growing number of other occupations as historical gender limitations to occupational choice have decreased.

Data on the scientific workforce, both internal and external to the diagnostics industry, often are incomplete and inaccurate. As a result, the ability to understand current and future workforce needs is limited. However, the diagnostics workforce is likely to see rapid growth over the next several decades, as the aging population increases demand for all health care services and the proportion of working age individuals decreases.

³⁹¹ Grover A. Clinical laboratory workers. Proceedings of the Clinical Laboratory Improvement Advisory Committee; 2002 Sept 12; Atlanta, GA. Accessed November 24, 2004. <http://www.phppo.cdc.gov/cliacc/pdf/Addenda/cliacc0902/Grover0902N.pdf>

³⁹² Ward-Cook K, Chapman S, Tannar S. 2002 wage and vacancy survey of medical laboratories. part II: modest easing of staffing shortage. *Lab Med* 2003;10(34):702-07. http://www.futurehealth.ucsf.edu/pdf_files/WageVacSurvey2002_2.pdf.

³⁹³ American Association of Clinical Chemistry. Accessed 2004. <http://www.ascls.org>, the American Society of Clinical Laboratory Science. Accessed 2004. <http://www.aacc.org>, and the US Department of Labor, Bureau of Labor Statistics. Accessed 2004. <http://www.bls.gov>.

³⁹⁴ Grover A 2002.

VII. The Value Chain of Diagnostics: Direct and Cumulative Impacts on Health Care, Outcomes and Costs

Diagnostics are an essential component of modern health care that deliver critical information to physicians and patients. Beyond informing an initial diagnosis, the utility of diagnostics spans the continuum of care from early detection to health outcomes. This chapter addresses the following key points on the health and economic value of diagnostics.

- Diagnostics comprise only a small fraction of total hospital and Medicare costs (5% and 1.6% respectively), but may influence as much as 60-70% of health care decision-making.
- Appropriate use of diagnostics is integral to high quality health care, including informing earlier, more targeted health care interventions and averting adverse health outcomes and unnecessary costs. Diagnostics have integral roles in nationally recognized, evidence-based health care quality measures and clinical practice guidelines.
- The value of diagnostics extends well beyond detecting and diagnosing disease. Diagnostics enable physicians and patients to:
 - assess disease risk sooner
 - detect and diagnose disease before symptoms occur
 - identify health or environmental threats before infection spreads
 - use more preventive and less invasive treatment options
 - access health interventions earlier to minimize or stop disease progress
 - select appropriate treatments that reduce patient risk and increase effectiveness
 - estimate patient prognosis and manage treatment
- Diagnostics have resulted in substantial reductions in morbidity and mortality, improvement in health outcomes and quality of life and reduction of per patient health care costs.
- Diagnostics serve a key role in the health care value chain by directly and indirectly influencing quality of care, outcomes and resource use. Current and future diagnostics offer the health system significant opportunities to increase the quality and efficiency of health services delivery and reduce downstream costs.
- While some diagnostics are overused, many diagnostics that are recommended as standards of care and supported by clinical evidence are grossly underused in practice. Diagnostic underuse has significant implications for quality and cost of care in the US.
- Advances in health information technology can further increase the value of diagnostics for more targeted/personalized patient decisions and broader health system decision-making.
- Optimizing the health and economic value of diagnostics will require collaboration of multiple health stakeholders, particularly in immediately actionable areas such as refining existing regulatory and reimbursement mechanisms.

This chapter examines ways in which diagnostic information affects health care decision-making across the continuum of care and the ability to deliver more effective and efficient health care services.

Also addressed are implications for technology innovation and access to diagnostic technologies, health reform and cost containment efforts, and opportunities for change in the US health system. Examples include “breakthrough” technologies that can significantly advance detection and management of disease, as well as commonly used tests that build value incrementally as tests are refined, integrated and offered in more flexible formats.

A. Overview of the Value of Diagnostics

Diagnostic tests are an essential link in the health care value chain. While diagnostic tests represent less than 5% of hospital costs and about 1.6% of total Medicare costs, these tests influence a much larger percentage of health care decision-making and spending.³⁹⁵ Diagnostics are used for much more than establishing a diagnosis. They also are essential in identifying individual risk for developing disease, selecting safe and effective treatments, planning disease management strategies and estimating treatment response throughout the course of care. Evidence quantifying the relationship between diagnostic interpretation and health care decision-making remains limited. A hospital-based estimated indicated that diagnostic information may leverage approximately 60-70% of health decision-making.³⁹⁶

Recommended use of diagnostics is linked to improvements in morbidity and quality of life, as well as reductions in overall mortality. The value of diagnostic information across the patient care continuum not only is evident in improved health status and patient outcomes, but in considerable cost savings that can accrue from informed health decision-making. In some cases, recommended diagnostic use has enabled 30-50% reductions in direct hospital and outpatient charges by detecting key changes in health status, allowing adjustment of treatment to improve health outcomes.³⁹⁷

Next-generation diagnostics typically improve on the efficiency, integration and other features of existing modalities. These diagnostics can add downstream value via evolving features such as greater accuracy, higher throughput, reduced testing/staff time, portability, etc.

Future diagnostics hold the potential to change existing paradigms for delivery of health services. Scientific and technological advances are positioning diagnostics to leverage an even greater proportion of health care decisions. These emerging diagnostics will improve understanding of complex patient-specific disease states and characterize population-level health risks and trends. This knowledge will enable delivery of therapies targeted to specific patient needs and more responsive and informed disease management. Emerging diagnostics will expand health assessment capabilities, enable more responsive real-time decisions and offer opportunities to achieve systematic and operational efficiencies in care. Such options may result in improved patient outcomes and quality of life, fewer side effects and more cost-effective care.³⁹⁸

At the health system level, diagnostic information will continue to influence and alter health assessment practices and care delivery in the 21st century. Since diagnostic information currently comprises about 60% of the content of electronic patient medical records, it can contribute to tracking utilization of health resources and understanding variations in the quality of available health services.

³⁹⁵ Medicare laboratory payment policy: now and in the future. Washington, DC: Institute of Medicine, National Academy Press, 2000. Accessed October 22, 2004. http://books.nap.edu/html/mlpp/index_pdf.html.

³⁹⁶ Forsman RW. Why is the laboratory an afterthought for managed care organizations? *Clin Chem* 1996;42:813-16.

³⁹⁷ Ibid.

³⁹⁸ Coverage and reimbursement of genetic technologies and services. Draft report of the Secretary's Advisory Committee on Genetics, Health and Society. Washington, DC 2004.

Diagnostic information is used more frequently by public and private payers, health care purchasers (e.g., employers) and other stakeholders to gauge the extent to which evidence-based quality health services are provided. This provides a means for continuous quality improvement in health services delivery and should contribute to significant improvements in quality and less wasteful health spending.

Among the Health Plan Employer Data and Information Set (HEDIS) quality measures used in 90% of US managed care organizations and thousands of individual provider sites nationwide, 23% involve measures of diagnostic use.³⁹⁹ When cross-referenced to evidence-based clinical practice guidelines, more than 60% of HEDIS quality measures are influenced by diagnostics. Of the 34 quality measures included in the CMS pilot study, the Premier Hospital Quality Incentive Demonstration involving 278 hospitals of Premier Inc., three are direct measures of diagnostic use and approximately 18 are informed by diagnostic tests. This indicates that diagnostics play a substantial role in evidence-based decision-making and are integrally tied to quality of care.

In diabetes, cardiovascular disease, colorectal cancer and breast cancer, the NCQA linked insufficient compliance with diagnostics-based quality measures to 56,200 avoidable adverse health events (e.g., heart attack, stroke, amputation), up to 34,000 avoidable deaths and \$899 million in avoidable health care costs in 2004.⁴⁰⁰ In these important instances, diagnostic information is essential to tracking quality of care available from health providers and identifying opportunities to intervene earlier and in a more targeted manner to avert unnecessary adverse health outcomes and spending.

Many diagnostics that are recommended as standards of care are grossly underused in practice. A recent sentinel study conducted by the RAND Corporation reported that diagnostics were underused on average 51% of the time, based on analysis of 102 diagnostics-based quality indicators in 30 preventive, acute and chronic condition areas. Such underuse may have significant implications for quality of care and outcomes. Even marginal improvements in many of these key disease areas could translate into substantial gains in health outcomes and lower costs.

Given escalating health care costs, stakeholders in the health care value chain are increasingly pressured to restrain costs while maintaining or improving quality. Considering their integral role in all phases of care, diagnostics afford substantial opportunity to improve quality and cost.

Despite their potential and realized value, certain internal and external constraints, including regulatory, reimbursement, market, scientific/technical issues, bureaucratic inertia and societal issues, can inhibit the development and adoption of diagnostic products. Progress in actionable areas, such as improvements in regulation and reimbursement of diagnostics, can stimulate innovation, expedite access to critical health technologies and further enhance their health and economic benefits.

³⁹⁹ HEDIS is a set of performance measures that are designed to ensure that patients have the necessary information to compare the performance of different managed care plans.

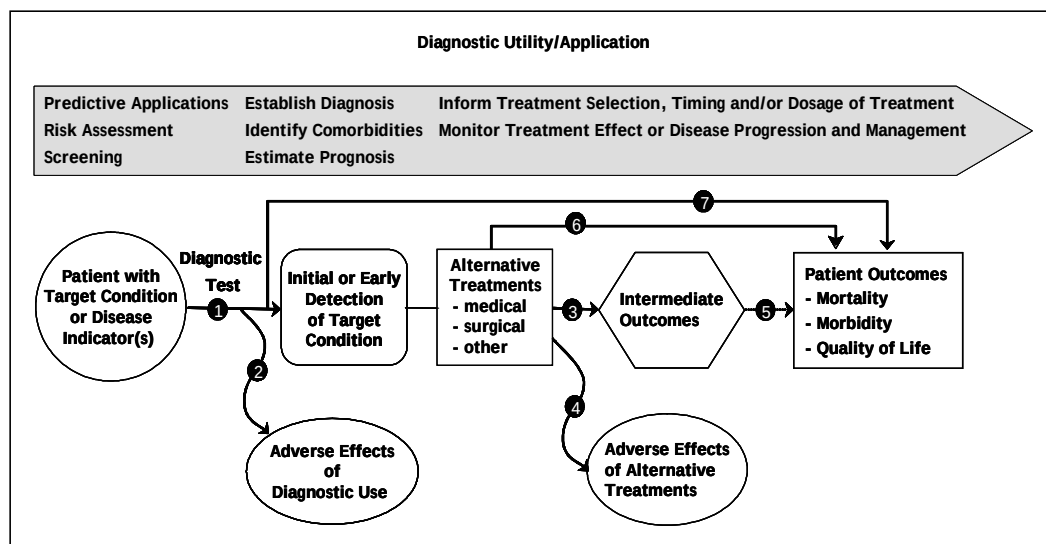
⁴⁰⁰ The NCQA is a private, not-for-profit organization committed to improving health care quality through provision of information to consumers and accreditation of managed care organizations.

B. The Clinical Analytic Framework as a Model for Assessing Value

The implications of diagnostic use across the continuum of care from disease detection or diagnosis to patient outcomes can be considered using a “clinical pathway” or “analytical framework” (**Figure 7.1**). These frameworks frequently are used by health care professionals (e.g., for technology assessment and developing practice guidelines), third-party payers and health services researchers to organize and evaluate evidence pertaining to the relationships among diagnostic test use, treatment decisions, adverse effects, intermediate or surrogate outcomes and health outcomes.

Direct evidence of causal relationships between diagnostic use and improved patient outcomes (#7 in **Figure 7.1**) is a persuasive way to demonstrate clinical impact of diagnostics.⁴⁰¹ However, given what may be multiple intervening steps between accurate diagnostic results and improved health outcomes, it can be complicated (in some cases, virtually impossible), costly and time-consuming to conduct studies that provide such direct evidence. Doing so may entail large patient populations, difficulty in accounting for confounding factors (e.g., use of various treatment modalities) that may affect outcomes and lengthy follow-up. In some instances, it may be difficult or impractical to randomize patients to alternative diagnostic arms of a trial or to a diagnostic arm vs. a usual care (or non-intervention or watchful waiting) arm.

Figure 7.1
Sample Clinical Analytic Framework: From Diagnosis to Patient Outcomes



1. Is a particular diagnostic test accurate for the target condition?
2. Does diagnostic use result in adverse effects or harms?
3. Do treatments change intermediate health outcomes? (e.g., cholesterol levels, tumor size)
4. Do treatments/health interventions result in adverse effects?
5. Are changes in intermediate outcomes associated with changes in health outcomes?
6. Does treatment improve health outcomes?
7. Is there direct evidence that diagnostic use improves health outcomes?

Source: Adapted from Harris, Helfand, Woolf, et al. 2001.

⁴⁰¹ Development of direct evidence typically involves conducting prospective, controlled clinical studies – ideally, randomized controlled trials (RCTs) – following patient populations from diagnostic use that influences treatment decisions that affect health outcomes.

More frequently, the impact of diagnostic use on health outcomes can be demonstrated by linking separate bodies of existing evidence across the analytic framework. For example, the first link is for evidence that a test produces accurate results (e.g., high sensitivity and/or specificity, #1 in the framework). In turn, this can inform treatment decisions, such as whether to use particular drugs, devices or surgical procedures. Also relevant is whether a test has adverse effects or changes the incidence of these compared to previous tests, such as through less invasive testing or even psychological/social effects of the knowledge of disease risk (#2). Further evidence may demonstrate that these treatments affect intermediate outcomes, such as lipid levels, blood pressure or tumor regression (#3).⁴⁰² Of course, alternative treatments may have their own adverse effects, such as drug reactions or surgical complications (#4). In turn, evidence may show that changes in intermediate outcomes result in improved health outcomes such as incidence of heart attacks or strokes or cancer survival (#5). In some instances, there may be direct evidence that the treatments result in improved health outcomes (#6).^{403,404}

Even a chain of indirect evidence can be difficult to assemble, given differences in patient groups, clinical study designs and other variations among separately conducted studies. Challenges of assembling rigorous evidence linking the use of a test to treatment decisions and to changes in intermediate outcomes and improvements in health outcomes can pose significant hurdles to access, particularly for being incorporated into clinical practice guidelines or coverage policies.⁴⁰⁵ As discussed in **Section V: US Reimbursement for Diagnostics**, differing evidence requirements for FDA approval and third-party reimbursement can complicate and add costs to efforts to build an evidence base that can address these hurdles to market and patient access.

Evidence supporting improvements in intermediate outcomes or surrogate markers (e.g., reduction of protein or enzyme levels in conditions, such as coronary heart disease or cancer), #3 in the framework, may be insufficient to secure regulatory approval and third-party reimbursement. This is because intermediate outcome measures not always are known to be linked to improvements in mortality, morbidity and quality of life. However, once intermediate outcomes or surrogate markers are validated as predictive of health outcomes, regulators and payers should not require that these relationships be re-established with costly and time-consuming studies for new technologies that achieve these intermediate outcomes or surrogate markers.

⁴⁰² In many instances, the latter links in the evidence chain are well established, and it is only necessary to demonstrate that a diagnostic test yields accurate results for detecting or diagnosing a patient condition (#1). For example, if it is well established that accurate information about lipid levels and patient history can be used to inform treatment decisions (e.g., regarding diet, exercise and use of statin drugs) that are known to improve intermediate endpoints (e.g., blood lipids) that are, in turn, known to result in longer term improvements in health outcomes (reduced angina and fatal and non-fatal heart attacks), then it only may be necessary to show that a new test for blood lipids is at least as accurate as existing tests, and perhaps that this test is easier to use, less expensive or has other benefits.

⁴⁰³ Harris R, Helfand M, Woolf S, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(3S):21-35.

⁴⁰⁴ Mulrow C, Langhorne P, Grimshaw J. Integrating heterogeneous pieces of evidence in systematic reviews. In: Mulrow CD, Cook DJ, eds. *Systematic reviews: synthesis of best evidence for health care decisions*. Philadelphia: American College of Physicians, 1998:103-12.

⁴⁰⁵ Ibid.

More transparent guidance regarding validation of intermediate outcomes and acceptance of validated intermediate measures as surrogates for longer-term outcomes offers significant benefits to all health stakeholders. These benefits would include reduction of product development times and more rapid patient access to diagnostic and treatment technologies that are demonstrated to improve health outcomes.⁴⁰⁶

Applying the Analytic Framework for Understanding Value

The analytic framework is useful for showing how diagnostics influence downstream care decisions and patient outcomes. Diagnostic information has a variety of care-related applications, including: a) determination of patient risk for developing disease before it occurs; b) ruling in/ruling out disease, detection of disease at an early stage and establishment of an accurate diagnosis; c) identification of appropriate medication, treatment risks and/or targeted treatment selection; d) determining patient prognosis, treatment effectiveness and applications for management of chronic conditions; and e) identification of environmental risks to patients or the public health. These applications and their impacts on patient care decisions and outcomes are discussed below.

C. Understanding the Value of Diagnostics in Patient Care

1. Estimating Patient Risks for Developing Disease

Recent advances in understanding the role of genetics and molecular biology in disease development have led to the emergence of a more diagnostic tests of disease susceptibility. These tests can help health practitioners estimate individual patient likelihood for developing a particular disease or condition (e.g., breast cancer, cystic fibrosis, colon cancer) or having certain genetic disease risks (e.g., for sickle cell anemia, Tay-Sachs disease, Huntington's disease).

Knowledge of certain predispositions can offer patients options for preventive action and early treatment.^{407,408,409,410} Maintained by NIH, the Gene Tests website provides current, authoritative information on over 700 genetic tests and their use in diagnosis and patient care and counseling and decision-making.⁴¹¹

Developing direct or even indirect evidence linking a test for predisposition to disease development, e.g., presence of genetic markers of risk for disease development, to improved health outcomes can be technically and clinically challenging and costly. Patients with particular susceptibility traits do not yet have detectable disease, only a certain risk level for developing disease and, in most cases, cannot be treated yet. Studies that link a subgroup of

⁴⁰⁶ Coverage and reimbursement of genetic tests and services. Draft report. Public comment draft. Washington, DC: US Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, April 2005.

⁴⁰⁷ Genomics and population health: United States, 2003. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, 2004. Accessed October 22, 2004. <http://www.cdc.gov/genomics/>.

⁴⁰⁸ Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA 2001;285:540-4.

⁴⁰⁹ Yang Q, Khoury MJ, Botto L, et al. Improving the prediction of complex diseases by testing for multiple disease susceptibility genes. Am J Hum Genet 2003;72:636-49.

⁴¹⁰ Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy-makers and the public. Am J Epid 2001;156(4):311-8.

⁴¹¹ Gene Tests. Seattle, WA: 2004. Accessed September 19, 2004. www.geneclinics.org.

patients with a particular disease to specific genetic traits that may have caused the disease commonly are performed in preclinical research settings. However, clinical studies that translate these observations into evidence that patients with one or a set of genetic traits actually will develop disease are much more difficult to conduct.

Although these tests identify patient-specific risk for disease development, this knowledge is not always actionable (e.g., via early treatment, behavioral modification). Many general health practitioners currently are not trained to interpret susceptibility results and provide appropriate genetic counseling. As such, emerging susceptibility diagnostics can pose significant challenges to the health care system.^{412,413} Some of the important challenges are the following.

- **Generation of sufficient evidence to establish medical necessity and support coverage determinations by third-party payers**, especially in cases where no clear treatment or preventive options exist.
- **Appropriate patient and practitioner interpretation and use of disease susceptibility test results.**
- **Circumstances for use and coverage of susceptibility diagnostics.** For example, coverage may be limited to patients at high risk (improved likelihood of detection at reduced costs) versus coverage of a broader population with a lower average risk (reduced likelihood of detection at higher costs).
- **Concerns regarding potential for discrimination** by health insurers, employers and others following identification of heightened risk for disease development.

Payers and providers demand substantial proof that such tests offer measurable value.^{414,415,416} BRCA I/II testing for genetic susceptibility to breast cancer is one example of a relatively new diagnostic that has faced significant coverage obstacles. In one survey published in 2000, only 4% of insurance providers (including HMOs, PPOs, indemnity plans and self-insured employer plans) had granted coverage of BRCA testing. In this survey, 55% of respondents cited concerns about the high cost of BRCA testing, averaging \$2,400 per patient.⁴¹⁷ However, the coverage and reimbursement climate for predictive genetic tests such as BRCA may have improved recently, as noted in recent testimony from an industry representative, as follows.

In 1996, two of the greatest barriers to genetic testing were the fear of discrimination and the unknown rate of reimbursement from insurance carriers. Since 1997, I have been responsible for securing coverage and reimbursement for genetic testing from health insurers and managed care organizations nationwide. [Our] experience is such that genetic testing for common hereditary cancer syndromes is paid by insurers 90 percent of

⁴¹² Col NF. The use of gene tests to detect hereditary predisposition to chronic disease: is cost-effectiveness analysis relevant? *Med Decis Making* 2003;5:441-8.

⁴¹³ Schoonmaker MM, Bernhardt BA, Holtzman NA. Factors influencing health insurers' decisions to cover new genetic technologies. *Int J Technol Assess Health Care* 2000;16(1):178-89.

⁴¹⁴ Bruns, D. Laboratory-related outcomes in healthcare. *Clin Chem* 2001;47(8):1547-52.

⁴¹⁵ Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy-makers and the public. *Am J Epid* 2001;156(4):311-18.

⁴¹⁶ Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Affairs* 2004;23(1):77-87.

⁴¹⁷ Schoonmaker MM, Bernhardt BA, Holtzman NA. Factors influencing health insurers' decisions to cover new genetic technologies. *Int J Technol Assess Health Care* 2000;16(1):178-89.

*the time at an average of 90 percent coverage. Therefore, the insurance coverage barrier has effectively been eliminated.*⁴¹⁸

Despite improvements in coverage opportunities, use of current and emerging genetic susceptibility tests is more likely to be initially limited to certain well defined high-risk subpopulations. Targeting coverage to subpopulations at greatest risk may be a more cost-effective strategy for many existing and emerging susceptibility tests.

A recently developed susceptibility test for cardiac channelopathies (certain heart rhythm abnormalities) illustrates current and potential benefits and challenges of predictive diagnostic use, including considerations for test innovation and patient access.⁴¹⁹ This example is explained in **Example 7.1**.

Example 7.1 **Cardiac Channelopathy Testing**

Cardiac channelopathies, which include familial long QT syndrome (LQTS) and Brugada syndrome, are conditions that affect the electrical system of the heart and predispose affected individuals to abnormal heart rhythms (dysrhythmias) that can result in severe angina, dizziness, cardiac arrest, and sudden death.^{420,421,422} These cardiac conditions can be genetically inherited or acquired. Currently, diagnostic tests are available that sequence the DNA of certain genes to identify genetic variations that increase risk for potentially fatal dysrhythmias.

The US incidence of sudden cardiac death (SCD) is an estimated 365,000 deaths per year.⁴²³ Of these deaths, familial LQTS (a common cardiac channelopathy) has been linked to SCD in young people (approximately 2,000-3,000 deaths per year) and is a potential cause of sudden infant death syndrome (SIDS). LQTS has been estimated to affect approximately 1 per 5,000 individuals in the US, with 500-1,000 new carriers born each year. There is no cure for cardiac channelopathies, and identification of those at risk does not directly predict the likelihood of an adverse cardiac event in a particular patient. However, this information does allow physicians and high-risk patients to identify proper medical management strategies, including lifestyle modification, β -blocker therapy and potential use of implantable cardioverter-defibrillators (ICDs).⁴²⁴ Such a preventive strategy would be analogous to use of medical management strategies to reduce the risk of seizures in epileptic patients.

⁴¹⁸ Testimony of Mr. Gary Martucci, Myriad Genetic Laboratories. Secretary's Advisory Committee on Genetics, Health, and Society meeting transcripts. Public comments 10/18. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, October 18-19, 2004. Accessed December 10, 2004. http://www4.od.nih.gov/oba/SACGHS/meetings/October2004/transcript/Public_Comments_101804.pdf.

⁴¹⁹ Molecular tests: cardiac mutations. New Haven, CT: Genaissance Pharmaceuticals, Inc. Accessed September 17, 2004. http://www.genaissance.com/products_services/cardiac_mutations.html.

⁴²⁰ Hampton CT. Long QT syndrome: more common than you thought. Clinician Reviews 2003;13(1):40-6.

⁴²¹ Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. Circulation 2001;104(5):557-62.

⁴²² Khositseth A, Ackerman MJ. Clinical evaluation, risk stratification, and management of congenital long QT syndrome. In Gussak I, Antzelevitch C, eds. Cardiac repolarization: bridging basic and clinical science. Totowa, NJ: Humana Press, 2003.

⁴²³ An overview of the inherited long QT syndrome and sample materials. Salt Lake City, UT: Sudden Arrhythmia Death Syndrome (SADS) Foundation. Accessed September 17, 2004. <http://www.sads.org/LQTS.html>.

⁴²⁴ Schwartz PJ, Priori SG, Dumaine R, et al. A molecular link between the sudden infant death syndrome and the long-QT syndrome. N Engl J Med 2000;343(4):262-67.

In addition to the inherited form of this condition, fatal LQTS can be environmentally triggered in individuals with certain genetic predispositions by the use of various common medications such as certain antibiotics, cancer treatments, anti-nausea drugs, and anti-psychotics. Many other drugs, such as certain appetite suppressants and decongestants, have been associated with heightened risk for LQTS. The University of Arizona Center for Education and Research on Therapeutics (CERTs), funded in part by AHRQ, currently tracks and conducts research on QT-prolonging drugs that pose significant risks to patients with cardiac channelopathies.⁴²⁵

As knowledge of diagnostic techniques for identifying cardiac channelopathies evolves, these tests may enhance clinical research and drug development. Also, it may help reduce medication errors by identifying individuals at risk for disabling or fatal cardiac events precipitated by certain medications. At present, cardiac channelopathy testing is only indicated for individuals with known risk factors, including patients with a personal or family history of certain abnormal cardiac events or abnormal electrocardiograms not attributable to QT-prolonging drugs.

Growing understanding of the applications of these technologies may contribute to an expanded role for susceptibility testing and effective disease prevention.⁴²⁶ Still, the current lack of well-defined processes for evaluating gene-based and other susceptibility tests will affect their adoption, diffusion and reimbursement. Ambiguous regulatory and reimbursement mechanisms can result in increased use of some clinically unsupported tests and exclusion of other beneficial ones. Inappropriate payment level determinations for some diagnostic technologies that can inhibit adoption and long-term data collection required to establish whether a novel technology offers advantages relative to existing diagnostic modalities.⁴²⁷

The value of susceptibility tests for improving outcomes, quality of life and cost-effectiveness will increase with understanding of the interactions among various metabolic/physiological systems and gene/environment relationships. Early evidence for benefits of identifying patients at high risk for developing certain diseases with viable preventive or treatment alternatives exists for diseases such as breast, colon, ovarian and pancreatic cancers; and heart and cerebrovascular diseases.^{428,429} This knowledge can enable patients to alter health and life strategies and adopt preventive regimens that reduce the likelihood of adverse health outcomes.

⁴²⁵ Drugs that prolong the QT interval and/or induce Torsades de Pointes ventricular arrhythmia. Tucson, AZ: The University of Arizona Center for Education and Research on Therapeutics (CERT), 2004. Accessed October 22, 2004. <http://www.torsades.org/medical-pros/drug-lists/drug-lists.htm>.

⁴²⁶ Melzer D, Raven A, Detmer D, et al. My very own medicine: what must I know? Information policy for pharmacogenomics. Cambridge, England: University of Cambridge, 2003. Accessed October 22, 2004. <http://www.phpc.cam.ac.uk/epg/Report.pdf>.

⁴²⁷ Coverage and reimbursement of genetic tests and services. Draft report. Public comment draft. Washington, DC: US Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, April 2005.

⁴²⁸ Ibid.

⁴²⁹ Hereditary cancer testing. Salt Lake City, UT: Myriad Genetics, Inc. Accessed September 19, 2004. <http://www.myriad.com/med/index.htm>.

2. “Rule In” or “Rule Out” Disease, Detect Diseases at the Earliest Stage and Establish an Accurate Diagnosis

a. Value of Ruling In or Ruling Out Disease

Diagnostics inform appropriate patient care decisions under specific clinical circumstances. A diagnostic used for ruling in a disease or condition confirms that it may be present and that further testing may be required or that a patient should be treated if the disease is present. Ruling out a disease enables the clinician to pursue other avenues of diagnosis or treatment, while not wasting resources or time pursuing the ruled out disease.

An example is the brain natriuretic peptide (BNP) assay, increasingly used for ruling out heart failure.^{430,431} In this instance, patients suspected or at high risk of having heart failure receive a BNP assay. If results are within normal range, clinicians can rule out heart failure. An abnormal BNP assay signals the clinician to conduct further diagnostic procedures (e.g., imaging tests) to make a final clinical determination.⁴³² In this way, BNP testing enables appropriate triage of patients and averts unnecessary and often more costly application of *in vivo* testing modalities. In this and other tests, accurate rule in/rule out determinations protect patients from unnecessary further testing and/or treatments that themselves can pose risks to safety and significantly increase costs.

b. Benefits of Detecting Disease at the Earliest Stages

Novel diagnostics are poised to play an even greater role in the health care value chain by enabling more timely, targeted and cost-effective interventions for a range of debilitating and costly conditions.^{433,434} The clinical scope and accuracy of diagnostics is increasing with knowledge of science and human health. The Human Genome Project and integrated scientific and computational approaches to understanding human biology and disease have enabled development of a new generation of gene-based and other molecular diagnostics. These emerging diagnostics can detect more diseases and risk factors earlier and with greater accuracy. Earlier detection, in turn, can inform selection of safe, effective and appropriate preventive or therapeutic interventions.

While many diagnostics can be used for screening asymptomatic patient populations, most currently are used for disease detection in symptomatic patients. The Medicare statute does not provide for reimbursement for screening and prevention services, except as the law has been amended by Congress for particular tests. Only in recent years has Congress granted coverage for such interventions, including three diagnostic tests (Pap smear, fecal occult blood test,

⁴³⁰ Cowie MR, Mendez GF. BNP and congestive heart failure. *Prog Cardiovasc Dis* 2002;44(4):293-321.

⁴³¹ Hobbs FD, Davis RC, Roalfe AK, et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. *BMJ* 2002;324(7352):1498.

⁴³² Remme WJ, Swedberg K. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22(17):1527-60.

⁴³³ French ME, Moore JB. Harnessing genetics to prevent disease and improve health: a state policy guide. Washington, DC: Partnership for Prevention, 2003.

⁴³⁴ Cancer prevention & early detection: facts and figures 2003. Atlanta, GA: American Cancer Society, 2002. Accessed October 22, 2004. http://www.cancer.org/docroot/STT/stt_0.asp.

prostate-specific antigen test).⁴³⁵ Also, as part of MMA 2003, Medicare beneficiaries will be eligible for preventive blood lipid (e.g., cholesterol) and diabetes screening tests effective January 2005.^{436,437}

There is a growing body of evidence supporting screening of asymptomatic patients with high risk for developing disease due to family history, comorbidities and other risk factors. This includes many diagnostics that have been reviewed by the US Preventive Services Task Force and the Cochrane Collaboration, two groups internationally regarded for high evidence standards and rigorous systematic reviews of evidence.^{438,439} Future diagnostics, including some currently in the R&D pipeline, will have strong potential as screening tests for pre-emergent and early disease in high-risk patients and stratifying individual and population risks for developing disease.^{440,441}

c. Implications of Establishing an Accurate Diagnosis

The importance of diagnostic information in establishing accurate diagnoses and informing subsequent testing, treatment and other health decisions is reflected in **Figure 7.2**. This table illustrates how diagnostics are used routinely in 15 of the leading medical condition categories in the US.⁴⁴² This table also reflects the potential for diagnostics to leverage decision-making and affect quality of care as gauged by existing evidence-based clinical practice guidelines and the magnitude of clinical and economic burden in each of these leading disease areas.

⁴³⁵ A better Medicare for healthier seniors: recommendations to modernize Medicare's prevention policies. Washington, DC: Partnership for Prevention, 2003.

⁴³⁶ Medicare preventive benefits begin January 2005 with a goal of healthier seniors. News release. Washington, DC: US Department of Health and Human Services, 2004. Accessed November 30, 2004. <http://www.hhs.gov/news/press/2004pres/20041109.html>.

⁴³⁷ CMS-1429-F Medicare Physician Fee Schedule final rule summary and significant issues fact sheet. Charlotte, NC: Premier, Inc., 2004. Accessed November 30, 2004. <http://www.premierinc.com/all/advocacy/issues/108/04/medicare/physician-fee-05-factsheet-1104.pdf>.

⁴³⁸ Topic index: A-Z. Rockville, MD: US Preventive Services Task Force, 2004. Accessed October 22, 2004. <http://www.ahrq.gov/clinic/uspstf/uspstoptics.htm>.

⁴³⁹ The Cochrane Collaboration. Oxford, England: 2004. Accessed October 22, 2004. <http://www.cochrane.org/index1.htm>.

⁴⁴⁰ Paul NW, Roses AD. Pharmacogenetics and pharmacogenomics: recent developments, their clinical relevance and some ethical, social, and legal implications. *J Mol Med* 2003;81:135-40.

⁴⁴¹ The genomics outlook to 2005: transforming pharmaceutical and diagnostic markets. Healthcare Reports. London, England: Reuters Business Insights, 2002.

⁴⁴² Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health care spending? *Health Affairs* 2004;W4-437.

Figure 7.2
Utility of Diagnostics in Detecting Disease or Disease-state in 15 Medical Conditions
where Spending Increased the Most During 1987-2000

Condition	Specific Diagnostics Used to Rule in Specific Disease or Condition	Specific Diagnostics Used to Rule Out Specific Disease or Condition	Diagnostic Recommended for Establishing Diagnosis by Evidence-based Clinical Practice Guidelines*	Diagnostic Recommended for Patient Care or Disease Management by Evidence-based Clinical Practice Guidelines*	Treated Prevalence+ (per 100,000)	US Health Care Spending (billions)
Heart disease	Y	Y	Y	Y	6,226	\$56.7
Pulmonary	Y	Y	Y	Y	15,526	\$36.5
Mental disorders	Y	Y	Y	Y	8,575	\$34.4
Cancer	Y	Y	Y	Y	3,348	\$38.9
Hypertension	N	Y	N	Y	11,382	\$23.4
Trauma	Y	Y	N	Y	12,338	\$41.1
Cerebrovascular	Y	Y	Y	Y	854	\$15.0
Arthritis	Y	Y	Y	Y	6,966	\$17.7
Diabetes	Y	Y	Y	Y	4,260	\$18.3
Back problems	N	N	N	N	5,092	\$17.5
Skin disorders	Y	Y	Y	Y	7,990	\$12.4
Pneumonia	Y	Y	Y	Y	1,370	\$12.6
Infectious disease	Y	Y	Y	Y	5,841	\$9.9
Endocrine	Y	Y	Y	Y	7,322	\$10.8
Kidney	Y	Y	Y	Y	908	\$8.2
Totals	86.7%	93.0%	80.0%	93.0%	NA^	\$159.7

*Based on analysis of clinical practice guidelines available from the National Guideline Clearinghouse maintained by the Agency for Healthcare Research and Quality and PubMed/MEDLINE maintained by the National Library of Medicine.

+ "Treated prevalence" is the prevalence of individuals diagnosed with and treated for a particular condition

^ NA = not applicable.

Source: Adapted from Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health care spending? *Health Affairs* 2004;V4-437.

Focused searches of the National Guideline Clearinghouse and PubMed/MEDLINE indicate that diagnostics frequently are used to rule in or rule out specific conditions in the great majority of these most burdensome medical conditions. With the exception of the category of back problems, evidence-based guidelines call for at least one diagnostic to rule in or rule out a specific disease or condition within each overarching disease category. For example, the infectious disease category includes multiple diagnostic tests used to rule in or out a broad spectrum of diseases (chlamydia, smallpox, *E. coli*, etc.).

Of these 15 most burdensome disease categories, 13 have at least one diagnostic (and often many) for ruling in a specific disease and 14 have at least one diagnostic (and often many) for ruling out a disease. Further, evidence-based clinical practice guidelines recommend diagnostic use for establishing a diagnosis or informing other patient care or disease management decisions across 12-14 of these overarching categories. While **Figure 7.2** does not reflect the utility of individual diagnostics per category, it underscores the broad applicability of diagnostic information across these most burdensome conditions.

The value of individual diagnostic tests in these categories is addressed below. To better relate the benefits of individual diagnostics for accurately diagnosing or characterizing specific

conditions in these categories, three common tests are presented in **Figure 7.3**. For each diagnostic and condition, the potential avoidable events, deaths and costs are shown as derived by NCQA. If properly used and interpreted, diagnostic information may demonstrably reduce medical costs associated with treating some of the most costly diseases/conditions and can have critical impacts on patient morbidity, mortality and quality of life.

Figure 7.3
Contribution of Selected Diagnostic Tests to Avoidable Adverse Events, Deaths and Costs

Disease/ Condition	Diagnostic Test	Use	Annual Avoidable Events	Annual Avoidable Deaths	Avoidable Costs
Diabetes	HbA1c level	Manage glucose levels	14,000 heart attacks, strokes, or amputations	4,300-9,600	\$573 million
Colorectal cancer	Fecal occult blood test	Rule in risk for cancer	20,000 cases of colorectal cancer diagnosed/treated at a later stage	4,200-6,300	\$191 million
Heart disease	Cholesterol test	Assess risk for heart disease or heart attack	14,600 major coronary events	6,900-17,000	\$ 87 million

**Adapted from: The state of health care quality: industry trends and analysis. Washington, DC: National Committee for Quality Assurance, 2004.*

3. Targeting the Best Treatment

a. Targeted Treatment Selection: Implications for Therapy and Access

While diagnostics always have helped health practitioners to refine and select appropriate treatment options (#1-#3 in the analytic framework), scientific advancements have expanded the use and value of diagnostic tests for this purpose. In particular, genomics, proteomics and metabolomics are improving our ability to identify disease-related markers and develop specialized therapies targeted to those markers. Pharmacogenomics (PGx) refers to the science of using genomic technologies to enhance drug development and generate targeted therapies that are safer and more effective. Emerging PGx diagnostics allow physicians and patients to assess individual risks and benefits associated with a particular drug. This evolving personalized approach to medicine offers the potential to improve drug effectiveness, reduce adverse side effects and enhance cost-effective care.^{443,444}

A prominent example of using PGx diagnostics to identify patients best suited for targeted drug therapy is testing for HER2/neu overexpression, long used to estimate patient risk and prognosis in certain cancers. Measurement of HER2/neu overexpression can help determine whether a specific patient would respond well to certain cancer treatments. HER2/neu testing is used to identify patients who are more likely to respond to the breast cancer drug Herceptin, a drug that blocks expression of the HER2 protein, as discussed in a case example below.

⁴⁴³ Higashi M, Veenstra DL. Managed care in the genomics era: assessing the cost effectiveness of genetic tests. *Am J Manag Care* 2003;9:493-500.

⁴⁴⁴ Emilien G, Ponchon M, Caldas C, et al. Impact of genomics on drug discovery and clinical medicine. *Q J Med* 2000;93:391-423.

While currently only a small number of available targeted therapies have a directly-associated diagnostic that aids in appropriate patient selection, improved diagnostics increasingly will be important for the success of these products. For example, in areas where HER2/neu testing is inadequately covered, Herceptin sales growth has been limited, due to lack of physician access to the test and resulting reduced patient access to Herceptin.⁴⁴⁵

PGx technologies increasingly are used in clinical development of targeted drugs and diagnostics. The number of specialty/targeted cancer drugs increased by 33% in 2003, and approximately 44% of cancer drugs in Phase I-III clinical development are anticipated to emerge as specialty/targeted drugs, about 30% of which are in Phase III.^{445,446} As drug makers continue to develop targeted therapies, companies that do not have a diagnostics arm will need to increase their use of in-licensing, co-development and co-marketing strategies with diagnostic manufacturers to ensure market access for their products. The Herceptin experience underscores the direct relationship between reimbursement policies for diagnostics and patient access to targeted treatments.

Developing clinical and economic evidence to support payment for targeted diagnostic and treatment technologies can be particularly complicated. This is due to multiple interrelated factors. Technical factors include the confounding effects of complex physiological, genetic and environmental interactions on the relationship between a genetic test and health outcomes. Epidemiological factors include genetic, physiological and other variability across patient populations and differential risks/effects of treatments in patients with comorbidities.

b. Implications for Reduction of Medication and Other Treatment Risks

Diagnostic information also is valuable in helping health practitioners to identify potential risks of therapy accurately (from #3-#5 or #6 in the analytic framework) and to reduce adverse treatment outcomes. Patient-specific risk information can be obtained either prior to initiating treatment or at various stages of care for acute and chronic diseases. This type of risk information differs markedly from the information generated by many of the familial susceptibility diagnostics, because it is almost always clinically actionable. For instance, slow drug metabolism may lead to build-up of toxic drug levels, while ultra-rapid drug metabolism may result in an insufficient dosage, drug resistance (e.g., anti-retrovirals for HIV, cancer drugs, antibiotics) and allergic reactions that cause a host of other complications. Diagnostic information that prospectively allows identification of such risks can help health practitioners select alternate treatment modalities best suited for a particular patient.

Aside from genetically-based drug response risks, diagnostic information can aid targeting treatment selection, including identification of related factors such as:

- comorbidities (e.g., hypertension, diabetes, cerebrovascular diseases)
- reduced patient compliance with treatment regimens

⁴⁴⁵ Targeted cancer therapeutics: innovative drugs and their impact on the future of oncology. Healthcare Reports. London, England: Reuters Business Insights, 2004.

⁴⁴⁶ New medicines in development for cancer. Washington, DC: PhRMA, 2003. Accessed October 3, 2004. www.phrma.org.

- detection of potentially harmful serum drug or biochemical levels

Each of these elements is discussed in more detail below. While various existing diagnostics are beneficial for reducing treatment errors, the potential benefits of gene-based and other molecular diagnostics are great and may alter patient assessment in the future. This potential future utility of diagnostics is discussed in **Example 7.2**.

Lack of well defined processes for evaluating PGx and other diagnostics for targeted treatment selection and increasing thresholds of clinical, economic and cost-effectiveness evidence required by public and private payers may result in disincentives for diagnostic (and drug) development and restrict patient access to available and future technologies.^{447,448} Harmonious approaches that encourage key steps in development and reimbursement for technologies will encourage the development of next generation diagnostics that identify the safest and most effective treatments.⁴⁴⁹

Example 7.2
Future Value of Diagnostics to Estimate Drug Response and
Reduce Adverse Drug Reactions

Adverse drug reactions (ADRs) affect as many as 2.2 million people, cause up to 106,000 deaths and cost more than \$177 billion per year.^{450,451} This clinical burden would place ADRs as the 4th-6th leading cause of death in the US.⁴⁵² Relative rates of drug metabolism among patients can have significant effects on adverse drug reactions.

A well-studied group of enzymes in the liver, cytochrome p450 (CYP450) enzymes, play a substantial role in drug metabolism. Certain CYP450 enzymes are influential in metabolism of prescription drugs. For example, the drug-metabolizing enzyme CYP3A is responsible for metabolism of more than 50% of currently marketed drugs.⁴⁵³ At present, these enzymes are primarily used to identify patients at risk for ADRs in drug development trials. However, despite such safeguards of the drug development process, when drugs are made available to broader patient populations, ADRs can occur in patients with unanticipated risks, highlighting the need for PGx diagnostics.⁴⁵⁴

While rates of drug metabolism by each enzyme differ from one individual to another, each patient's CYP450 profile captures unique genetic information. Knowledge of patient CYP450 profiles for certain of these enzymes offers opportunities for health practitioners and patients to evaluate individual risks and prevent some proportion of ADRs. One small study of 100 psychiatric

⁴⁴⁷ Danzon P, Towse A. The economics of gene therapy and pharmacogenetics. *Value Health* 2002;5(1):5-13.

⁴⁴⁸ Danzon P, Towse A. The genomic revolution: is the real risk under-investment rather than bankrupt health care systems? *J Health Serv Res Policy* 2000;5(4):252-5.

⁴⁴⁹ Califf R. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Affairs* 2004;23(1):77-87.

⁴⁵⁰ To err is human: building a safer health system. Washington, DC: Institute of Medicine, National Academy Press, 2000.

⁴⁵¹ Lazarou J, Pomeranz B, Corey P. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279(15):1200-5.

⁴⁵² Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost of illness model. *J Am Pharm Assoc* 2001;41(2):192-9.

⁴⁵³ Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. *Ann Pharmacol Toxicol* 1998;38:389-430.

⁴⁵⁴ O'Kane D, Weinshilboum R, Moyer T. Pharmacogenomics and reducing the frequency of adverse drug events. *Pharmacogenomics* 2003;4(1):1-4.

patients taking anti-psychotic/anti-depressant medications reported preliminary data that the cost of treating patients with certain CYP2D6 genetic variants was \$4,000-6,000 per year more (\$4-6 million per 1,000 patients) than the cost of treating patients with average drug metabolism.⁴⁵⁵ While it is uncertain whether these savings apply to larger populations, these findings indicate the potential value of CYP450 diagnostics as they begin to emerge.

Of course, diagnostics cannot prevent all ADRs, particularly since validation of the relationship between patient genetic profiles, drug metabolism and patient outcomes is difficult. Still, these advances should result in significant gains in patient safety and quality of care. Also, identification of population subgroups that respond safely and effectively to therapies can enhance access to and distribution of health services.

4. Estimating Prognosis, Monitoring Treatment Effectiveness and Management of Chronic Diseases

Diagnostic tests can be used to: a) estimate patient prognosis (i.e., prediction of the probable course and outcome of a particular disease or condition; #1 or #3 in the analytic framework); b) monitor the effectiveness of treatment regimens (#3); and c) inform changes in treatment patterns necessary to achieve desired health outcomes (#5 or #6). Characterization of disease stage or severity informs treatment selection, timing and dose at key decision points.

a. Prognostic Information: Estimating Clinical Status and Selecting Treatment

Prognostic information is used to inform a variety of patient care decisions. The range of prognostic test applications can include, but is not limited to:

- **estimating patient-specific risks for initial or recurrent adverse health events** (e.g., stroke, heart attack, cancer metastasis)
- **identifying pre-surgical/pre-treatment risks** (e.g., comorbidities, infection, inflammation)
- **staging patients based on level of disease progression and other health-related risk factors** (e.g., obesity, smoking status)
- **determining patient admission and/or triage decisions** (e.g., for surgical, trauma, critically ill patients).

In addition to detecting presence or absence of disease, prognostic information helps health practitioners evaluate the benefits and risks of treatment options. While patient history and physician experience are important in estimating prognosis, modern diagnostics can offer more accurate characterization of patient status. An example of this is detection of cardiac biomarkers for rapid and accurate diagnosis of heart attack for patients presenting in the emergency room with chest pain. A key biomarker for this purpose, the protein troponin (see *Section 7.B.1*), is excreted by heart muscle cells in distress. Troponin testing has improved the ability of physicians to diagnose heart attacks substantially (nearly 100% specificity and

⁴⁵⁵ Chou WH, Yan FX, de Leon J, et al. Extension of a pilot study: impact from the cytochrome P450 2D polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol* 2000;20(2):246-51.

93-100% sensitivity for detecting heart muscle damage) within approximately 4-6 hours of symptoms and reduce the risk of debilitating heart damage or death.^{456,457}

b. Utility of Diagnostics for Monitoring Treatment Effectiveness

In addition to estimating patient prognosis, diagnostics are used to monitor safety and effectiveness of medical and surgical treatments. They can assist clinicians in determining whether a course of treatment should be changed, augmented or maintained in order to improve patient compliance or optimize treatment. Diagnostic tests for monitoring treatment effectiveness are valuable for detection of the following.

- **Change in disease status (i.e., gauged by changes in particular biomarkers such as blood lipids, hormones, enzymes, inflammatory markers)**

Alpha-fetoprotein (AFP) tests are used to monitor the effectiveness of therapy for patients with cancers of the liver, testes or ovaries. High levels of AFP usually indicate more advanced disease and a less favorable prognosis.⁴⁵⁸ Because AFP testing can help detect tumor growth, preliminary evidence suggests that serial estimation of AFP may be more effective than conventional imaging procedures alone in detecting metastasis and recurrence.⁴⁵⁹

- **Unintended adverse effects or harmful biochemical levels**

Clozapine, a medication for schizophrenia, is associated with liver toxicity and, in some cases, cirrhosis and other harmful health effects.⁴⁶⁰ In a study of 7,263 schizophrenic patients taking clozapine, 78% had elevated liver enzymes, an indicator of toxicity, as a result of treatment.⁴⁶¹ Because the medication has demonstrated substantial effectiveness in management of psychosis, diagnostic monitoring of liver enzymes is critical to enabling physicians to balance the beneficial treatment effects of clozapine with prevention of serious side effects that increase health risks and decrease patient compliance.

- **Patient compliance with certain prescribed health interventions**

Carbohydrate deficient transferrin (%CDT) is a diagnostic test for monitoring patient compliance with interventions for alcoholism. Blood levels of %CDT are elevated with continuous alcoholic consumption and persist for 2-3 weeks after the person ceases alcohol use.⁴⁶² In the US, 70-80% of alcoholics relapse; approximately 20,000 alcohol-induced deaths (not including motor vehicle fatalities) and 27,000 deaths from chronic liver disease and cirrhosis occur per year, and alcoholism-related direct and indirect costs are estimated at

⁴⁵⁶ Abadie JM. Cardiac markers and a failed algorithm: can accurate assessment of acute myocardial infarction be cost effective? *Military Medicine* 2002;167:683-7

⁴⁵⁷ Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2:75-84.

⁴⁵⁸ AFP Tumor Marker. Washington, DC: American Association for Clinical Chemistry, 2002. Accessed October 22, 2004. http://www.labtestsonline.org/understanding/analytes/afp_tumor/test.html.

⁴⁵⁹ Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. *Clin Liver Dis* 2001;5(1):145-59.

⁴⁶⁰ Erdogan A, Kocabasoglu N, Yalug I, et al. Management of marked liver enzyme increase during clozapine treatment: a case report and review of the literature. *Int J Psychiatry Med* 2004;34(1):83-9.

⁴⁶¹ Gaertner I, Altendorf K, Batra A, Gaertner HJ. Relevance of liver enzyme elevations with four different neuroleptics: a retrospective review of 7,263 treatment courses. *J Clin Psychopharmacol* 2001;21(2):215-22.

⁴⁶² Laboratory diagnostics: alcohol related disease. Roskilde, Denmark: Axis-Shield, 2000. Accessed October 22, 2004. <http://www.axis-shield.com/product/labdiag.cfm>.

\$185 billion per year. As such, monitoring of alcoholism treatment is important to adjustment of individual treatment strategies, prevention of relapse and avoidance of adverse health effects.^{463,464,465,466}

An important aspect of monitoring treatment effectiveness is therapeutic drug monitoring (TDM), which primarily involves the measurement of serum drug concentrations to track individual pharmacologic responses.⁴⁶⁷ Because of the safety risks and variable efficacy associated with certain medications (alone and in combination), TDM has evolved as an important tool for informing patient management decisions for many chronic diseases (e.g., diabetes, asthma and epilepsy) and for identifying or monitoring drug resistance risks (e.g., in HIV, cancer and tuberculosis). As the range of TDM tests continue to expand, health practitioners will be better equipped to understand medication risk and effects and tailor medical management strategies to the needs of individual patients.

A recent analysis of the impact of TDM in adults with generalized tonic-clonic epilepsy revealed that the patients undergoing TDM had reduced incidence of adverse events, such as hospital admissions, compared to those without TDM (8% vs. 40%).

In HIV, TDM diagnostics are evolving that allow health practitioners to identify particular strains of the HIV virus and select drugs to which the virus is not yet resistant. This not only ensures that patients are receiving suppressive medication that delays progression to AIDS, but reduces the rate by which various viral strains become resistant, extending the utility of existing treatments.

As predictive testing, treatment selection and TDM methods to adjust treatment regimens become increasingly integrated in the future, greater opportunities for improving quality of care and health outcomes (i.e., via safety and effectiveness improvements) will emerge. This more streamlined patient management approach also can generate downstream efficiencies in health resource utilization.

c. Applications in Chronic Disease Management

Chronic diseases are among the most prevalent and costly, yet preventable, of all health problems in the US. More than 25 million Americans suffer chronic disabling conditions that result in decreased quality of life, and more than 1.7 million Americans die per year from chronic diseases.⁴⁶⁸ Improvements in prevention and chronic disease management have been

⁴⁶³ Alcoholism: getting the facts. Bethesda, MD: The National Institute on Alcohol Abuse and Alcoholism, 2004. Accessed October 22, 2004. <http://www.niaaa.nih.gov/publications/booklet.htm>.

⁴⁶⁴ Fast stats A to Z: alcohol use. Hyattsville, MD: National Center for Health Statistics, 2004. Accessed October 22, 2004. <http://www.cdc.gov/nchs/fastats/alcohol.htm>.

⁴⁶⁵ Becker HC. Kindling in alcohol withdrawal. *Alcohol Health and Research World* 2001;22(1):25-34.

⁴⁶⁶ Special report to the US Congress on alcohol and health. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, 2000. Accessed October 22, 2004. <http://www.niaaa.nih.gov/publications/10report/intro.pdf>.

⁴⁶⁷ Schumacher GE, Barr JT. Total testing process applied to therapeutic drug monitoring: impact on patients' outcomes and economics. *Clin Chem* 1998;44(2):370-4.

⁴⁶⁸ Chronic disease overview. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 2004. Accessed October 22, 2004. <http://www.cdc.gov/nccdphp/overview.htm>.

shown to reduce the number of adverse health events and save unnecessary medical costs.⁴⁶⁹ Several types of diagnostic tests are used commonly in chronic disease management for monitoring clinical status, including, e.g., finger stick tests to measure blood sugar levels in diabetics, cholesterol tests for patients with coronary artery disease (CAD) and viral load and CD4 tests for patients with HIV/AIDS.

The use of diagnostic tests in chronic disease management includes informing treatment decisions and patient education to facilitate lifestyle changes. In this way, diagnostics serve as a tool for assessing progress and establishing attainable goals, e.g., maintenance of cholesterol levels below recommended thresholds, as illustrated below:

Testing for cholesterol, a key modifiable risk factor and marker for heart disease, has been shown to reduce the disability and mortality caused by CAD, particularly in high-risk patients. Aggressive cholesterol management can reduce the rates of re-infarction by 30% and result in a 21% reduction in all cause mortality. Regular cholesterol testing has been shown to help physicians individualize disease management regimens and motivate patients to implement lifestyle changes because of increased awareness of health factors known to reduce the risk of future cardiac events.^{470,471}

Comorbidities also can affect management of chronic diseases. Diagnostics are essential for detecting certain comorbid conditions and providing clinicians more complete picture of patient status at multiple stages of disease progression. This information then can contribute to development of a comprehensive treatment or disease management approach. For example, effective diabetes management often involves glucose control and management of contributing comorbidities such as hyperlipidemia, heart disease and hypertension. The American Diabetes Association sets standards for detecting comorbid conditions associated with diabetes, including lipid testing and an annual urinalysis to detect urine albumin (a sign of emerging kidney disease).⁴⁷² These tests contribute to comprehensive diabetes care, particularly when the risk of developing cardiovascular disease is two-to-four times higher for Type 2 diabetics than in the general population, and diabetes is the leading cause of end-stage renal disease.⁴⁷³

d. Implications for Comprehensive Care

An example of the value of diagnostics in estimating patient prognosis, monitoring treatment effectiveness and management of chronic diseases is management of patients with chronic kidney disease. For these patients, diagnostics are essential in establishing early or initial diagnosis and are used to stratify patients by level of disease progression; establish stage-appropriate treatment regimens; and define or adjust the selection, timing, dose and/or frequency of treatments matched to disease state. This example is discussed in **Example 7.3**.

⁴⁶⁹ The state of health care quality: industry trends and analysis. Washington, DC: National Committee for Quality Assurance, 2004. Accessed October 22, 2004. <http://www.ncqa.org/communications/SOMC/SOHC2004.pdf>.

⁴⁷⁰ Ibid.

⁴⁷¹ Patel B, Perez HE. A means to an end: an overview of a hyperlipidemia outcomes management program. *Am J Med* 2001;110(Suppl 6A):12S-16S.

⁴⁷² American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004;27(Suppl 1):S15-35.

⁴⁷³ Haffner SM, American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004;27(Suppl 1):S68-71.

Example 7.3

Benefits of Prognostic Data in Guiding Care Decisions for Patients with Chronic Kidney Disease

As a group, kidney diseases are among the most clinically and economically burdensome disease categories in the US, accounting for as much as \$8.2 billion in annual health care expenditures.^{474,475} Chronic kidney disease (CKD) is one of the most devastating forms of kidney disease, currently affecting approximately 20 million Americans (1 in 9 adults), with another 20 million considered to be at increased risk for developing CKD.⁴⁷⁶ In addition to kidney failure, complications of CKD can include development of cardiovascular disease (including increased risk for stroke or heart attack), high blood pressure, anemia, osteoporosis, neuropathy and nerve and eye damage. As this disease progresses, the incidence of adverse effects increases dramatically, particularly when kidney function fails and patients require dialysis or a kidney transplant. Despite its severity and a strong body of evidence indicating that adverse outcomes can be prevented or delayed through early detection and treatment, the disease is believed to be significantly under-diagnosed and under-treated.⁴⁷⁷

Many diagnostic tests are recommended by evidence-based clinical practice guidelines to estimate the severity and rate of progression of CKD and to identify associated comorbidities (e.g., diabetes, hypertension, cardiovascular disease). These diagnostics include: a) serum retaining and various urine protein markers (e.g., albumin, low weight globulins) indicative of the level of kidney function and damage; b) hemoglobin testing to identify anemic patients; c) measurement of calcium, phosphorous and other chemical/biological levels; and d) various tests related to detection of the presence and level of progression of common comorbidities such as diabetes, cardiovascular disease and osteoporosis.

This diagnostic information, collected at various disease stages, is then used to diagnose CKD patients, estimate disease progression, stratify patients into likely outcomes categories (e.g., near-term kidney failure with dialysis) and select stage-appropriate treatments. Depending on the level of disease progression, appropriate treatments for CKD can range from basic dietary and behavioral modifications (e.g., reduced protein, fat and sugar intake) to treatment of cardiovascular and other symptoms with ACE inhibitors or beta-blockers and, ultimately, dialysis or transplant for end-stage renal disease patients.⁴⁷⁸ **Figure 7.4** illustrates the basic steps of CKD progression and provides an overview of evidence-based disease management steps. At each key decision-making phase, diagnostic information is essential to patient care, particularly in later disease stages where comorbidities and complications warrant increased use.

Early identification and informed treatment via proper staging of patients with this devastating disease (prior to more complicated and costly care decisions resulting from disease progression) helps to ensure quality patient care and reduce the burden of suffering. Such staging and regular prognostic assessment would not be possible without the use of diagnostics.

A 2004 study of 13,796 CKD patients by the Kaiser Permanente Center for Health Research underscores the value of diagnostics in detecting disease and informing accurate care decisions at the earliest possible stage of disease progression. Appropriate use of diagnostics in this study

⁴⁷⁴ Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health care spending? *Health Affairs* 2004;W4-437.

⁴⁷⁵ Deaths: final data for 2001. Hyattsville, MD: US National Center for Health Statistics, 2003. (DHHS publication no. (PHS) 2003-1120). Accessed October 22, 2004. <http://www.cdc.gov/nchs/pressroom/03facts/mortalitytrends.htm>.

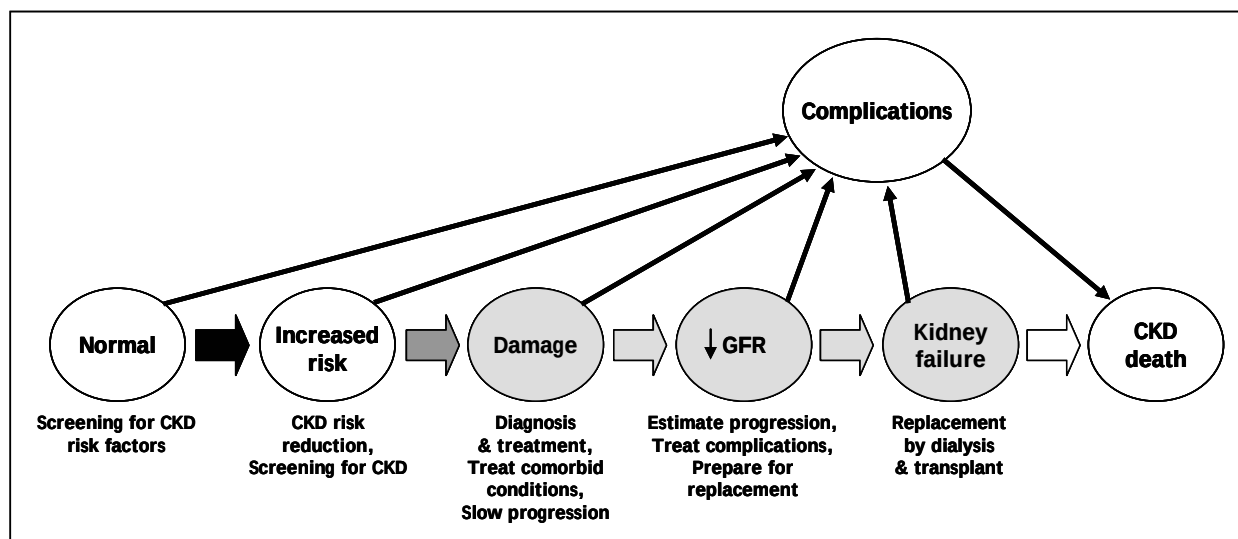
⁴⁷⁶ About chronic kidney disease (CKD). New York, NY: National Kidney Foundation, 2003. Accessed October 22, 2004. <http://www.kidney.org/kls/patients/aboutckd.cfm>.

⁴⁷⁷ Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139(2):137-49.

⁴⁷⁸ Ibid.

was found to avert \$28-46M in prescription drug, outpatient and inpatient costs. Also, CKD patients with co-morbid conditions who received appropriate diagnostic testing were found to have health care expenditures that were 50% less than similar patients not receiving appropriate diagnostic testing.⁴⁷⁹ Better patient management of CKD and prevention of comorbidities, as guided by diagnostic information, has strong potential to reduce overall clinical and economic burdens associated with ESRD significantly.

Figure 7.4
The National Kidney Foundation Evidence Model for Diagnosis and Management of Chronic Kidney Disease



Source: National Kidney Foundation. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(suppl 1):S20.

Diagnostics provide valuable insights into patient prognosis, treatment course and overall disease management. They often allow for more holistic and adaptable treatment decisions, incorporating a spectrum of factors individual to the patient, such as relevant risk factors and comorbidities, pharmacologic response and therapeutic compliance. Increases in quality of life and productivity and decreases in morbidity and mortality are clear evidence of the value of diagnostics for such applications.

5. Identifying Environmental Risks to Patients and the Public Health

Public health is challenged continually by threats from infectious diseases and environmental agents, hospital infections and bioterrorism. A critical response to such health threats is identification of specific biological/chemical causative agent via diagnostic tests. Once a causative agent is identified, steps can be taken to treat affected individuals, contain or respond to the threat and minimize future threats or damage. The CDC and other public health

⁴⁷⁹ Smith DH, Gullion CM, Nichols G, et al. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. J Am Soc Nephrol 2004;15(5):1300-6.

organizations often create guidance documents for identifying and responding to particular threats in these categories.⁴⁸⁰

a. Applications for Bioterrorism Response

Bioterrorism poses a significant and growing threat to US and global populations. Increased international travel, expanded communications (e.g., the Internet and wireless telecommunications) and scientific/technological advances applicable to production and delivery of biological/chemical agents can provide potential terrorists with an array of options and opportunities to inflict harm.⁴⁸¹ Diagnostic technologies represent a first-line resource for responding to any bioterrorism strike.

Diagnostics not only are relevant to accurate identification of specific causative agents (e.g., anthrax, smallpox, botulism, tularemia, plague), but also are essential for determining whether certain bacterial or viral strains are treatment-resistant, for estimating the prognosis of infected/injured patients and for informing treatment decisions. **Example 7.4** illustrates the role of diagnostics in public health response to a specific threat of bioterrorism.

Example 7.4 Role of Diagnostics in Responding to a Bioterrorism Event

Anthrax, a disease caused by the bacterium *Bacillus anthracis*, can affect the skin, lungs or the gastrointestinal system. Of the three types of anthrax, cutaneous (skin) anthrax is the least severe form of the disease (20% death rate), the gastrointestinal form is more severe (25-50% death rate) and inhalation anthrax is the most severe (50% death rate).⁴⁸² Anthrax typically is treated with a 60-day course of antibiotics, and early detection and treatment largely determine treatment success and patient prognosis. Anthrax is best treated before symptoms arise; treatment begun after the eighth day of infection is not likely to improve morbidity or mortality outcomes significantly.⁴⁸³

In October 2001 in Washington, DC, letters containing anthrax spores were sent through the Brentwood Post Office to the offices of Senators Daschle and Leahy on Capitol Hill. The incident received national attention, particularly since this attack closely followed the September 11 terrorist attacks. After postal workers showed evidence of anthrax exposure, all individuals in both the Brentwood Post Office and on Capitol Hill who may have been exposed to the bacteria were tested. Culture tests were performed on 689 nasal swabs from individuals at Capitol Hill and 3,247 nasal swabs from individuals at the Brentwood Post Office.⁴⁸⁴ Testing protocol included a series of diagnostic tests (e.g., Gram stains and motility tests) on bacterial colonies with anthrax-consistent and inconsistent morphology (i.e., to rule out other possible infectious agents). In all, five cases of inhalation anthrax were reported at the Brentwood postal facility, and two

⁴⁸⁰ Sewell DL. Laboratory safety practices associated with potential agents of biocrime or bioterrorism. *J Clin Microbiol* 2003;41(7):2801-9.

⁴⁸¹ Teich JM, Wagner MM, Mackenzie CF, Schafer KO. The informatics response in disaster, terrorism, and war. *J Am Med Inform Assoc* 2002;9(2):97-104.

⁴⁸² Anthrax: what you need to know. Atlanta, GA: Centers for Disease Control and Prevention, 2003. Accessed October 22, 2004. <http://www.bt.cdc.gov/agent/anthrax/needtoknow.asp>.

⁴⁸³ Teich JM, Wagner MM, Mackenzie CF, Schafer KO. The informatics response in disaster, terrorism, and war. *J Am Med Inform Assoc* 2002;9(2):97-104.

⁴⁸⁴ Kiratisin P, Fukuda CD, Wong A, et al. Large-scale screening of nasal swabs for *Bacillus anthracis*: descriptive summary and discussion of the National Institute of Health's experience. *J Clin Microbiol* 2002;40(8):3012-6.

individuals died as a result of their infections.⁴⁸⁵ While 28 individuals received positive initial nasal swabs on Capitol Hill, they all were negative upon subsequent testing.⁴⁸⁶ Antibiotic treatment was prescribed for individuals at risk of infection and, due to this prompt initiation of antibiotic treatment, no additional cases of anthrax were reported when exposed individuals complied with recommended treatment.⁴⁸⁷

Analyses following this bioterrorism episode cited the need for a high level of suspicion among health care providers with a keen eye to the sometimes subtle early symptoms of anthrax infection.⁴⁸⁸ The US government is working toward more coordinated public health responses to future incidents and increased research on bioterrorism agents.⁴⁸⁹

Currently, emphasis is placed on diagnostic techniques that increase accuracy while decreasing response time to threat containment.⁴⁹⁰ Molecular techniques including nucleic acid amplification testing (NAT), which uses sequences of DNA specific to the pathogen to detect a sample, often are favored because of their speed and accuracy. Fluorescence-based immunoassays that use antibodies for targeted detection are another emerging alternative that can be up to four times faster than standard methods.⁴⁹¹

Diagnostic tests for bioterrorism agents are becoming smaller and increasingly portable. Field-based rapid NAT testing is one adaptation of real-time NAT tests.⁴⁹² Other advancements, such as chip-based microfluidics that enable rapid analysis of complex fluids (e.g., whole blood), expand options for point-of-care diagnostics.^{493,494} As tests are refined for bioterrorism applications, there is strong potential for crossover into mainstream medical applications such as NAT-based near-patient testing for infectious agents.^{495,496}

⁴⁸⁵ Borio L, Frank D, Mani V, et al. Death due to bioterrorism-related inhalational anthrax: report of 2 patients. *JAMA* 2001;286:2554-9.

⁴⁸⁶ Hsu VP, Lukacs SL, Handzel T, et al. Opening a bacillus anthracis-containing envelope, Capitol Hill, Washington, DC: the public health response. *Emerg Infect Dis* 2002;8:1039-43.

⁴⁸⁷ Jernigan DB, Raghunathan PL, Bell BP, et al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* 2002;8(10):1019-28.

⁴⁸⁸ Borio L, Frank D, Mani V, et al. Death due to bioterrorism-related inhalational anthrax: report of 2 patients. *JAMA* 2002;286:2554-9.

⁴⁸⁹ Atlas RM. Responding to the threat of bioterrorism: a microbial ecology perspective – the case of anthrax. *Int Microbiol* 2002;5:161-7.

⁴⁹⁰ Andreotti PE, Ludwig GV, Peruski AH, et al. Immunoassay of infectious agents. *Biotechniques* 2003;35:850-9.

⁴⁹¹ Khan AS, Cao CJ, Thompson RG, Valdes JJ. A simple and rapid fluorescence-based immunoassay for the detection of staphylococcal enterotoxin B. *Mol Cell Probes* 2003;17:125-6.

⁴⁹² Bowers HA, Tengs T, Glasgow HB Jr., et al. Development of real-time PCR assays for rapid detection of *Pfiesteria piscicida* and related dinoflagellates. *Applied & Environmental Microbiology* 2000;66:4641-8.

⁴⁹³ Microfluidics and the microanalytical laboratory. Gaithersburg, MD: National Institute of Standards and Technology, 2003. Accessed October 22, 2004. <http://www.cstl.nist.gov/nist839/839.04/microfluidics.html>

⁴⁹⁴ Hietela SK, Ardans AA. Molecular weapons against agricultural vulnerability and the war on terror. *J Vet Med Educ* 2003;30:155-6.

⁴⁹⁵ ZymeTx launches flu season surveillance amid bioterrorism fears; NFSN viewed as potential tool in national counter bioterrorism. Oklahoma City, OK: National Flu Surveillance Network, 2001. Accessed October 22, 2004. http://www.fluwatch.com/output_press_1.cfm?pageid=63&ID=37.

⁴⁹⁶ Rodriguez WJ, Schwartz RH, Thorne MM. Evaluation of diagnostic tests for influenza in a pediatric practice. *Pediatr Infect Dis J* 2002;21:193-6.

While health care personnel play a critical role in initial recognition of an unannounced bioterrorist attack, diagnostics are essential for characterizing specific pathogens.⁴⁹⁷ As is often the case in other emergency response scenarios, a combination of clinician and facility preparedness and rapid diagnostic testing is the best defense against immediate and unexpected instances of bioterrorism.

b. Applications for Infectious Disease Detection and Response

Infectious diseases, which account for 25% of annual worldwide deaths (approximately 13.3 million), are caused by a wide variety of microorganisms, including bacteria, viruses, fungi and prions.⁴⁹⁸ Specific disease outbreaks can stem from microorganisms that previously were unknown (e.g., SARS), at one time successfully controlled (e.g., small pox, dengue fever) or regionally isolated (e.g., West Nile virus, mad cow disease) or have developed drug-resistance (e.g., tuberculosis, malaria). The global economy and greater international travel increase the spread of infectious diseases by infected people, animals, insects and commercial shipments of contaminated food.

Early detection of infectious disease using diagnostic technologies is critical to informing appropriate preventive (e.g., inoculations, patient quarantine) and treatment strategies to contain disease and reduce adverse health outcomes. Diagnostic information also is important for tracking spread of infectious disease from the local to the international level and predicting and monitoring emerging and aggressive disease outbreaks.

Trends in infectious disease detection and surveillance reflect the demand for speed, accuracy and portability. There is greater attention to rapid and point-of-care methods including NAT, immunoassays and chip-based microfluidic methods, which provide real-time information using direct patient samples without extensive preparation.⁴⁹⁹ Multiplexing (simultaneous detection of more than one infectious disease marker in the same container) is emerging for rapid assessment of infectious diseases.⁵⁰⁰ The value of diagnostics in responding rapidly to unexpected infectious disease threats was demonstrated in the SARS outbreak of 2003.

⁴⁹⁷ Moser R Jr, White GL, Lewis-Younger CR, Garrett LC. Preparing for expected bioterrorism attacks. *Mil Med* 2001;166:369-74.

⁴⁹⁸ Leading causes of death. WHO Infectious Diseases Report. Geneva, Switzerland: World Health Organization, 1999. Accessed October 22, 2004. <http://www.who.int/infectious-disease-report/pages/graph1.html>.

⁴⁹⁹ Andreotti PE 2003.

⁵⁰⁰ Jani IV, Janossy G, Brown DW, Mandy F. Multiplexed immunoassays by flow cytometry for diagnosis and surveillance of infectious diseases in resource-poor settings. *Lancet Infect Dis* 2002;2:243-50.

SARS, a viral respiratory illness that causes a high fever and may lead to headache, body aches and death, was first reported in Asia in February 2003. Within a few months, this virus had spread to more than 24 countries on four continents. The disease affected more than 8,000 people globally, of which more than 700 died. In the US, pre-emptive containment strategies developed by the CDC and laboratory diagnostic testing allowed rapid identification and containment of the infection, limiting reported disease transmission to eight individuals.^{501,502} Currently, the CDC recommends preparation for potential recurrence of SARS and continues to emphasize detection, containment and contact tracing as effective control measures.⁵⁰³

Diagnostics provide important information regarding antibiotic resistance. Antibiotic resistance is becoming an increasingly serious and widespread problem in treating and managing certain infectious diseases. Drug resistance in tuberculosis (*Mycobacterium tuberculosis*), second only to HIV/AIDS among infectious diseases as a cause of global mortality, is a prominent example of this resistance problem. Multi-drug resistant tuberculosis is associated with failed treatment and high mortality.⁵⁰⁴ Real-time diagnostic tests have been developed, along with surveillance and prevention strategies to detect drug resistance early and tailor treatments for optimal effectiveness.^{505,506,507} The utility of diagnostics in detecting antibiotic resistance is illustrated by the following example of community-acquired pneumonia (**Example 7.5**).

Example 7.5
Emerging Utility of Diagnostics in the Early Detection and Management of Drug Resistant Community-Acquired Pneumonia

Each year in the US there are between 3 million and 6 million cases of community-acquired pneumonia, corresponding to 500,000-800,000 hospitalizations and approximately 45,000 deaths. As the sixth leading cause of death, this infection can be attributed to a variety of bacteria including *S. pneumoniae*, *H. influenzae*, *L. pneumophila* and *M. pneumoniae*.^{508,509} Chest x-ray is the primary method of identifying pneumonia and can help distinguish it from acute bronchitis. However, chest x-rays do not provide information regarding the causative bacteria, so diagnostic tests including blood and sputum cultures are employed to characterize these infectious agents.⁵¹⁰

⁵⁰¹ Shi Y, Yi Y, Li P, et al. Diagnosis of severe acute respiratory syndrome (SARS) by detection of SARS Coronavirus nucleocapsid antibodies in an antigen-capturing enzyme-linked immunosorbent assay. *J Clin Microbiol* 2003;41(12):5781-2.

⁵⁰² Basic information about SARS. Atlanta, GA: Centers for Disease Control and Prevention, 2004. Accessed October 22, 2004. <http://www.cdc.gov/ncidod/sars/factsheet.htm>.

⁵⁰³ In the absence of SARS-CoV transmission worldwide: guidance for surveillance, clinical and laboratory evaluation, and reporting version 2. Atlanta, GA: Centers for Disease Control and Prevention, 2004. Accessed October 22, 2004. <http://www.cdc.gov/ncidod/sars/absenceofsars.htm>.

⁵⁰⁴ Dye C, Williams BG. Criteria for the control of drug-resistant tuberculosis. *Proc Natl Acad Sci* 2000;97(14):8180-5.

⁵⁰⁵ Torres MF, Criado A, Palomares JC, Aznar J. Use of real-time PCR and fluorimetry for rapid detection of rifampin and isoniazid resistance-associated mutations in *Mycobacterium tuberculosis*. *J Clin Microbiol* 2000;38(9):3194-9.

⁵⁰⁶ Garcia de Viedma D. Rapid detection of resistance in *Mycobacterium tuberculosis*: a review discussing molecular approaches. *Clin Microbiol Infect* 2003;9(5):349-59.

⁵⁰⁷ Djuretic T, Herbert J, Drobniewski F, et al. Antibiotic resistant tuberculosis in the United Kingdom: 1993-1999. *Thorax* 2002;57(6):477-82.

⁵⁰⁸ Nicolau D. Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections. *J Antimicrob Chemother* 2002;50(Suppl S1):61-70.

⁵⁰⁹ Singer ME, Harding I, Jacobs MR, Jaffe DH. Impact of antimicrobial resistance on health outcomes in the outpatient treatment of adult community-acquired pneumonia: a probability model. *J Antimicrob Chemother* 2003 51(5):1269-82.

⁵¹⁰ Johnson PDR, Irving LB, Turnidge JD. Community-acquired pneumonia. *Medical Journal of Australia* 2002;176:341-7.

Obtaining results from contemporary culture tests can take 1-2 days, often with poor success rates.⁵¹¹ As a result, most patients with community-acquired pneumonia are treated empirically with broad-spectrum antibiotics before the pathogen is identified. While early initiation of treatment benefits the patient, increasing concerns about antibiotic resistance are driving efforts to develop rapid diagnostic tests that can identify resistant strains and help tailor timely and targeted antibiotic treatments.

Recent studies document rising rates of antibiotic resistance, especially among strains of *S. pneumonia* that now demonstrate close to 40% resistance to penicillin.⁵¹² Patients treated with antibiotics to which the infectious agent is resistant demonstrate worse clinical outcomes versus those appropriately treated.⁵¹³ While certain rapid diagnostic tests currently are available (e.g., *Legionella* urinary antigen test, viral immunofluorescence testing of nasopharyngeal aspirate), existing tests often are too narrow to determine the causative pathogen for all patients. Rapid NAT-based diagnostics that identify causative pathogens and antibiotic resistant strains in 3-4 hours are anticipated to emerge in the next few years.⁵¹⁴ These should increase the likelihood that patients receive effective treatment for this potentially fatal infection and reduce the rate at which pathogens develop resistance to medications by reducing doses of empirical antibiotics, providing an important benefit to public health.⁵¹⁵

c. Applications for Infections Acquired During Routine Patient Care

Infections acquired at hospitals and from health providers, known as nosocomial infections, are a major source of morbidity and mortality in the US, costing an estimated \$4.5 billion per year.^{516,517} Approximately 2 million people acquire these infections annually, due to transmission of infectious agents to hospital patients, visitors and health staff during the process of delivering routine patient care.⁵¹⁸ Sources of infection include contaminated supplies, equipment and instruments, as well as ventilation systems, improper food preparation and contact with ill or contaminated staff.

Diagnostics play a major role in early detection, prevention and treatment of nosocomial infections. Emerging molecular diagnostics shorten the time for diagnosing certain nosocomial infections (e.g., candidiasis in immunocompromised patients) compared to traditional lengthy

⁵¹¹ Alves DW, Kennedy MT. Community-acquired pneumonia in casualty: etiology, clinical features, diagnosis, and management (or a look at the “new” in pneumonia since 2002). *Curr Opin Pulm Med* 2004;10(3):166-70.

⁵¹² Fogarty CM, Kohno S, Buchanan P, et al. Community-acquired respiratory tract infections caused by resistant pneumococci: clinical and bacteriological efficacy of the ketolide telithromycin. *J Antimicrob Chemother* 2003;51:947-55.

⁵¹³ Lujan M, Gallego M, Fontanals D, et al. Prospective observational study of bacteremic pneumococcal pneumonia: effect of discordant therapy on mortality. *Crit Care Med* 2004;32(3):625-31.

⁵¹⁴ Johnson PDR 2002.

⁵¹⁵ Peterson LR, Dalhoff A. Towards targeted prescribing: will the cure for antimicrobial resistance be specific, directed therapy through improved diagnostic testing? *J Antimicrob Chemother* 2004;53:902-5.

⁵¹⁶ Emori RG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. *Clin Microbiol Rev* 1993;6(4):428-442.

⁵¹⁷ Martone WJ, Jarvis WR, Culver DH, Haley RW. Incidence and nature of endemic and epidemic nosocomial infections. In: Bennet, JV, Brachman PS, eds. *Hospital infections*, 3rd ed. Boston, MA: Little, Brown and Co., 1992:577-596.

⁵¹⁸ Gaynes R, Richards C, Edwards T, et al. Feeding back surveillance data to prevent hospital-acquired infections. *Emerg Infect Dis* 2001;7(2):295-8.

microbiological culture tests.⁵¹⁹ These new tests allow physicians to prevent wound infections (e.g., early detection of *Staphylococcus* carrier status in cardiac surgery patients), estimate prognosis, initiate appropriate treatment and monitor patient response and recovery.^{520,521} This monitoring enables treatment adjustment to reduce patient risks and may improve outcomes and reduce costs.⁵²² The following example of sepsis management illustrates the potential of diagnostics to improve quality and avoid unnecessary harms and costs (**Example 7.6**).

Example 7.6
Emerging Utility of Diagnostics in the
Early Detection and Management of Sepsis

Sepsis, a condition marked by presence of bacteria, fungi or other pathogens in the blood, is a compelling example of diagnostic utility in treating nosocomial infections. Each year in the US sepsis causes an estimated 120,000 deaths and costs an estimated \$16.7 billion. When sepsis occurs, early detection of the causative pathogen is critical to informing treatment decisions and reducing adverse health outcomes. In 23-30% of cases, inappropriate antimicrobial treatment is the leading avoidable treatment error related to mortality.⁵²³

While culture tests (requiring 24-48 hours) to determine the causative pathogen have an important role in diagnosis and treatment, rapid tests are needed to inform antimicrobial treatment before septic infection progresses and results in compromised patient health or death. While broad spectrum antibiotics are typically given to sepsis patients as a routine preventive measure, administration of an antibiotic regimen that works optimally (i.e., no antibiotic resistance) in these patients can make the difference between life and death. This also allows health practitioners to assess the need to use third- and fourth-line antibiotics, which can be particularly expensive, and reduces the risks of further antibiotic resistance via targeted treatment.

Several biomarker assays for sepsis are under development as a more targeted and rapid alternative to conventional methods of pathogen detection. Perhaps the most promising strategy is the use of real-time diagnostic panels to monitor an array of sepsis markers. Increasingly accurate and rapid diagnostics for sepsis hold the potential to substantially reduce patient suffering and costs associated with this condition.

Diagnostics also are useful in controlling the spread of nosocomial infections via testing other patients for infection following detection of outbreak or routine monitoring of hospital surfaces, supplies and equipment for potential contaminants.⁵²⁴ When a case of nosocomial infection is confirmed, clinicians have critical information to select appropriate preventive measures including use of antiseptics, quarantine of certain patients, and decisions regarding post-exposure prophylactic therapy.

⁵¹⁹ Erjavec Z, Verweij PE. Recent progress in the diagnosis of fungal infection in the immunocompromised host. *Drug Resist Updat* 2002;5:3-10.

⁵²⁰ Banbury MK. Experience in prevention of sternal wound infections in nasal carriers of *Staphylococcus aureus*. *Surgery* 2003;134:S18-22.

⁵²¹ Erjavec Z 2002.

⁵²² Carrigan SD, Scott G, Tabrizian M. Toward resolving the challenges of sepsis diagnosis. *Clin Chem* 2004;50:1301-4.

⁵²³ Ibid.

⁵²⁴ Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology* 2003;8:S9-14.

7. Emerging and Future Diagnostics: Improving Patient Care

Evolving with our understanding of biological systems and disease, emerging and future diagnostics hold the potential to significantly alter health care. Although manual in-house diagnostics still are developed, primarily for biomedical research purposes or early-phase product development (e.g., certain genetic assays), most emerging diagnostic technologies are designed for broader markets.

Genomic, proteomic, metabolomic and other advancements (e.g., advances in health information systems and computer technology) will serve as a foundation for development of diagnostics that enable health practitioners to:

- **accurately characterize pre- or early disease states and inform earlier prevention and treatment** (e.g., correlation of various protein and metabolic markers to identify pre-emergent diseases such as diabetes, heart disease, cancer)
- **identify treatment benefits and risks prior to treatment initiation** (e.g., pharmacogenomic profiling for prediction of drug metabolism and response)
- **accurately estimate prognosis and track disease progression in “real-time”** (e.g., through more affordable and accurate “point-of-care” or “home-based” testing)
- **comprehensively understand how components of a patient’s biological system are interacting and influencing health status** (e.g., using microarray and gene/protein/metabolic expression profiling, using correlative information or neural networks to identify patterns in complex diagnostic information)
- **better estimate how patients are responding to treatment and optimize treatment regimens** (e.g., evolved applications of therapeutic drug monitoring)
- **consider individual data in the context of population-level data to inform health decisions** (e.g., comparison of individual genetic or other health information profiles to patient populations with similar profiles and identify risks and treatment options)

To meet these challenges, one group of molecular diagnostic tests, known as “theranostics,” is one of the fastest growing segments of the diagnostics industry.⁵²⁵ Due to recent advances in genomics and PGx, these tests are designed to tailor individual therapy by providing the right drug at the right dose at the right time for the right person. The main goals of theranostic tests are to improve the clinical utility, safety and cost-effectiveness of drug therapies. Theranostic strategies are broader approaches to patient care, addressing multiple aspects of the disease management continuum by linking diagnostic use to treatment decisions, encompassing:

- risk prediction
- diagnosis
- prognostic assessment

⁵²⁵ Magrez P, Shapiro F. Theranostics: Turning tomorrow’s medicine into today’s reality. London, England: Current Drug Discovery, 2002. Accessed October 22, 2004. http://www.currentdrugdiscovery.com/pdf/2002/9/SHAPIRO_FEATURE.pdf.

- stratification of patients into groups most likely to respond to a certain treatment
- monitoring therapeutic response to pharmacological and other interventions
- monitoring and management of disease state

As pharmacogenomic, theranostic and other emerging diagnostics mature, they may fundamentally alter clinical practice. Health practitioners and patients will be better able to assess risks and benefits of various care options and develop custom health management strategies for maximizing individual health and quality of life.

Consistent with greater public and private sector interest in the implications of emerging tests, the CDC Office of Genomics and Disease Prevention initiated in 2005 a three-year model project on Evaluation of Genomic Applications in Practice and Prevention (EGAPP). Modeled in part after the USPSTF, EGAPP will support the first phase of a coordinated process for systematic evaluation of genetic tests and other genomic applications that are in transition from research to clinical and public health practice. Using an independent, non-federal working group, this effort is intended to strengthen methods and processes, to set priorities for review, to oversee evidence reports and to develop evidence-based findings for these emerging technologies.

D. Understanding the Value of Diagnostics to the Health Care System

1. Cost and Economic Implications

Stakeholders in the health value chain increasingly are pressured to identify, maintain and improve quality while holding costs in check.^{526,527,528} While they represent a small fraction of total health spending, diagnostics are often first-line clinical decision support tools that influence a much larger proportion of total health spending.^{529,530,531,532} They can leverage care across the phases of patient care, including screening, diagnosis, treatment monitoring/disease management and research. Used appropriately, new diagnostics can respond to cost pressures by enabling earlier, accurate detection and characterization of health risks and disease, improved treatment and disease management and diminishing subsequent health problems and their associated costs.

The prior section covering the role of diagnostics in clinical decision-making highlighted the ways in which diagnostics can inform patient care. This section illustrates broader health

⁵²⁶ Snyderman R, Williams RS. Prospective medicine: the next health care transformation. *Acad Med* 2003;78(11):1079-84.

⁵²⁷ Cutler DM, McClellan M. Is technological change in medicine worth it? *Health Affairs* 2001;5:11-29.

⁵²⁸ Mark DB, Hlatky MA. Medical economics and the assessment of value in cardiovascular medicine: part I. *Circulation* 2002;106(4):516-20.

⁵²⁹ Raab GG 2001.

⁵³⁰ Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Affairs* 2004;23(1):77-87.

⁵³¹ The worldwide market for in vitro diagnostic tests: 3rd edition. New York, NY: Kalorama Information, 2002. Accessed October 22, 2004. <http://www.kaloramainformation.com/pub/691381.html>.

⁵³² O'Farrell B. IVD industry overview: manufacturing equipment and supplies. *Medical Device Link, IVD Technology Magazine*, 2002. Accessed October 22, 2004. <http://www.devicelink.com/ivdt/archive/00/10/009.html>

system considerations regarding the impact and value of diagnostic information, including recommended use in clinical practice guidelines, impacts of use on quality of care and health care spending, implications for improving quality of care and health spending patterns and the potential of emerging and future diagnostics to alter patterns of care and influence health system change.

2. Clinical Practice Guidelines: Evidence Supporting the Value of Diagnostics in Clinical Decision-making

In the form of clinical practice guidelines, many diagnostics have moved into the health care mainstream supported by well-founded evidence.⁵³³ These guidelines are intended to assist health practitioners in making step-wise care decisions related to specific diseases and conditions.

Clinicians must consider many factors in patient care decisions, including the stage of disease, nature and severity of symptoms, comorbidities, contraindications, psychosocial factors, etc. In general, guidelines address key decision points that span the clinical analytic framework, including diagnostic assessment, estimation of prognosis, selection among various treatment modalities and weighing disease management options.^{534,535} Third-party payers and managed care organizations also increasingly look to guidelines to inform their health benefits and coverage policies.

Clinical practice guidelines, and the underlying approach to assembling and interpreting evidence, are an increasingly visible and important resource for high quality and, in many cases, cost-effective health care. These guidelines address not only the most clinically and economically burdensome diseases in the US (heart disease, cancer, diabetes, infectious and sexually transmitted diseases, asthma, etc.), but a wide variety of other diseases such as thyroid disease, newborn inherited metabolic diseases, dyspepsia, food allergies and sepsis. The role of diagnostics in evidence-based practice guidelines across virtually all disease areas reflects their actual and potential leverage across the spectrum of health care.

3. Influence of Diagnostic Information in Diseases with Highest Burden

Focused searches of the National Guideline Clearinghouse (NGC) and PubMed/MEDLINE identified more than 460 evidence-based clinical practice guidelines pertaining to diagnostics. This search included individual assessment of more than 1,230 guidelines covering the 23 main

⁵³³ While it continues to expand, the current body of practice guidelines does not cover the full array of health care, including all uses of diagnostics. Recommendations for diagnostic use in guidelines represent only a small fraction of uses of diagnostics approved by the FDA and covered by third-party payers. Given the limited time and resources for developing and updating guidelines, it often is not possible to maintain current and comprehensive ones reflecting recent technological advances.

⁵³⁴ Jackson R. Guidelines for clinical guidelines. *BMJ* 1998;317:427-8.

⁵³⁵ Guidelines have become increasingly evidence-based and derived using systematic processes, particularly during the past 10 years. Public and private sector groups have been integral to this transition. Such medical professional groups as the American College of Physicians, American College of Cardiology and American Society of Clinical Oncology have been leaders in guideline development. In the federal government, AHRQ, the US Preventive Services Task Force (located in AHRQ) and the CDC have been particularly active, including providing data and evidence reports that support guideline development by groups in the private sector.

disease/condition categories defined by the NGC (e.g., bacterial infections and mycoses, cardiovascular diseases, neoplasms, digestive system diseases).⁵³⁶ Approximately 26% of these guidelines pertained only to specific aspects of treatment, use of psychosocial assessment instruments or were in other ways not relevant to diagnostic use and about half of the remaining guidelines specifically recommend use of diagnostics.

These 460 guidelines span recommendations for initial diagnosis and determining patient prognosis or staging to disease management. **Figure 7.5** reflects instances of such guideline recommendations for diagnostic use in the 15 leading causes of death and 15 most clinically and economically burdensome conditions in the US.

Figure 7.5
Clinical Practice Guideline (CPG) Recommendations for Diagnostic Use
for Leading Causes of Death and Most Burdensome Conditions in the US

Rank	Leading US Causes of Death	Diagnostic Use Supported by CPG	Most Clinically and Economically Burdensome US Conditions	Diagnostic Use Supported by CPG
1	Diseases of heart	Y	Ischemic heart disease	Y
2	Malignant neoplasms (cancer)	Y	Motor vehicle accidents	N
3	Cerebrovascular diseases	Y	Acute respiratory infection	Y
4	Chronic lower respiratory diseases	Y	Arthropathies	Y
5	Accidents (unintentional injuries)	N	Hypertension	Y
6	Diabetes mellitus	Y	Back problems	N
7	Influenza and pneumonia	Y	Mood disorders	Y
8	Alzheimer's disease	N	Diabetes	Y
9	Nephritis and nephrotic syndromes	Y	Cerebrovascular disease	Y
10	Septicemia	Y	Cardiac dysrhythmias	N
11	Suicide	N	Peripheral vascular disorders	Y
12	Chronic liver disease and cirrhosis	Y	COPD	Y
13	Homicide	N	Asthma	Y
14	Hypertension	Y	Congestive heart failure	Y
15	Pneumonitis	Y	Respiratory malignancies	Y
	Total all category	73%	Total all category	80%

Sources:

1. Deaths: final data for 2001. Hyattsville, MD: US National Center for Health Statistics, 2003. (DHHS publication no. (PHS) 2003-1120).
2. Druss BG, Marcus SC, Olsson M, Pincus A. The most expensive medical conditions in America. *Health Affairs* 2002;12(4):105-11.

At least one practice guideline (and often multiple ones) recommending diagnostic use as a standard of care was identified for 11 of the 15 leading causes of death (73%) and 12 of the 15 most burdensome health conditions (80%) in the US. In many of these very broad categories, such as diseases of the heart (e.g., congestive heart failure, coronary heart disease, cardiac

⁵³⁶ NGC and PubMed searches were limited to English language only and to guidelines released between January 1, 1995 and September 30, 2004.

dysrhythmias), cancer (e.g., breast, colorectal, lung, prostate, pancreatic), diabetes (Type I and II) and chronic lower respiratory diseases (asthma, COPD), there were multiple guidelines recommending diagnostic use at multiple decision points along the clinical analytic framework.

Illustrating this is the instance of CKD, discussed above. For CKD, evidence-based clinical practice guidelines recommend use of:

- serum creatinine and various urine protein markers (e.g., albumin, low-weight globulins) indicative of the level of kidney function and damage
- hemoglobin testing to identify anemic patients
- measurement of calcium, phosphorous and other chemical/biological levels
- various tests for detection of the presence and level of progression of common comorbidities, such as diabetes, cardiovascular disease and osteoporosis

In CKD, diagnostics are essential to informing care decisions at each stage of disease, from opportunities for early detection and treatment to ESRD. In other categories listed in **Figure 7.5** (e.g., cardiac dysrhythmias, accidents/motor vehicle accidents and Alzheimer's disease), diagnostics are routinely used in making care decisions, despite the absence of specific recommendations in practice guidelines.

Only a fraction of diagnostics (or other technologies) may be listed explicitly in clinical practice guidelines. This is largely because it often takes years to accrue sufficient evidence and practitioner experience to enable technologies, including diagnostics, to transition to standards of care eventually introduced into practice guidelines. More routinely, FDA market approval and third-party reimbursement analysis for diagnostic technologies in these leading disease areas operate to support assessment and provision of safe and effective technologies. Even so, **Figure 7.5** shows that diagnostics broadly influence health care decisions and are integral to quality patient care for most of the diseases and conditions of greatest health impact in the US.

4. Health Care Quality Measures: Evidence for the Impact of Diagnostics

In addition to their role in guidelines, the essential role of diagnostics is increasingly reflected in quality standards and performance measures. Although the US health care system is the most technologically advanced in the world, certain inefficiencies, errors and lack of access and continuity contribute to unnecessary adverse effects, mortality and morbidity, procedures and services and costs. Current health quality challenges in the US are summarized by the NCQA in its State of Health Care Quality 2004: Industry Trends and Analysis report, as follows.⁵³⁷

Most Americans would undoubtedly agree that the goals of the health care system should be to keep healthy people healthy and to help the chronically ill manage their conditions to avoid serious and expensive complications. But as first reported last year, 1,000 Americans or more die each week because the health care system regularly fails to deliver appropriate care, and thousands more are hospitalized as a result of this failure. Yet Americans pay more and more for the care they receive and nearly 45 million Americans

⁵³⁷ The state of health care quality: industry trends and analysis. NCQA, 2004.

are uninsured. This combination of increasing costs, declining access and varying performance is entirely unacceptable.

This section describes how diagnostics are being incorporated into quality standards and performance measures used by hundreds of health plans and thousands of health care providers nationwide. Tracking of quality measures also allows identifying opportunities to optimize the use of diagnostics.

a. Definition and Role of Quality Measures in Health Care

The IOM has defined quality of care as, “the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”⁵³⁸ Consistent with this definition, AHRQ has defined health quality measures as mechanisms that allow health decision-makers to compare quality of certain aspects of care to relevant reference standards.⁵³⁹

Quality measures typically have the following general characteristics:⁵⁴⁰

- Of significant clinical importance
- Of significant financial/strategic importance
- Reliable, valid and comprehensible
- Strongly supported by available clinical and economic evidence
- Applicable to evaluating the equitable distribution of health care
- Have value for reducing variations in quality
- Feasible to develop, implement and operationalize.

Tracking particular quality measures enables health purchasers, patients, providers and payers to evaluate the performance of individual health care organizations. Originally envisioned as a means of facilitating continued quality improvements within health organizations, quality measures increasingly are being used to inform the purchasing decisions of payers and individual/organized purchasers of health care (e.g., employers and employer coalitions).

b. Value-based Purchasing of Health Care Using Quality Standards

In response to rapidly rising health care costs, employers and employer coalitions (e.g., The Leapfrog Group, the Employer Health Care Alliance Cooperative of Wisconsin, Pacific Business

⁵³⁸ Lohr KN, ed. Medicare: a strategy for quality assurance, volume I. Washington, DC: National Academy Press, Committee to Design a Strategy for Quality Review and Assurance in Medicare, Division of Health Care Services, Institute of Medicine, 1990.

⁵³⁹ Understanding and choosing clinical performance measures for quality improvement: development of typology: final report. Rockville, MD: Agency for Healthcare Research and Quality, Center for Health Policy Studies, Harvard School of Public Health, Center for Quality of Care Research and Education, 1995.

⁵⁴⁰ Using measures: desirable measure attributes. Rockville, MD: Agency for Health Care Research and Quality, National Quality Measures Clearinghouse, 2004. Accessed October 22, 2004.
http://www.qualitymeasures.ahrq.gov/resources/measure_use.aspx.

Group on Health) increasingly are seeking to leverage their purchasing power by developing pay-for-performance (P4P) strategies and initiatives. These programs use quality measures to gauge and compare the quality and cost of health care from available sources and then provide differential financial incentives to those payers and providers that can offer the highest quality care at reduced cost.⁵⁴¹

Many health plans (e.g., Anthem Southeast, Harvard Pilgrim, Tufts Health Plan, Blue Cross Blue Shield of Florida) have adapted to this changing environment and begun to integrate or pilot test quality measures in P4P strategies with providers in their networks. Medicare, the largest health care payer in the US, initiated a P4P health demonstration program in 2003 with Premier Inc., a nationwide organization of not-for-profit hospitals. In this demonstration project, CMS will use quality measure data to reward Premier's hospitals that provide the highest quality of care with increased reimbursement for Medicare patients (**Figure 7.18**). Other quality measure initiatives at CMS, such as the Robust Measures Project that will help evaluate and further implement quality measure data into Medicare and Medicaid data reporting mechanisms and P4P initiatives, also are indicative of the increasing emphasis on quality measure data as a means to monitor, improve upon and reward quality health services.⁵⁴²

c. Use of Diagnostics as an Indicator of Health Care Quality

Though still evolving, these efforts toward quality improvement and management will significantly affect health care services and outcomes. The June 2004 testimony of the National Medical Director for quality management at Aetna, delivered to the National Committee on Vital Health Statistics (NCVHS), underscores the value of diagnostic information in evaluating and guiding delivery of quality health services, as follows.⁵⁴³

Laboratory data is critical to measuring the outcomes of a number of diseases and is currently a prominent part of the HEDIS data set. These measures are already being used in pay for performance programs based on HEDIS or qualification for the NCQA Diabetes Performance Recognition Program. They also are useful in risk adjusting populations. Laboratory data can be collected from providers directly or from laboratories. In either case, a standard data methodology would be very useful. Our experience using data supplied by the vendors is that it is highly accurate. It would be very valuable to have common coding for lab data.

NCVHS, the statutory public advisory body on information needs underlying health policy, acknowledged the vital role of diagnostic information in health care in its 2004 report, *Measuring Health Care Quality: Obstacles and Opportunities*. This report advanced

⁵⁴¹ Baker G. Pay for performance incentive programs in healthcare. San Francisco, CA: MedVantage, Inc., 2003. Accessed October 22, 2004.

http://www.medvantageinc.com/documents/Final%20P4P_Executive%20Briefing.pdf.

⁵⁴² Robust measures project. Centers for Medicare & Medicaid Services fact sheet. Baltimore, MD: Centers for Medicare & Medicaid Services. Accessed October 28, 2004. <http://www.cms.hhs.gov/quality/hospital/RobustMeasuresFactSheet.pdf>.

⁵⁴³ Comments on proposed NCVHS recommendations for measuring quality: testimony of Dr. Charles Cutler. Washington, DC: US Department of Health and Human Services, National Committee on Vital Health Statistics, 2004. Accessed October 22, 2004. <http://www.ncvhs.hhs.gov/040625p1.htm>.

recommendations to overcome barriers to clinical laboratory and vital statistics data essential to targeting health care delivery areas in greatest need of quality improvement and measuring the effectiveness of various local, regional and national quality improvement strategies. The following excerpt from the report underscores the value of diagnostic information for informing health decision-making and assessing its quality.⁵⁴⁴

Laboratory values and vital signs represent proximate clinical outcomes, the measurement of which requires clinical information that is often available only through chart abstraction. Risk adjustment of clinical outcomes such as complication mortality rates can also depend on the availability of physiologic measurements (e.g., kidney function in diabetics, peak flow measurements for asthmatics, ejection fraction for heart failure), which themselves can serve as proximate outcomes for priority health conditions, can be ascertained through vital signs and/or objective data, such as blood pressure and weight. Vital signs and most laboratory and radiology test results are currently not available in claim transaction records, and the claims attachment standard has not yet been finalized. Administrative transactions represent a short-term option for capturing the additional data elements necessary to determine these important health outcomes.

Among the NCVHS recommendations relevant to better harnessing of diagnostic information to evaluate and improve the quality of care are the following:

- Create a mechanism for reporting selected inpatient and outpatient laboratory results in a standard transaction, focusing on tests that represent important clinical outcomes for the priority health conditions identified by the IOM report, *Priority Areas for National Action: Transforming Health Care Quality* (2003).
- Facilitate reporting of a diagnosis modifier to flag diagnoses that were present on admission on secondary diagnosis fields in all inpatient claims transactions (e.g., to accurately track and address nosocomial infections and medical errors that often lead to the development of preventable complications or comorbidities among hospitalized patients).
- Review the available options for coding patient functional status in administrative transactions, EHRs (electronic health records) and other clinical data sets and recommend standard approaches.

The key role of diagnostic information increasingly is recognized in unfolding quality initiatives. It also is important to understand how use of diagnostics is assessed to measure and influence quality of care, as described below.

⁵⁴⁴ Measuring health care quality: obstacles and opportunities. Washington, DC: US Department of Health and Human Services, National Committee on Vital Health Statistics, 2004. Accessed October 22, 2004. <http://www.ncvhs.hhs.gov/040531rp.pdf>.

d. Relationship of Diagnostic Information to Quality Health Care

We evaluated two national sources of validated quality measures, the HEDIS and the National Quality Measures Clearinghouse (NQMC), to determine the extent to which diagnostics are incorporated into widely recognized quality assessment instruments.⁵⁴⁵ Further, we cross-referenced disease-specific quality measures from these sources to clinical practice guidelines identified in the NGC and MEDLINE/PubMed.

HEDIS measures currently are used in approximately 90% of managed care organizations in the US and are applicable to the commercial, Medicare and Medicaid beneficiary populations. Other quality measures, such as those available in the NQMC, increasingly are being adopted by health purchasers, payers and providers. The disease-related quality measures covered in this analysis include disease areas that are among those accounting for the greatest impacts on health status and costs, such as cardiovascular disease, diabetes, cancer, infectious and sexually transmitted diseases, chronic kidney and liver diseases and asthma.^{546,547}

Figure 7.6
Influence of Diagnostics on Disease-specific
Health Care Quality and Quality Improvement Initiatives

Source of the Quality Measure (QM)	QM is a Direct Measure of the Use of Diagnostics*	QM Influenced by Diagnostic Use as Recommended in a Published Clinical Practice Guideline
HEDIS measures^	23.1%	61.5%
NQMC measures+	13.9%	78.9%

*Although both *in vitro* and *in vivo* diagnostics may be applicable for disease detection and/or management, these figures include only quality measures where IVDs are recommended by clinical practice guidelines found in the MEDLINE/PubMed or National Guideline Clearinghouse databases.

^Maintained by NCQA, HEDIS is a set of standardized quality measures that allows purchasers and others to evaluate and compare health plan performance.

+AHRQ's National Quality Measures Clearinghouse (NQMC) includes specific evidence-based health care quality measures and measure sets developed and used by health care organizations, network and associations that have developed and use quality measures to evaluate payer and provider performance.

As shown in **Figure 7.6**, 23% of HEDIS measures and 14% of NQMC measures used to gauge the quality of care available from a particular provider or health plan are direct measures of diagnostic use for assessing particular health risks, diseases or conditions.⁵⁴⁸ Of the 26 effectiveness of care quality measures in HEDIS, six are for diagnostics. Examples are quality measures for cervical cancer screening, screening of LDL cholesterol following a heart attack and chlamydia screening. Of the 660 disease-related quality measures in the NQMC, 92 are for

⁵⁴⁵ The Health Plan Employer Data and Information Set effectiveness of care measures are maintained by the National Committee for Quality Assurance (www.ncqa.org) and the National Quality Measures Clearinghouse disease measures are maintained by AHRQ.

⁵⁴⁶ Thorpe KE 2004.

⁵⁴⁷ Druss BG, Marcus SC, Olfson M, Pincus HA. The most expensive medical conditions in America. *Health Affairs* 2002;21(4):105-11.

⁵⁴⁸ While some individual measures also included *in vivo* diagnostics as a disease detection alternative, each of these measures include *in vitro* diagnostics for these purposes.

diagnostics. Examples are hemoglobin A1c testing to assess glycemic control, hepatitis C testing for patients at high risk and measurement of immunoreactive parathyroid hormone within three months following diagnosis with advanced chronic kidney disease.

The use of diagnostics in quality measures often is supported by clinical practice guidelines. Of all quality measures in HEDIS and NQMC, we identified guidelines specifically recommending diagnostic use in the NGC for 61.5% of those in HEDIS and 78.5% of those in the NQMC.

Of course, the development of measures for HEDIS, NQMC and other quality assessment initiatives is a relatively new process and represents only a sample of evidence-based use of diagnostics. Nevertheless, this analysis conveys the essential role of diagnostics in health care quality. Further, the incorporation of diagnostics into quality measures serves as a benchmark for assessing underuse of diagnostics and the health and economic impact of such underuse.

In its annual report on the state of health care quality in the US, NCQA assessed the impact of under-compliance with HEDIS measures, including those pertaining to diagnostics, on avoidable adverse health events, deaths and costs.⁵⁴⁹ **Figure 7.7** shows these impacts for measures pertaining to diagnostics used in breast cancer detection, cholesterol management, colorectal cancer screening and diabetes management.

Figure 7.7
Relationship between Application of Selected HEDIS Diagnostic Quality Measures and Avoidable Adverse Health Events, Deaths and Costs

HEDIS Quality Measure	Percent National Under-use in HEDIS Compliant Health Plans	Estimated Annual Avoidable Adverse Health Events	Estimated Annual Avoidable Deaths	Estimated Annual Avoidable Costs
Breast cancer screening (biopsy, needle aspiration or mammography)	19.3%	7,600 breast cancer cases treated in Stage IV due to late diagnosis	600-1,000	\$ 48 million
Cholesterol management	48.9	14,600 major coronary events	6,900-17,000	\$ 87 million
Colorectal cancer screening (FOBT or colonoscopy)	51.9	20,000 cases of colorectal cancer diagnosed/treated at a later stage	4,200-6,300	\$191 million
Diabetes management (HbA1c control)	20.2	14,000 heart attacks, strokes, or amputations	4,300-9,600	\$573 million

**Source: The state of health care quality: industry trends and analysis. Washington, DC: National Committee for Quality Assurance, 2004.*

These and other findings of the 2004 NCQA report on the state of health care quality demonstrate the potential for evidence-based use of diagnostics to improve health care quality and to avoid unnecessary adverse health events, deaths and costs.

⁵⁴⁹ The state of health care quality: industry trends and analysis. NCQA, 2004.

E. Emerging and Future Diagnostics: Implications for the Health System

Many factors have influenced the pace of biomedical innovation over the past 15-20 years. These include breakthroughs in science (e.g., sequencing of the human genome), engineering (e.g., device miniaturization), computer/information sciences (e.g., the Internet), changing health care systems and market pressures (e.g., increasingly global business environment). These and other technology drivers have spurred development of a broad spectrum of diagnostic products. Products that are smaller, faster, cheaper and increasingly accurate are more likely to be adopted rapidly. Refinement of these product characteristics will continue to shape emerging diagnostics. Among these, for example, are home-based diagnostics that use a personal digital assistant as a standard test platform. These products will allow multiple functions (e.g., self-testing, test analysis, data transfer and storage) for patients to manage chronic diseases (e.g., diabetes, hypertension) in an affordable and convenient format.

In addition to the patient-specific benefits of emerging diagnostics discussed in **Section 7.A** that offer system benefits via improved health outcomes and reduced costs, evolving diagnostic technologies will benefit the health system in other ways. Among the advances in health information networks, particularly relevant to diagnostics is the development of the Logical Observation Identifiers Names and Codes (LOINC). With LOINC terminology, which is recognized by the HL7 Standards Development Organization, diagnostic test orders and results can be standardized across health care facilities, such as laboratories, hospitals and public health departments, to facilitate efficient and effective exchange of clinical health information.⁵⁵⁰ As health information networks are developed and refined, diagnostic information will be more readily available for health decision-making and tracking the extent to which health care services are delivered as recommended, along with individual- and population-level health trends in outcomes and spending.⁵⁵¹

1. Educational and Distributive Challenges of New Diagnostic Technologies

One of the challenges of applying results of genetic tests is that the clinicians and patients will require substantial education, in order to weigh some types of emerging diagnostic information with other factors, such as family history and behavioral or environmental factors, appropriately.⁵⁵² For instance, although certain genetic mutations in the BRCA1 and BRCA2 genes indicate a substantially increased *risk* for breast or ovarian cancer, their presence does not confer certainty of developing cancer. Although tests for these genes only indicate risk, these results still can influence treatment decisions, sometimes disproportionately so. Positive identification of BRCA1 and BRCA2 mutations may lead some woman to pursue prophylactic treatment for breast cancer, such as chemoprevention or mastectomy.⁵⁵³ The complex information resulting from genomic, proteomic, metabolomic and other emerging diagnostics

⁵⁵⁰ Unified Medical Language System, Logical Observation Identifiers Names and Codes (LOINC). Bethesda, MD: National Library of Medicine, 2004. Accessed April 29, 2005. http://www.nlm.nih.gov/research/umls/loinc_main.html

⁵⁵¹ Measuring health care quality: obstacles and opportunities. National Committee on Vital Health Statistics, 2004.

⁵⁵² Khoury MJ. Genetics and genomics in practice: the continuum from genetic disease to genetic information in health and disease. *Genet Med* 2003;5(4):261-8.

⁵⁵³ Genomics and population health: United States 2003. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, 2004. Accessed October 22, 2004. <http://www.cdc.gov/genomics>.

will pose interpretive challenges to practitioners, patients and families. As these technologies evolve, so too must consideration of human factors and decision support tools.⁵⁵⁴

Another system-wide consideration for emerging technologies is the impact of targeted diagnostics and therapeutics on patient access. As we uncover relationships between genetics and health, we also discern more benefits and harms of interventions. In some cases, diagnostic information may enhance care options for certain subpopulations (e.g., by gender or ethnicity) but, in others, it may be used to preclude patients from accessing care, particularly if payers determine not to cover care for patients who are unlikely to respond well to available interventions (i.e., ultra-rapid or slow drug metabolizers). Such concerns regarding equity of care must be addressed carefully, to ensure that industry has incentives to develop targeted technologies, patients have appropriate and affordable access to these technologies and wider health disparities are prevented.⁵⁵⁵

2. Value of Diagnostics in the Patient Electronic Medical Record

Although electronic medical records (EMRs) hold great potential for improving health care efficiency, adoption of EMRs has been inconsistent and slow. In April 2004, President Bush set a goal for most Americans to have EMRs by 2014.⁵⁵⁶ Currently, it is estimated that 60% of the information stored in EMRs are diagnostic results.⁵⁵⁷

The increasing ability of information systems to incorporate vital diagnostic information directly into EMRs benefits the health care system in several ways. Having test results stored in this manner enables multiple clinicians to access actionable information and can reduce unnecessary or duplicate test orders. Existing evidence indicates that diagnostic information in EMRs improves the functioning of multidisciplinary clinician teams and are a means of quality assurance, since EMRs can alert doctors to potential complications based on diagnostic results.⁵⁵⁸ EMRs also offer a means to track patient care and outcomes, identify areas for quality improvement and inform performance enhancement strategies of individual clinicians and provider organizations.⁵⁵⁹

⁵⁵⁴ Plapp F, Essmyer CE, Byrd AB, Zucker ML. How to successfully influence laboratory test utilization. *Clin Leadersh Manag Rev* 2000;14(6):253-60.

⁵⁵⁵ Ibid.

⁵⁵⁶ President Bush touts benefits of health care information technology: remarks by the President in a conversation on the benefits of health care information technology. Baltimore, MD: Department of Veterans Affairs Medical Center, 2004. Accessed September 30, 2004. <http://www.whitehouse.gov/news/releases/2004/04/20040427-5.html>.

⁵⁵⁷ Bufton A. Information management trends in in vitro diagnostics. Business Briefing: Medical Device Manufacturing & Technology, 2002. Accessed September 30, 2004. http://www.bbriefings.com/pdf/753/mdev02_p_bufton.pdf.

⁵⁵⁸ Podichetty V, Penn D. The progressive roles of electronic medicine: benefits, concerns, and costs. *Am J Med Sci* 2004;328(2):94-9.

⁵⁵⁹ Measuring health care quality: obstacles and opportunities. Washington, DC: US Department of Health and Human Services, National Committee on Vital Health Statistics, 2004. Accessed October 22, 2004. <http://www.ncvhs.hhs.gov/040531rp.pdf>.

3. Increasing Role of Diagnostics in Health Practitioner Decision Support

Twenty years ago, clinicians had much smaller menus of diagnostics. Their knowledge did not include today's emerging fields of genomics or proteomics, and treatment for many diseases followed a "one size fits all" model. Today, practitioners must understand not only clinical medicine, but must be able to properly order and interpret a wider array of diagnostics to provide appropriate care. While diagnostics alone do not provide all of the data needed for diagnosis, prognosis or treatment decisions, they are an indispensable part of health care.

As diagnostics become more sophisticated, practitioners must be able to interpret and incorporate their results into clinical practice in a way that enhances quality of care and corresponds with evidence-based practice. Clinical practice guidelines are tools for accomplishing these requirements. However, the profuse number of guidelines and their evolving nature challenges practitioners to remain apprised of the latest relevant guidelines. One means for practitioners to cope with this challenge is to use computer-based diagnostic decision support systems (DDSS). Based on a specific patient's characteristics, which the practitioner can enter into a computer or hand-held personal digital assistant, DDSS provide suggestions for initial clinical assessment and tests to confirm a diagnosis.⁵⁶⁰ While DDSS do not replace practitioner assessment and judgment in patient care, they have been demonstrated to enhance the ability of practitioners to predict and characterize disease more accurately, monitor the impact of treatment efforts and predict health status changes in individual patient.^{561,562}

Computer-based DDSS are used in many clinical settings, including emergency rooms, psychiatric care, intensive care units and nursing, though type of application varies. Large academic medical centers are more likely than small physician practices to use DDSS. These systems have been found not only to improve quality of care, but to provide automated access to guidelines and improving processes within health systems.⁵⁶³

4. Realizing the Value of Future Diagnostics for Health System Improvement

A 2005 Commonwealth Fund study of physicians and quality of health care in the US reported that, of 3,598 physicians surveyed, around 80%, "found it difficult or were unable to find out which of their patients have abnormal laboratory results or were taking high-risk medications (and may require additional follow-up)." This inability of physicians to access easily and act on diagnostic and other critical health data has significant implications for the efficiency and quality of health care in the US.⁵⁶⁴

⁵⁶⁰ Ramnarayan P, Kapoor RR, Coren M, et al. Measuring the impact of diagnostic decision support on the quality of clinical decision-making: development of a reliable and valid composite score. *J Am Med Inform Assoc* 2003;10(6):563-72.

⁵⁶¹ Friedman CP, Elstein AS, Wolf FM. Enhancement of clinicians' diagnostic reasoning by computer-based consultation: a multisite study of 2 systems. *JAMA* 1999;282(19):1851-6.

⁵⁶² Trivedi MH, Kern JK, Grannemann BD, et al. A computerized clinical decision support system as a means of implementing depression guidelines. *Psychiatr Serv* 2004;55(8):879-85.

⁵⁶³ Varon J, Marik PE. Clinical information systems and the electronic medical record in the intensive care unit. *Curr Opin Crit Care* 2002;8(6):616-24.

⁵⁶⁴ Audet A, et al. Measure, learn, and improve: physician's involvement in quality improvement. *Health Affairs* 2005;24(3):843-53.

In order to realize the potential of diagnostics to improve health system efficiency, continued integration with complementary technology, such as EMRs and decision support systems, will be necessary. As health providers and payers expand use of information management, patient diagnostic and vital information can be aggregated to enable evaluation of trends in the provision of health care, identification of quality improvement and cost saving opportunities, as well as an information source for health policy and reform efforts.^{565,566}

The rate of this advancement will be limited by:

- The degree of focused and harmonious efforts among various health stakeholders
- Incentives for stakeholder buy-in and participation
- Availability of federal, state, private and philanthropic funding to support information networks and data analysis efforts
- Extent to which regulated patient information can be anonymized, aggregated and examined (e.g., use of patient information protected by HIPAA or the Genetic Information Discrimination Act of 2003)

Successful application of these advances will require education of clinicians, patients, regulators, payers and others regarding their use and health and economic impacts.

F. Comparing Costs of Diagnostic Testing and Care per Patient Episode: Four Case Studies

This section presents four case studies that illustrate different ways in which diagnostics have beneficial effects on patient health, quality of health services and health care spending. Three of these pertain to diagnostics for each of heart disease, cancer and diabetes. These three disease categories account for nearly two-thirds of all US deaths and more than \$700 billion in direct and indirect costs annually.⁵⁶⁷ The final example examines diagnostics for *Chlamydia trachomatis*, the bacteria that causes common, yet often undiagnosed, chlamydial infection, a disease responsible for more than \$6.5 billion in direct medical costs in the most affected age group of 15-24 year olds alone.⁵⁶⁸

⁵⁶⁵ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁵⁶⁶ Measuring health care quality: obstacles and opportunities. Washington, DC: US Department of Health and Human Services, National Committee on Vital Health Statistics, 2004. Accessed October 22, 2004. <http://www.ncvhs.hhs.gov/040531rp.pdf>.

⁵⁶⁷ Eyre H, Kahn R, Robertson RM, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* 2004;109(25):3244-55.

⁵⁶⁸ Chesson HW, Blandford JM, Gift TL, et al. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. *Perspect Sex Reprod Health* 2004;36(1):11-9.

In each case study, the burden for each of the specific diseases is presented from a clinical and economic standpoint, along with a description of a specific test used for its diagnosis and/or monitoring. Contributions of that diagnostic to quality of care, improved patient outcomes and health care costs, including an analytic framework that shows these impacts across the continuum of patient care, are described. For each disease presented here, early and accurate diagnoses are critical to averting additional complications, adverse outcomes and costs.⁵⁶⁹

Case Study 1: Troponin Testing for Identification of Heart Attack

a. Magnitude and Importance of Heart Disease

Cardiovascular disease is the leading cause of mortality in the US. Including heart attack and heart failure, approximately 700,000 people die annually from cardiovascular disease.⁵⁷⁰ Heart failure accounts for between \$21 billion and \$40 billion annually, representing approximately 1.5-3% of national health expenditures.⁵⁷¹

Angina, a common sign of a heart attack, accounts for approximately 5.6 million emergency department visits annually and is second only to abdominal pain as the most common reason for an emergency department visit.^{572,573,574} At least two undesirable scenarios can result when patients with angina are not properly evaluated. In the first, patients who are not experiencing an acute myocardial infarction (AMI, or heart attack), are inappropriately admitted to the hospital. The cost of unnecessary hospital admissions for chest pain is estimated to exceed \$12 billion annually. In the second scenario, patients who truly are experiencing an AMI are discharged without treatment. Some 2-10% of individuals experiencing AMI mistakenly are sent home due to incorrect diagnoses, increasing risks for sudden death or heart damage due to treatment delay.^{575,576} Misdiagnosed AMIs also can have legal consequences, ranking as the leading cause of malpractice lawsuits and settlements among emergency department patients.⁵⁷⁷

⁵⁶⁹ For example, when undiagnosed and poorly managed, diabetes can lead to additional serious health problems such as kidney failure and blindness. Though it rarely exhibits symptoms, untreated chlamydia can lead to infertility in infected males and females and potentially fatal ectopic pregnancies.

⁵⁷⁰ Summary health statistics for US adults: national health interview survey 2002. Hyattsville, MD: US Department of Health and Human Services, National Center for Health Statistics, 2002. Accessed September 27, 2004. <http://www.cdc.gov/nchs/fastats/heart.htm>.

⁵⁷¹ Abraham W, Scarpinato L. Higher expectations for management of heart failure: current recommendations. *J Am Board Family Practice* 2002;15:39-49.

⁵⁷² A heart attack usually occurs when the blood supply to part of the heart muscle (myocardium) is severely reduced or stopped due to fatty plaque buildup or a blood clot.

⁵⁷³ Hamm C, Goldmann B, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *NEJM* 1997;337:1648-53.

⁵⁷⁴ Clinical evaluation of patients who present with angina includes a medical history, physical examination, electrocardiogram (ECG) and blood tests for certain cardiac biomarkers to indicate whether a patient has experienced an AMI.

⁵⁷⁵ Roberts R, Kleinman N. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mind-set." *Circulation* 1994;89:872-881.

⁵⁷⁶ Pope J, Aufderheide T, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *NEJM* 2000;342:1163-70.

⁵⁷⁷ Green G, Green S. Markers of myocardial injury in the evaluation of the emergency department patient with chest pain. In: Wu AHB, ed. *Cardiac markers*. Totawa, NJ: Humana Press, 1998:75-89.

Several cardiac biomarkers indicate occurrence of an AMI with varying degrees of specificity. One such common marker is creatine kinase (CK), an enzyme found in brain, heart and skeletal tissue and, therefore, is not specific to heart muscle damage. The existence of CK in tissue outside of the heart makes it difficult for practitioners to determine the origin of increased CK levels and to diagnose heart muscle damage accurately. Until recently, this was the most widely used test for heart muscle damage.⁵⁷⁸

Recent evidence demonstrates that the protein troponin is a more specific and sensitive marker than CK for detection of AMI.⁵⁷⁹ Current tests to detect troponin use antibodies specific to cardiac forms of the protein excreted by heart cells in distress, allowing for nearly 100% specificity and 93-100% sensitivity for detection of heart muscle damage.^{580,581} Troponin testing recently has been proposed as the new standard for identifying AMI by the American College of Cardiology and the European Society of Cardiology.⁵⁸² There is also a growing body of research suggesting that troponin measurement is useful in detecting heart damage in ESRD and pre-AMI patients. Further research is being conducted to better understand these emerging applications and related prevention opportunities (**Figure 7.8**).

⁵⁷⁸ Abadie JM. Cardiac markers and a failed algorithm: can accurate assessment of acute myocardial infarction be cost effective? *Military Medicine* 2002;167:683-7.

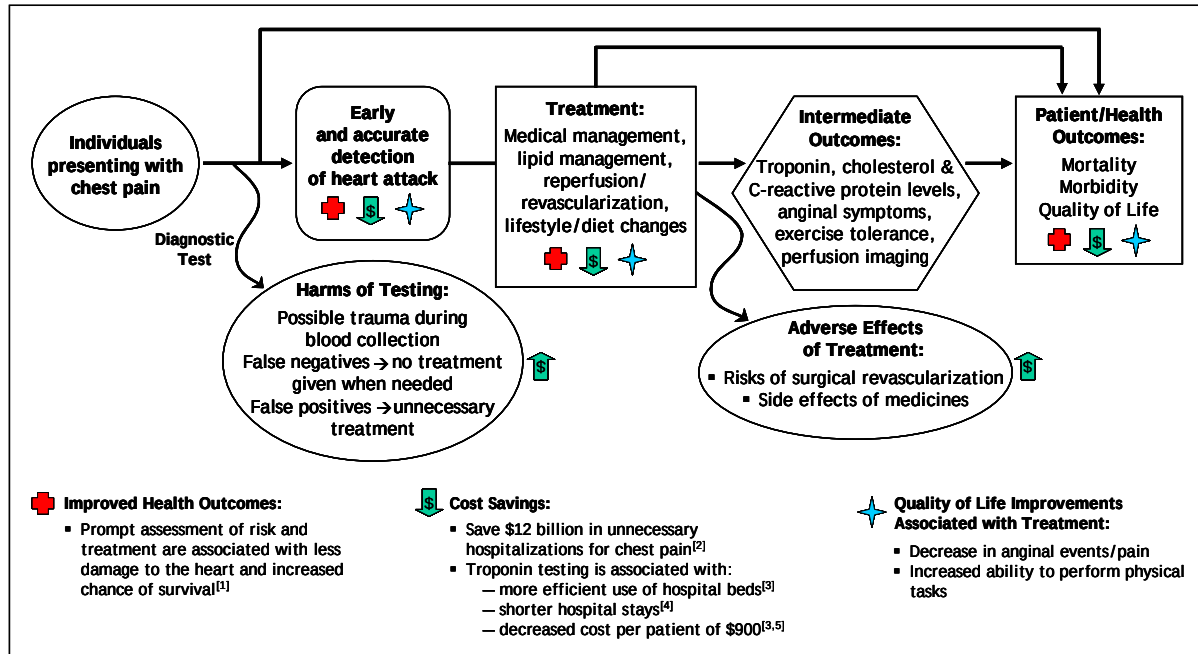
⁵⁷⁹ Craig J, Bradbury I, Collinson P, et al. The organization of troponin testing services in acute coronary syndromes. Health Technology Assessment Report 4. Glasgow, Scotland: NHS Quality Improvement Scotland, 2004.

⁵⁸⁰ Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2(2):75-84.

⁵⁸¹ Abadie JM. Cardiac markers and a failed algorithm: can accurate assessment of acute myocardial infarction be cost effective? *Military Medicine* 2002;167:683-7

⁵⁸² Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined - a consensus document of The Joint European Society of Cardiology/ American College of Cardiology Committee for the redefinition of myocardial infarction - The Joint European Society of Cardiology/ American College of Cardiology Committee. *J Am Coll Cardiol* 2000;36:959-69.

Figure 7.8
Analytic Framework for Troponin Testing for Detection of AMI



Sources:

1. Heart & stroke facts. Dallas, TX: American Heart Association, 2003.
2. DRG Handbook. Washington, DC: Academic Press, 1997.
3. Ng SM, Krishnaswamy P, Morissey R, et al. Ninety-minute accelerated critical pathway for chest pain evaluation. *American Journal of Cardiology* 2001;88(6):611-7.
4. Zarich S, Bradley K, Seymour J, et al. Impact of troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischemia. *American Journal of Cardiology* 2001;88:732-6.
5. Cavanaugh N, Cassidy M. The effect of a change from conventional cardiac enzymes to troponin I on overall hospital costs in patients with suspected myocardial infarction. *The Irish Journal of Medicine* 2002; 95(1):16-7.

b. Clinical Value of Troponin Measurement in Detecting AMI

Because current tests detect troponins released only from dead and injured heart muscle cells and not other cells of the cardiovascular system, circulating troponin levels normally are very low and usually undetectable.⁵⁸³ However, troponin levels increase substantially and can be detected within 4-6 hours of the onset of an AMI. These factors allow for sensitive, specific and rapid detection of even minor damage to the heart.

One recent study revealed the impact of troponin's increased sensitivity and specificity relative to CK. When CK was used to detect AMI, the detected incidence of heart attack was 8.3%, whereas with troponin testing, detected AMI incidence increased 160%.⁵⁸⁴ This finding suggests that using troponin to detect AMI may uncover more cases of early heart damage and allow for

⁵⁸³ Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2(2):75-84.

⁵⁸⁴ Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004;109:2749-54.

earlier preventive treatment. Troponin also remains in the blood for up to 10-14 days, allowing for more accurate triage decisions for patients presenting to the emergency department.⁵⁸⁵

Rapid diagnosis of AMI in patients with chest pain can prevent further heart damage and improve outcomes in many patients. The amount of time required to establish a diagnosis of AMI depends on the time taken to receive blood test results (at least 6-12 hours or longer following admission).⁵⁸⁶ The four-hour window following onset of an AMI is optimal for salvaging the myocardium and preventing further damage.⁵⁸⁷

One of the beneficial aspects of troponin testing is that it can be conducted at the patient's bedside, i.e., point-of-care testing (POCT). Troponin POCT is reported to decrease the time to obtain test results by 55% compared to central laboratory procedures.⁵⁸⁸ In a separate study of multi-marker POCT strategies, joint use of myoglobin and troponin testing was reported to be 96.9% sensitive and 99.6% specific for detection of AMI in under three hours, or 66% faster than central laboratory turn-around time, suggesting that POCT measurement of troponin can be a time-saving and effective alternative to conventional methods of detecting AMI.⁵⁸⁹

c. Economic Value of Troponin in Detecting AMI

Evaluation and accurate triage of patients with chest pain remains challenging and costly, with more than \$12 billion attributable to inappropriate admissions each year. More accurate and timely methods of detecting AMI could reduce this economic burden. Troponin testing, which has been cited as a new gold standard for detecting heart muscle injury,⁵⁹⁰ offers greater specificity and sensitivity than other diagnostic modalities⁵⁹¹ and options for rapid patient assessment (within 4-6 hours of AMI) and triage. Studies addressing economic benefits of troponin testing include the following.

A study of nearly 1,000 patients conducted at Yale University assessed the economic value of troponin tests in addition to CK and ECG tests. Compared to patients who did not undergo troponin testing, patients receiving troponin testing in addition to standard assessment with CK and ECG had significant reductions in hospital admissions (average 6%), time to rule out AMI (9.6 hours), hospital length of stay (1.1 days) and critical care unit stay (1 day). Total hospital charges also were lower in patients tested for presence of troponin. Patients experiencing AMI who were diagnosed using troponin averaged \$15,004 in hospital charges, compared to \$19,202 for patients diagnosed using other methods. Patients with negative troponin test results (i.e., those found not to be experiencing an AMI) averaged \$4,487 in hospital charges, compared

⁵⁸⁵ Adama J, Schechtman K, Landt Y, et al. Comparable detection of acute myocardial infarction by creatine kinase MB isoenzyme and cardiac troponin I. *Clin Chem* 1994;40:1291-5.

⁵⁸⁶ McCord J, Nowak R, McCullough P, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation* 2001;104(13):1483-8.

⁵⁸⁷ Abadie JM. Cardiac injury markers and a failed algorithm: can accurate assessment of acute myocardial infarction be cost effective? *Mil Med* 2002;167:683-7.

⁵⁸⁸ Caragher T, Fernandez B, Jacobs F, Barr L. Evaluation of quantitative cardiac biomarker point-of-care testing in the emergency department. *J Emerg Med* 2002;22:1-7.

⁵⁸⁹ McCord J 2001.

⁵⁹⁰ Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2:75-84.

⁵⁹¹ Craig J 2004.

to \$6,187 in charges for patients diagnosed with other methods. On average, cost savings for patients whose diagnosis included troponin test information were \$900 lower.⁵⁹²

While the addition of troponin testing to diagnostic tests for CK and myoglobin initially is more expensive, the downstream cost savings from troponin's contribution to treatment decisions are significant. In one hospital lab, combined CK, myoglobin and troponin testing represented 3.5% of the total tests ordered, yet these accounted for 20% of the laboratory supply budget.⁵⁹³ However, the use of troponin in conjunction with CK and myoglobin testing is reported to yield a 30% savings in hospital costs for patients experiencing AMI and for those found to have chest pain due to other reasons.⁵⁹⁴ If more research confirms beneficial clinical and economic impacts of troponin testing, this tool could replace other cardiac markers used to diagnose AMI.⁵⁹⁵

Figure 7.9 details cost savings, differences in hospital stay and lab test utilization for patients with and without AMI based on the type of diagnostic used. Of course, testing for troponin and other cardiac markers are only a subset of the laboratory tests conducted for each patient as the physician makes a diagnosis and treatment decisions.

Figure 7.9
Cost Savings and Utilization Differences with Troponin Testing
in Patients With and Without AMI

	Mean Number of Laboratory Tests	Mean Length of Stay	Total Costs*	Percent Savings
Patients with AMI				
CK+myoglobin	36.0	5.69	\$7,452	
Troponin+CK+myoglobin	26.8	4.31	5,256	
Difference	-9.2	-1.38	-2,196	29.5%
Patients without AMI				
CK+myoglobin	14.7	2.02	2,019	
Troponin+CK+myoglobin	11.6	1.26	1,415	
Difference	-3.1	-0.76	-604	29.9%

*Total cost accounts for nursing, bed and laboratory costs.

Adapted from: Caragher TE, Fernandez BB, Barr LA. Long-term experience with an accelerated protocol for diagnosis of chest pain. *Arch Pathol Lab Med* 2000;124(10):1434-9.

⁵⁹² Zarich S, Bradley K, Seymour J, et al. Impact of Troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischaemia. *American Journal of Cardiology* 2001;88:732-6.

⁵⁹³ Abadie JM 2002.

⁵⁹⁴ Caragher TE, Fernandez BB, Barr LA. Long-term experience with an accelerated protocol for diagnosis of chest pain. *Arch Pathol Lab Med* 2000;124(10):1434-9.

⁵⁹⁵ Abadie JM 2002.

d. Conclusion

Many patients who visit emergency rooms with AMI are misdiagnosed based on normal ECG results alone, which appear in up to half of those experiencing AMI.⁵⁹⁶ Troponin is a highly specific, highly sensitive indicator of heart damage that more reliably detects AMI, leading to faster application of treatment and a reduction in adverse events associated with AMI. Because current troponin tests detect forms of the protein excreted only by heart cells in distress, troponin testing enables greater specificity (nearly 100%) and sensitivity (93-100%)⁵⁹⁷ than other diagnostics in detecting heart muscle damage.^{598,599} By improving the ability to triage patients presenting with chest pain accurately, troponin testing can reduce patient deaths, unnecessary hospital admissions and inefficient utilization of hospital resources.

Recently it has been shown that troponin is a good prognostic indicator in patients presenting with angina, even when CK levels are not elevated.⁶⁰⁰ The growing body of evidence of troponin's value as a reliable indicator of AMI has led to the addition of this cardiac biomarker to existing diagnostic protocols and guidelines.^{601,602}

Case Study 2: Hemoglobin A1c

a. Magnitude and Importance of Diabetes

Diabetes is the sixth leading cause of death in the US, affecting 18.2 million people, or 6.3% of the population.^{603,604} By the year 2030, there are projected to be 30.3 million diabetics in the US.⁶⁰⁵ When diabetes is not managed properly, serious problems, such as kidney disease, blindness, nerve damage and skin complications, can occur.⁶⁰⁶ Diabetes also is associated with an increased risk for heart attack, stroke and poor circulation.

⁵⁹⁶ Goldman L, Kirtane AJ. Triage of patients with acute chest pain and possible cardiac ischemia: the elusive search for diagnostic perfection. *Ann Intern Med* 2003;139:987-95.

⁵⁹⁷ Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2(2):75-84.

⁵⁹⁸ Adams J, Bodor G, Davila-Roman V, et al. Cardiac troponin I: A marker with high specificity for cardiac injury. *Circulation* 1998;88:101-6.

⁵⁹⁹ Craig J 2004.

⁶⁰⁰ Maisel A, Templin K, Love M, et al. A prospective study of an algorithm using cardiac troponin I and myoglobin as adjuncts in the diagnosis of acute myocardial infarction and intermediate coronary syndromes in a veteran's hospital. *Clinical Cardiology* 2000;23:915-20.

⁶⁰¹ ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Bethesda, MD: American College of Cardiology Foundation (ACCF), 2002.

⁶⁰² Wu AH, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem* 1999;45:1104-21.

⁶⁰³ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁰⁴ All about diabetes. Alexandria, VA: American Diabetes Association, 2004. Accessed September 24, 2004. <http://www.diabetes.org/about-diabetes.jsp>.

⁶⁰⁵ Study finds diabetes will double in world by 2030: predicts rapid US increase that greatly exceeds prior CDC projections. Alexandria, VA: American Diabetes Association, 2004. Accessed September 24, 2004. <http://www.diabetes.org/for-media/2004-press-releases/4-26.jsp>.

⁶⁰⁶ In diabetes, the body does not produce or use the hormone insulin sufficiently, which is essential for metabolism of blood sugar (glucose) and maintenance of proper blood sugar levels. In healthy individuals, insulin naturally

Type 1 diabetes, often called juvenile diabetes, typically occurs in childhood and adolescence.⁶⁰⁷ About 5–10% of people diagnosed with diabetes in the US have Type 1 diabetes.⁶⁰⁸ Type 2 diabetes, the most common form of diabetes, occurs when the body fails to produce sufficient insulin or to properly use the insulin that the pancreas does produce. Type 2 diabetes tends to affect adults and increases with age and obesity.

Although there is no cure for diabetes, it can be managed with behavioral and pharmacological interventions. Adequate management of diabetes can prevent severe complications and improve quality of life, in addition to averting the considerable health care costs resulting from uncontrolled diabetes and its associated complications.⁶⁰⁹

b. Background of Hemoglobin A1c Testing

The diagnostic test for hemoglobin A1c (HbA1c) reflects average blood glucose levels over the previous 2-3 months. HbA1c (also referred to as glycated or glycosylated hemoglobin) is formed when glucose in the blood binds to hemoglobin, a protein carried by red blood cells. Since blood glucose binds irreversibly to hemoglobin, measurement of HbA1c allows clinicians to gauge long-term glucose control better and adjust treatment strategies accordingly than does conventional glucose testing alone. HbA1c concentration is expressed as a percentage of total hemoglobin, with an HbA1c level of 7% or below as the target for control of diabetes. A level of 8% or higher indicates that action such as insulin level adjustment should be taken. As a complement to daily self-monitoring of blood glucose, HbA1c testing provides a more rounded picture of patient compliance with recommended care and overall patient health (**Figure 7.10**).

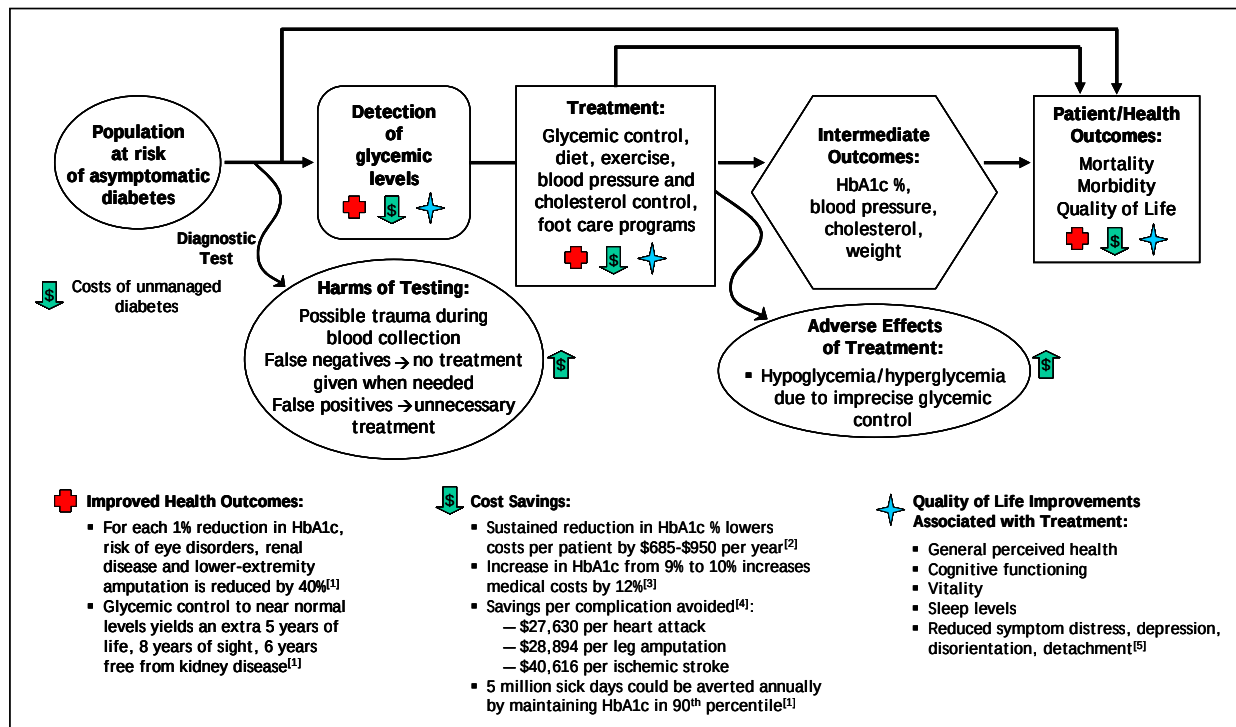
is manufactured by the beta cells of the pancreas and helps the body move glucose from the blood into cells to be used for energy.

⁶⁰⁷ With Type I diabetes, the body's immune system destroys the pancreatic beta cells, diminishing or ceasing the production of insulin.

⁶⁰⁸ All about diabetes. Alexandria, VA: American Diabetes Association, 2004. Accessed September 24, 2004. <http://www.diabetes.org/about-diabetes.jsp>.

⁶⁰⁹ Type 1 diabetes primarily is managed through insulin replacement, either through an injection or insulin pump, which delivers insulin throughout the day via a small catheter. Type 2 diabetes mainly is managed with diet and exercise and also may be controlled with insulin and other medications. Regular monitoring of blood sugar levels contributes to diabetes management.

Figure 7.10
Analytic Framework for Hemoglobin A1c Testing
to Evaluate Glycemic Control in Diabetic Patients



Sources:

1. National Committee for Quality Assurance, 2004.
2. Wagner EH, Sandhu N, Newton KM, et al. Effect of improved glycemic control on health care costs and utilization. *JAMA* 2001;285(2):182-9.
3. National Committee on Quality Assurance 2004.
4. O'Brien JA, Shomphe LA, Kavanaugh PL, et al. Direct medical costs of complications resulting from type 2 diabetes in the U.S. *Diabetes Care* 1998;21(7):1122-8.
5. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998;280(17):1490-6.

Advances in HbA1c diagnostic techniques are contributing to testing efficiency and standardization, including ion exchange, affinity chromatography and electrophoresis tests that include manual, semi-automated and automated tests. POCT HbA1c tests for use in physician's offices or as home testing devices have been available since the late 1990s, allowing more rapid assessment of HbA1c levels and prompt treatment (**Figure 7.11**).⁶¹⁰

⁶¹⁰ Type 1 diabetes primarily is managed through insulin replacement, either through an injection or insulin pump, which delivers insulin throughout the day via a small catheter. Type 2 diabetes mainly is managed with diet and exercise and also may be controlled with insulin and other medications. Regular monitoring of blood sugar levels contributes to diabetes management.

Figure 7.11
Milestones for Hemoglobin A1c Testing

Date	Milestone
1922	Discovery of insulin.
1974	Congress enacts the National Diabetes Mellitus Research and Education Act (P.L. 93-354), which requires NIH to develop a long-range plan to combat diabetes. A Commission, formed to create this plan, recommends a long-term clinical study.
Pre-1975	Reliance on urine sugar/glucose and ketone tests to diagnose and treat diabetes.
1976	Research demonstrates that hemoglobin becomes glycosylated (attached to glucose molecules) easily. Glycohemoglobin (HbA1c) measurements become widespread as a way to assess more long-term blood sugar control.
Early-1980s	HbA1c testing becomes widely available in laboratories. Home glucose monitoring enables individualized dosing of insulin.
1983	Beginning of a 10-year RCT, the DCCT, to determine the effectiveness of intensive diabetes management in the prevention or delay of diabetes complications. Study relies on measurements of HbA1c to determine blood glucose levels.
1993	DCCT results are published, showing risk for development and progression of complications from Type 1 diabetes is closely related to degree of glycemic control, as measured by HbA1c.
1994	American Diabetes Association issues diabetes treatment goals, consistent with DCCT study, and states specific HbA1c targets based on DCCT results.
1996	National Glycohemoglobin Standardization Program begins.
1999-2000	HbA1c testing incorporated into HEDIS performance measurement for managed care organizations (optional measure in 1999; mandatory measure in 2000).
Late 1990s	Availability of point-of-care and home tests for HbA1c.

Source: Provided by Raab & Associates 2004.

c. Clinical Value of HbA1c Testing for Diabetes Management

Measurement of HbA1c is the gold standard method for long-term monitoring of glycemic control in diabetics. Glycemic control has been associated with a nearly 50% gain in quality of life in patients with Type 2 diabetes.⁶¹¹ Specifically, glycemic control leads to increased cognitive functioning and general perceived health, less symptom distress and lower rates of depression and detachment.⁶¹²

HbA1c is the only laboratory test validated through RCTs to be a predictor of risk for microvascular complications such as retinopathy, nephropathy and neuropathy associated with diabetes.⁶¹³ Numerous authoritative clinical practice guidelines,^{614,615,616} including those from the

⁶¹¹ Testa MA, Simonson DC, Turner RR. Valuing quality of life and improvements in glycemic control in people with type 2 diabetes. *Diabetes Care* 1998;21:C44-52.

⁶¹² Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998;280:1490-6.

⁶¹³ Management of diabetes mellitus in the primary care setting. Washington, DC: Department of Veterans Affairs, 1999.

⁶¹⁴ American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004;27:S5-S10.

⁶¹⁵ Goldstein D, Little R, Lorenz R, et al. Tests of glycemia in diabetes. *Diabetes Care* 2004;27:S91-3.

⁶¹⁶ US Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: recommendation and rationale. *Ann Intern Med* 2003;138:212-4.

International Diabetes Center,^{617,618} Department of Veteran Affairs⁶¹⁹ and California Department of Health Services,⁶²⁰ recommend HbA1c monitoring every 3-4 months as an essential step in informing appropriate and ongoing management and treatment of diabetes.

Evidence supporting HbA1c management of Type 2 diabetes has led to its inclusion as an evidence-based quality measure with national standard-setting groups. In 2000, HbA1c testing became incorporated into the NCQA HEDIS⁶²¹ used to gauge health plan performance in more than 90% of US managed care organizations.

d. Economic Value of HbA1c Testing for Diabetes Management

The economic impact of diabetes is enormous. In 2002, diabetes accounted for an estimated \$132 billion in combined direct and indirect expenditures, including \$91.8 billion in direct medical expenditures and \$39.8 billion in indirect costs associated with mortality, permanent disability, lost workdays and restricted activity days. More than half of the direct medical costs associated with diabetes were attributable to people age 65 and older.⁶²² Diabetes is the eighth most costly health care condition in the US.⁶²³

Lack of glycemic control in diabetics is associated with higher health care utilization and costs. For example, costs to a large HMO were found to increase significantly as the average HbA1c levels in that HMO's patients increased (**Figure 7.12**). For each percent increase in HbA1c levels over 6%, diabetes-related direct charges increased from 4% to 30%.⁶²⁴ Failure to achieve glycemic control in patients with Type 2 diabetes has been linked to high rates of productivity loss. **Figure 7.12** depicts key economic differences between patient groups that undergo glycemic control and those that do not. As many as 5 million sick days could be prevented annually by maintaining HbA1c levels in the 90th percentile of the recommended range.⁶²⁵

⁶¹⁷ Type 2 diabetes practice guidelines. Minneapolis, MN: International Diabetes Center, 2003.

⁶¹⁸ Type 1 diabetes practice guidelines. Minneapolis, MN: International Diabetes Center, 2003.

⁶¹⁹ Management of diabetes mellitus in the primary care setting. 1999.

⁶²⁰ Basic guidelines for diabetes care. Sacramento, CA: California Department of Health Services, Diabetes Control Program, 2002.

⁶²¹ Adapted from Raab & Associates, 2002. <http://www.raab-associates.com>.

⁶²² Hogan P 2002.

⁶²³ Druss BG, Marcus SC, Olsson M, Pincus HA. The most expensive medical conditions in America. *Health Affairs* 2002;21:105-11.

⁶²⁴ Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans for poor glycemic control. *Diabetes Care* 1997;20:1847-53.

⁶²⁵ The state of health care quality: industry trends and analysis. NCQA, 2004.

Figure 7.12
Cost Differences between Patients
Undergoing and Not Undergoing Glycemic Control

Economic Measure	With Glycemic Control	Without Glycemic Control
Work absenteeism	\$24 lost per worker/month	\$115 lost per worker/month
Cost of bed days	\$1,539 per 1,000 person-days	\$1,843 per 1,000 person-days
Cost of restricted-activity days	\$2,660 per 1,000 person-days	\$4,275 per 1,000 person-days

Source: Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. JAMA 1998;280:1490-6.

Much of the direct cost savings of glycemic control is attributable to avoidance of serious complications. Each 1% reduction in HbA1c, can reduce the risk of eye disorders, renal disease and lower-extremity amputation by 40% over the previous HbA1c level.⁶²⁶ Aggressive reduction of HbA1c levels for patients with HbA1c levels higher than 8% is associated with significant reduction in key cardiovascular risk factors.⁶²⁷ Considering that the cost per heart attack is \$27,630, per leg amputation is \$28,894 and per ischemic stroke is \$40,616 in patients with Type 2 diabetes, avoiding these outcomes through more intensive management with HbA1c testing can translate into significant cost savings.⁶²⁸

e. Conclusion

Diabetes is a costly condition characterized by elevated blood glucose levels that can lead to serious complications such as kidney disease, blindness, nerve damage, lower limb amputation, skin complications, heart attacks and stroke. Although there is no cure for diabetes, effective management through a combination of blood glucose monitoring, insulin replacement, diet and exercise is essential to avoiding these complications.

HbA1c testing reflects average blood glucose levels over the previous 2-3 months, informing clinicians and patients about long-term glycemic control. HbA1c levels of 8% or higher indicate the need to control blood glucose levels. HbA1c testing currently is used in combination with self-monitoring of blood glucose levels. The essential role of HbA1c testing has evolved over the past 50 years, along with technical advances in testing methods. Among these advances, modern HbA1c tests have become more standardized and now include POCT and home tests.

There is clear evidence of the economic benefits of HbA1c testing for the purpose of glycemic control. Lack of glycemic control results in increased health care costs, while implementing glycemic control is associated with reductions in health care utilization, productivity losses and health care costs.

⁶²⁶ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶²⁷ Gilmer TP 1997.

⁶²⁸ O'Brien JA, Strompfe LA, Kavanaugh PL, et al. Direct medical costs of complications resulting from type 2 diabetes in the US Diabetes Care 1998;21:1122-8.

Case Study 3: Chlamydia Testing

a. Magnitude and Importance of the Disease

Chlamydial infection is the most commonly reported bacterial sexually transmitted disease (STD) in the US. However, chlamydia cases are significantly underreported since most (75% of women and 50% of men) who are infected do not exhibit symptoms.⁶²⁹ According to the CDC, 2.8 million people are infected with chlamydia each year in the US, and 834,555 chlamydia infections were reported to the agency in 2002.⁶³⁰ Chlamydia is especially prevalent among adolescents and young adults. Some 40% of all cases occur in people ages 15-19, and the prevalence of chlamydia in adolescent females often exceeds 10%.⁶³¹

Left untreated, chlamydia can lead to serious complications. As many as 40% of infected women develop pelvic inflammatory disease (PID), which leads to infertility in one of five affected women and may lead to ectopic pregnancy and chronic pelvic pain. While treatment cannot reverse the damaging effects of PID to a woman's reproductive organs, prompt treatment with 2-4 carefully chosen antibiotics can reduce further damage.⁶³² Patients with PID should be monitored carefully, to ensure success of treatment and any recent sexual partners should be treated promptly with antibiotics.

Undetected and untreated, the disease can have further consequences. Women with chlamydia who are exposed to HIV are 3 to 5 times more likely to become infected with HIV.⁶³³ A CDC analysis found that 3,249 out of 5,052 new HIV cases (64%) were preceded by a chlamydial infection.⁶³⁴ There also is preliminary evidence that a current or past chlamydial infection may increase the risk of cervical cancer.⁶³⁵

Diagnostic tests for chlamydia have evolved over time. Tests for chlamydia fall into two main categories: a) batch tests performed in a laboratory; and b) POCTs performed while patients

⁶²⁹ Chlamydia infection is caused by the *chlamydia trachomatis* bacterium. Of those infected women who do have symptoms, the most common are abnormal vaginal discharge, a burning sensation when urinating, abdominal pain, lower back pain, nausea, fever, pain during intercourse and bleeding between menstrual periods. Infected men may exhibit discharge from the penis, a burning sensation when urinating and pain and swelling of the testicles. Chlamydia also can be transmitted during sexual intercourse and can be passed from an infected mother to her baby during delivery. Chlamydia infection that is transmitted from infected mothers to infants during birth may result in neonatal ophthalmia (severe inflammation of the eye) and pneumonia.

⁶³⁰ Chlamydia fact sheet. Atlanta, GA: Centers for Disease Control and Prevention, 2004. Accessed September 15, 2004. <http://www.cdc.gov/std/Chlamydia/STDFact-Chlamydia.htm>.

⁶³¹ Tracking the hidden epidemics: trends in STDs in the United States. Atlanta, GA: Centers for Disease Control and Prevention, 2000. Accessed September 24, 2004. http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf.

⁶³² Ibid.

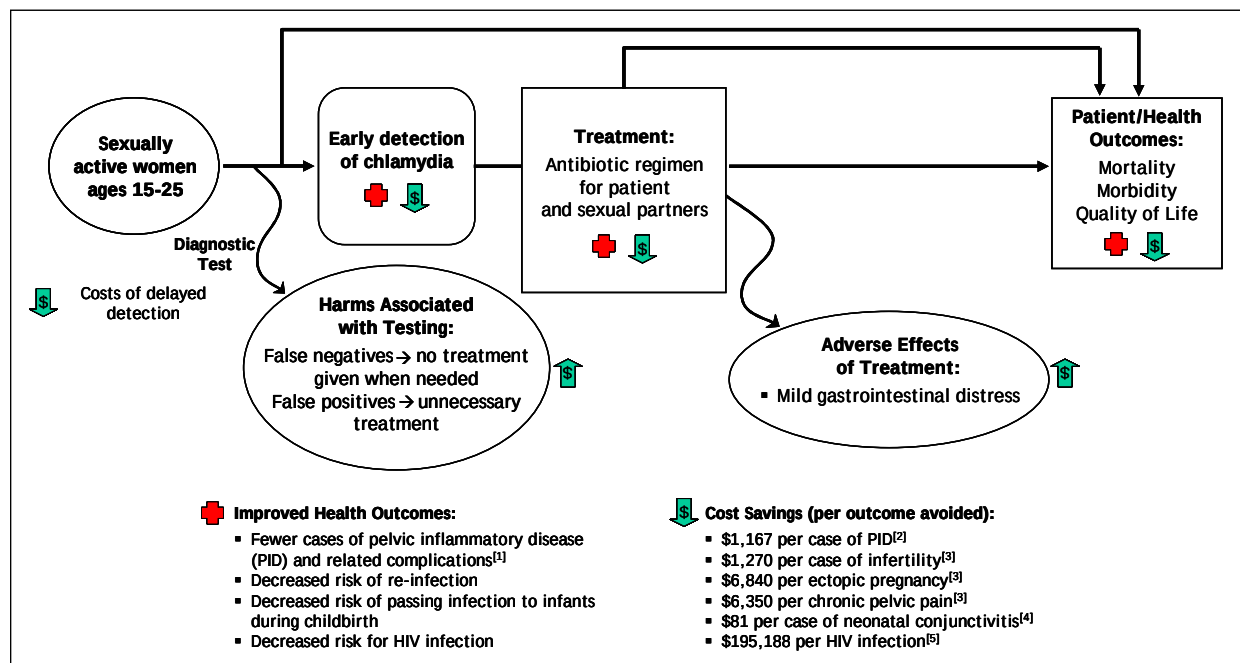
⁶³³ The state of health care quality: industry trends and analysis. Washington, DC: National Committee for Quality Assurance, 2004. Accessed October 22, 2004. <http://www.ncqa.org/communications/SOMC/SOHC2004.pdf>.

⁶³⁴ Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk of HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr* 2000;24:48-56.

⁶³⁵ Anttila T, Saikku P, Koskela P, et al. Serotypes of *Chlamydia trachomatis* and risk for development of cervical squamous cell carcinoma. *JAMA* 2001;285:47-51.

wait for the results.⁶³⁶ Culture tests, in which a sample from the patient is monitored for bacterial growth in the laboratory, were the first diagnostics used for detection of the infection. Drawbacks associated with culture tests, such as low sensitivity, difficulties in standardization, technical complexities, long waiting periods for results and relatively high test costs, prompted the development of non-culture tests that detect certain elements of the bacteria from the specimen (Figure 7.13).

Figure 7.13
Analytic Framework for Chlamydia Testing



Sources:

1. National Committee on Quality Assurance 2004.
2. Rein D, Kasser W, Irwin K, Rabiee L. Direct medical cost of pelvic inflammatory disease and its sequelae: decreasing, but still substantial. *Obstetrics & Gynecology*. 2000;95(3):397-402.
3. Yeh JM, Hook EW III, Goldie SJ. A refined estimate of the average lifetime cost of pelvic inflammatory disease. *Sexually Transmitted Diseases* 2003;30(5):369-78.
4. Magid D, Douglas J, Schwartz S. Doxycycline compared with azithromycin for treating women with genital chlamydia trachomatis infections: an incremental cost-effectiveness analysis. *Annals of Internal Medicine* 1996;124(4):389-99.
5. Holtgrave DR, Pinkerton SD. Updates on cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;16(1):54-62.

One type of non-culture test, nucleic acid amplification testing (NAT), offers a potential way to reduce costs of screening.⁶³⁷ NAT can use a urine sample that enables easier testing of men and women and, perhaps more importantly, enables chlamydia screening in the home and other non-traditional settings. With the current push toward screening for STDs in non-traditional and non-clinic settings, use of NAT may offer the advantages of easy specimen collection and increased compliance with recommended care.

⁶³⁶ Laboratory-based batch tests include culture tests that detect the presence of the living bacteria, enzyme immunoassays (EIAs) that detect chlamydia antigens, direct fluorescent antibody (DFA) tests that bind antibodies to bacterial antigens and nucleic acid hybridization tests and nucleic acid amplification tests that detect DNA or RNA sequences of chlamydia bacteria. POCT for chlamydia includes EIAs and optical immunoassays.

⁶³⁷ Kohl KS, Markowitz LE, Koumans EH. Developments in the screening for Chlamydia trachomatis: a review. *Obstet Gynecol Clin North Am* 2003;30:637-58.

Testing now has evolved to include home-based testing strategies that enable patients to obtain a sample at home and mail it to a laboratory without consulting a doctor.⁶³⁸ A positive result on the home-based chlamydia test indicates that a physician visit is necessary. Although the CDC recommends that sex partners of infected individuals be referred for testing and treated if necessary,⁶³⁹ the reported rates of chlamydial infection among men are substantially lower than those of females, even though it is estimated that the numbers of infected men and women are similar.⁶⁴⁰ The high prevalence of re-infection among women is attributable primarily to sex partners who have not received treatment. Re-infection is associated with an increased risk of developing PID.⁶⁴¹ With proper clinical follow-up, home-based testing has the potential to increase detection of this infected male sex partner population.

b. Clinical Value of Chlamydia Testing

Diagnostics for chlamydia allow detection of the infection at an early stage. Early treatment is associated with fewer complications and comorbid conditions, leading to better outcomes. Chlamydia screening programs are associated with a 60% decrease in cases of PID among young women.⁶⁴² Identifying and treating patients with chlamydia prevents transmission of the infection to sexual partners and to infants of infected pregnant women. Due largely to increased screening and treatment, the national incidence of chlamydia infection is estimated to have declined from more than 4 million infections per year in the early 1980s to 3 million infections per year today.⁶⁴³

The benefits of identifying and treating chlamydia infection have led to recommendations for testing from national organizations. The CDC and US Preventive Services Task Force recommend routine screening of all sexually active adolescent and young adult women.^{644,645} Chlamydia screening of sexually active women aged 15-25 has recently been incorporated as an NCQA HEDIS measure and, therefore, is used as a performance measure in more than 90% of managed care organizations in the country.

⁶³⁸ Chlamydia screening with home testing – an HTA. Denmark: Danish Centre for Evaluation and Health Technology Assessment, 2002. Accessed September 24, 2004. http://www.sst.dk/publ/Publ2004/CEMTV_eng/klamydia_1805.pdf.

⁶³⁹ Sexually transmitted diseases treatment guidelines. Morbidity and Mortality Weekly Report 51 (No. RR-6). Atlanta, GA: Centers for Disease Control and Prevention, 2002.

⁶⁴⁰ Tracking the hidden epidemics: trends in STDs in the United States. Atlanta, GA: Centers for Disease Control and Prevention, 2000. Accessed September 24, 2004. http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf.

⁶⁴¹ Sexually transmitted diseases treatment guidelines. Morbidity and Mortality Weekly Report 51(No. RR-6). Atlanta, GA: Centers for Disease Control and Prevention, 2002.

⁶⁴² The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁴³ Tracking the hidden epidemics: trends in STDs in the United States. Atlanta, GA: Centers for Disease Control and Prevention, 2000. Accessed September 24, 2004. http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf

⁶⁴⁴ Sexually transmitted diseases treatment guidelines. Morbidity and Mortality Weekly Report 51 (No. RR-6). Atlanta, GA: Centers for Disease Control and Prevention, 2002.

⁶⁴⁵ Berg AO. Screening for Chlamydia infection. Recommendations and rationale. *Am J Prev Med* 2001;20:90-4.

Despite the strong recommendations for chlamydia testing, it remains underused. NCQA reports that the 2003 average rate of chlamydia screening within Medicaid was 44.3-46.0%, while the average rate among commercial insurance plans was 29.1-30.4%.⁶⁴⁶

c. Economic Value of Chlamydia Testing

Chlamydial infection accounts for more than \$3.5 billion in annual health care costs in the US.⁶⁴⁷ Early detection enables timely treatment, translating into cost savings by averting complications and comorbid conditions associated with prolonged infection.

Considerable cost savings are realized with the prevention of PID, whose direct medical costs were estimated at \$1,167 per case.⁶⁴⁸ About 70% of the direct medical costs comprise the cost of treating PID, as opposed to costs of diagnosis and treatment sequelae. One review conducted in the late 1990s showed that universal screening of sexually active women aged 18-24 would prevent 140,113 cases of PID annually and save \$45 per woman screened.⁶⁴⁹ A recent study estimated the average lifetime cost for women with major complications of PID to include \$6,350 for chronic pelvic pain, \$6,840 for ectopic pregnancy and \$1,270 for infertility.⁶⁵⁰

Since chlamydia is associated with an increased risk for HIV infection, early detection and treatment may save costs through avoidance of HIV. Lifetime costs for an individual living with HIV are estimated at \$195,188.⁶⁵¹ As noted above, early detection and treatment of chlamydia may help prevent the eye infections (neonatal conjunctivitis) and pneumonia experienced by 60% of infants born to infected mothers.⁶⁵² Each case of neonatal conjunctivitis costs \$81 to treat and costs per case of neonatal pneumonia range from \$225 to \$3,023, depending on severity.⁶⁵³

According to one review, for every \$1 spent on screening, \$12 is saved by averting complications.⁶⁵⁴ The cost-effectiveness of chlamydia screening depends on the strategy used. A screening intervention for women aged 25 and younger resulted in a cost savings of \$3,300 per case of PID prevented compared to no screening, while a school-based screening program compared to a non-school-based screening program saved \$1,523 per PID case prevented.^{655,656}

⁶⁴⁶ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁴⁷ Ibid.

⁶⁴⁸ Rein D, Kasser W, Irwin K, Rabiee L. Direct medical cost of pelvic inflammatory disease and its sequelae: decreasing, but still substantial. *Obstet Gynecol* 2000;95:397-402.

⁶⁴⁹ Mangione-Smith R, O'Leary J, McGlynn EA. Health and cost-benefits of chlamydia screening in young women. *Sex Transm Dis* 1999;26(6):309-16.

⁶⁵⁰ Yeh JM, Hook EW 3rd, Goldie SJ. A refined estimate of the average lifetime cost of pelvic inflammatory disease. *Sex Transm Dis* 2003;30:369-78.

⁶⁵¹ Holtgrave DR, Pinkerton SD. Updates on cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;16:54-62.

⁶⁵² The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁵³ Magid D, Douglas J, Schwartz S. Doxycycline compared with azithromycin for treating women with genital chlamydia trachomatis infections: an incremental cost-effectiveness analysis. *Ann Intern Med* 1996;124:389-99.

⁶⁵⁴ Mangione-Smith, 1999.

⁶⁵⁵ Howell MR, Gaydos JC, McKee KT, et al. Control of Chlamydia infections in female army recruits: cost-effective screening and treatment in training cohorts to prevent pelvic inflammatory disease. *Sex Transm Dis* 1999;26:519-26.

⁶⁵⁶ Wang LY, Burstein GR, Cohen DA. An economic evaluation of a school-based sexually transmitted disease screening program. *Sex Transm Dis* 2002;29:737-45.

d. Conclusion

Diagnostics are critical to early detection of chlamydial infection. Early identification of patients with chlamydia is associated with decreased transmission and lower incidence of complications such as PID and infertility. Due to increased screening and treatment, the US incidence of chlamydial infection is reported to have declined since the early 1980s. The CDC, US Preventive Services Task Force and other authoritative bodies recommend regular screening of sexually active young women. Also, chlamydia screening for sexually active females aged 15-25 has been accepted as an NCQA HEDIS measure. Despite strong evidence for clinical benefit and cost savings, chlamydia testing remains significantly underused.

Early detection and treatment of chlamydia may reduce the costs of treating PID and its serious complications, including infertility, ectopic pregnancy and chronic pelvic pain. Further, it prevents transmission to sexual partners and newborns and lowers the risk for HIV infection and its considerable associated costs. Consistent with authoritative clinical guidelines and quality standards, chlamydia testing offers significant clinical and economic benefits for patients and the health care system.

Case Study 4: HER-2/neu Testing for Breast Cancer

a. Burden of Breast Cancer

Breast cancer, a disease that will affect an estimated 1 in 7 women during their lifetime, was responsible for an estimated 40,000 deaths in 2004. The annual direct and indirect costs of breast cancer treatment are estimated to range between \$2.4 billion and \$3.1 billion.⁶⁵⁷ Breast cancer patients may suffer losses in quality of life related to physical limitations, bodily pain and ability to function socially.⁶⁵⁸ Even with increasing survival rates,⁶⁵⁹ quality of life is diminished for many breast cancer survivors.

Breast cancer is treated most successfully in the early stages, when the tumor is small and less invasive; however, early-stage breast cancer is typically asymptomatic. Recommended methods for detecting breast cancer, including in its early stages, are clinical breast examinations and mammography. Annual clinical breast examinations are recommended for women over the age of 40 and every three years for women aged 20-39, although there is some disagreement among authoritative groups.⁶⁶⁰ Mammography is recommended every 1-2 years for women over the age of 40.⁶⁶¹

⁶⁵⁷ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁵⁸ Kroenke CH, Rosner B, Chen WY, et al. Functional impact of breast cancer by age at diagnosis. *J Clin Oncol* 2004;22:1849-56.

⁶⁵⁹ American Cancer Society report finds breast cancer death rate continues to decline. Atlanta, GA: American Cancer Society, 2003. Accessed September 27, 2004. http://www.cancer.org/docroot/MED/content/MED_2_1x_American_Cancer_Society_Report_Finds_Breast_Cancer_Death_Rate_Continues_to_Decline.asp.

⁶⁶⁰ Gotay CC, Muraoka MY. Quality of life in long-term survivors of adult-onset cancers. *J Natl Cancer Inst* 1998;90:656-67.

⁶⁶¹ Screening for breast cancer. Rockville, MD: US Preventive Task Force, 2002. Accessed September 27, 2004. <http://www.ahrq.gov/clinic/uspstf/uspstfbrca.htm>.

The stage of cancer at the initiation of treatment is known to affect survival rates. The American Cancer Society reported that more than 90% of breast cancers are detected before having spread to other areas of the body. For these localized breast cancers, the 5-year survival rate is 97%; for regional breast cancers (that have spread within the breast tissue but have not metastasized to other organs) the 5-year survival rate is 79%.⁶⁶² Survival decreases with later stages of the disease, with a nearly 100% survival rate for stage 0 to a 16% survival rate for stage IV.⁶⁶³

b. HER-2/neu and Its Relevance to the Drug Herceptin

Over-expression of HER-2/neu protein occurs in 25-37% of breast cancers and indicates a more aggressive form of the disease.⁶⁶⁴ The human epidermal growth factor receptor-2 gene (HER-2/neu) gene is involved in regulation of normal cell growth. Normally, there are two copies of this gene in every cell, but cancer cells can have more than two copies of the gene, resulting in more HER-2/neu protein on the surface of cells. Binding of this protein to growth factors in the blood can result in uncontrolled tumor growth.

HER-2/neu testing informs physicians as to whether a patient's breast cancer should be targeted for treatment with the drug Herceptin (trastuzumab) (**Figure 7.14**). Developed in 1998 by Genentech, Herceptin is one of the first successful targeted cancer chemotherapies. It works by targeting HER-2/neu receptors in breast tumors, as opposed to traditional chemotherapies that do not target cancer cells and can damage other cells (**Figure 7.15**). Herceptin is approved for use in patients with metastatic breast cancer whose tumors over-express the HER-2 protein and who have received one or more chemotherapy regimens for their metastatic disease. It typically is delivered in conjunction with chemotherapy for indicated patients with the genetic profile of HER-2/neu overexpression. Treatment with Herceptin has been found to provide substantial survival benefits to some women with metastatic breast cancer.⁶⁶⁵

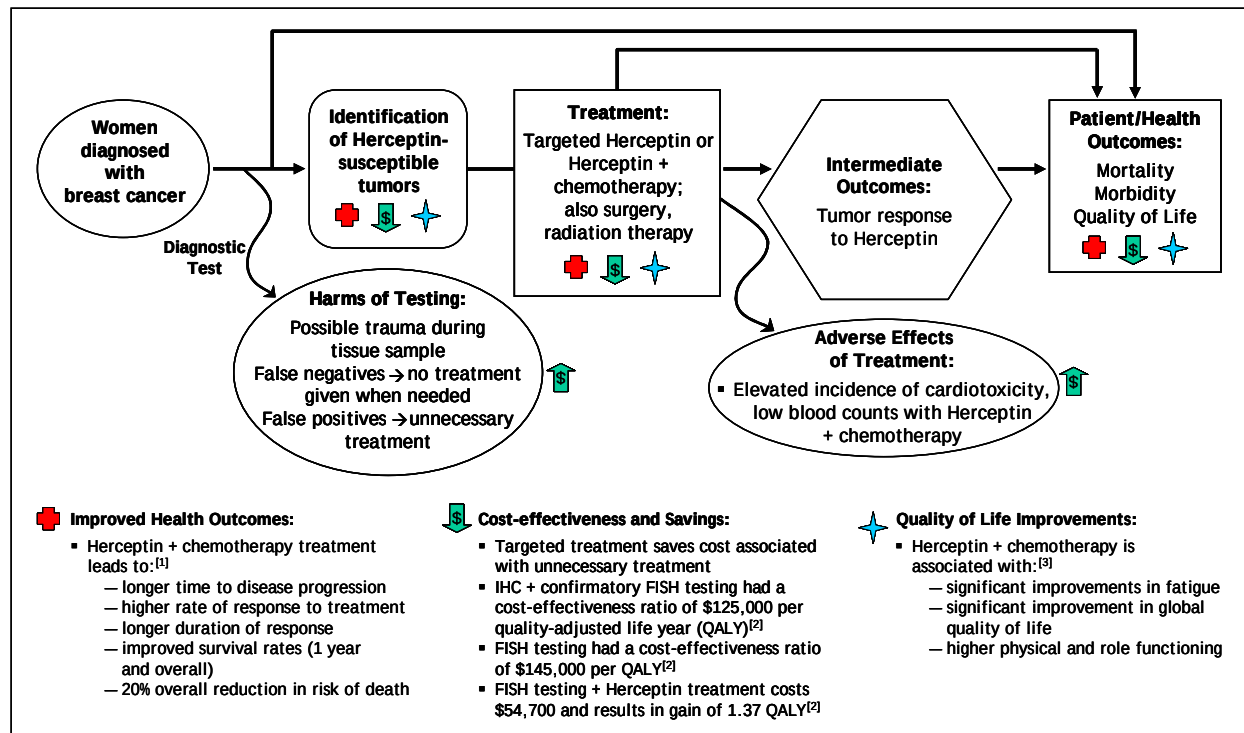
⁶⁶² American Cancer Society report finds breast cancer death rate continues to decline. Atlanta, GA: American Cancer Society, 2003. Accessed September 27, 2004. http://www.cancer.org/docroot/MED/content/MED_2_1x_American_Cancer_Society_Report_Finds_Breast_Cancer_Death_Rate_Continues_to_Decline.asp.

⁶⁶³ Detailed guide: how is breast cancer staged? Atlanta: GA, American Cancer Society, 2003. Accessed September 27, 2004. http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_breast_cancer_staged_5.asp?nav=cri.

⁶⁶⁴ Carney WP, Neumann R, Lipton A, et al. Potential clinical utility of serum HER-2/neu oncoprotein concentrations in patients with breast cancer. Clin Chem 2003;49:1579-98.

⁶⁶⁵ Breast cancer facts & figures 2003-2004. Atlanta, GA: American Cancer Society, 2003. Accessed September 27, 2004. <http://www.cancer.org/downloads/STT/CAFF2003BrFPWSecured.pdf>.

Figure 7.14
Analytic Framework for HER2/neu Testing
to Identify Patients Suitable for Herceptin Therapy for Breast Cancer



Sources:

- Slamon DJ, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England Journal of Medicine* 2001;344(1):783-92.
- Elkin EB, et al. HER-2 testing and trastuzumab therapy for metastatic breast cancer: A cost-effectiveness analysis. *Journal of Clinical Oncology* 2004;22(5):854-63.
- Osoba D, Slamon DJ, Burchmore M, Murphy M. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. *Journal of Clinical Oncology* 2002;20(14):3106-13.

Two types of diagnostics—immunohistochemical assays (IHC) and fluorescence in situ hybridization (FISH)—are used for HER-2/neu testing. IHC detects protein overexpression; FISH detects gene amplification. Each has its merits. IHC is relatively inexpensive and easily performed, but interpretation of results is subjective. While FISH is more expensive and time-consuming to conduct, it provides objective, quantitative results. Test choice involves trade-offs between the additional costs associated with using FISH and the higher rate of false-positive results associated with IHC.⁶⁶⁶

⁶⁶⁶ Elkin EB, Weinstein MC, Winer EP, Kuntz KM. Her-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol* 2004;22:854-63.

Figure 7.15
Evolution of a Targeted Diagnostic Application for Breast Cancer

Date	Milestone
1975	Discovery of potential use of monoclonal antibodies in vitro to fight disease by British scientists Kohler and Milstein
1985	HER-2/neu gene cloned
1987	Link discovered by Slamon et al. between HER-2/neu overexpression and more aggressive form of breast cancer
1990	Antibody directed at HER-2 humanized by Genentech scientists
1998	Herceptin (produced by Genentech) is approved by the FDA for targeted treatment of HER-2/neu positive metastatic breast cancer
June 2003	Consensus workshop calls for development of National Institute of Standards and Technology certifiable standard and National Committee for Clinical Laboratory Standards guideline to increase reliability of HER-2/neu testing
Currently	Two FISH and two IHC tests are FDA approved for detection of Herceptin-susceptible tumors

Sources:

1. Hammond ME, Barker P, Taube S, Gutman S. Standard reference material for HER-2 testing: report of a National Institute of Standards and Technology-sponsored Consensus Workshop. *Appl Immunohistochem Mol Morphol* 2003;11:103-6.
2. Herceptin development timeline. San Francisco, CA: Genentech, Inc.
3. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of HER-2/neu oncogene. *Science* 1987;235:177-82.

c. Clinical Value

Testing for HER-2/neu informs treatment decisions, as Herceptin is indicated solely for treatment of metastatic breast cancers whose tumors over-express the HER-2/neu protein. Testing for HER-2/neu limits the likelihood that Herceptin will be given to patients whose tumors do not have HER-2/neu gene amplification. Given the potential costs and side effects of Herceptin (e.g., possible development of ventricular dysfunction, congestive heart failure, pulmonary events and hypersensitivity reactions), only those women who may benefit from the drug should be treated. Targeted treatment for tumors that overexpress the HER-2/neu protein may lead to increased survival and quality of life. The American Society of Clinical Oncology recommends that HER-2/neu protein overexpression be evaluated in every primary breast cancer at diagnosis or at recurrence.⁶⁶⁷

d. Economic Value

Each year, \$2.4 billion to \$3.1 billion is spent for the treatment of breast cancer.⁶⁶⁸ The National Cancer Institute reports that, during the first year after diagnosis with breast cancer, the average

⁶⁶⁷ Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1865-78.

⁶⁶⁸ The state of health care quality: industry trends and analysis. Washington, DC: National Committee for Quality Assurance, 2004. Accessed October 22, 2004. <http://www.ncqa.org/communications/SOMC/SOHC2004.pdf>.

reimbursement for a Medicare patient is \$9,230.⁶⁶⁹ Some direct and indirect costs associated with breast cancer treatment include the following.

Figure 7.16
Direct and Indirect Costs Associated with Breast Cancer Treatment

Treatment/Therapy	Direct Costs	Associated Costs, if any (e.g., lost wages, travel, lodging)
Radiation therapy	\$15,000	\$3,000
Evaluation of recurrence via imaging	2,000	200
Biopsy and pathology	1,000	n/a
Aggressive surgery	10,000	2,000
Systemic chemotherapy	10,000	3,000

Adapted from cost data in Marks LB, Hardenbergh PH, Winer ET, Prosnitz LR. Assessing the cost-effectiveness of postmastectomy radiation therapy. Int J Rad Onc Biol Phys 1999;44:91-8.

One way of reducing costs associated with breast cancer is through the early detection of tumors. Another important strategy for reducing health care costs associated with breast cancer is to use diagnostics to support more cost-effective treatment decisions, such as using HER-2/neu testing to inform treatment decisions with Herceptin.

HER-2/neu gene testing limits the risk that patients whose breast cancers do not overexpress HER-2/neu are not put at risk for potentially costly side effects of treatment with Herceptin. This testing also is a relatively cost-effective way of screening for susceptible cancers. IHC with confirmatory FISH testing results in an incremental cost-effectiveness ratio (ICER) of \$125,000 per QALY and initial FISH testing (without IHC) results in an ICER of \$145,000 per QALY.⁶⁷⁰ While these ratios are somewhat higher than the \$100,000 per QALY level cited as an acceptable threshold by some health economists,⁶⁷¹ they are similar to or less than those for various other cancer therapies and many other widely used health care interventions.⁶⁷² Further refinements in testing, improvements in targeted treatments and lower costs that may arise with competing treatments should improve the cost-effectiveness of HER-2/neu testing and related diagnostics for breast cancer further.

e. Conclusion

Breast cancer affects an estimated 1 in 7 women during their lifetime, costs \$2.4 billion to \$3.1 billion annually and significantly affects the quality of life of patients and their families. HER-2/neu is a gene involved in cell growth regulation and in certain breast cancers. Overexpression of this gene is associated with a more aggressive form of cancer. Diagnostic

⁶⁶⁹ Cost of cancer care. Bethesda, MD: National Cancer Institute, 2003. Accessed September 27, 2004. <http://progressreport.cancer.gov/doc.asp?pid=1&did=21&chid=13&coid=33&mid=vpco>.

⁶⁷⁰ Elkin EB, Weinstein MC, Winer EP, Kuntz KM. Her-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol 2004;22:854-63.

⁶⁷¹ Ubel PA, Hirth RA, Chernew ME, et al. What is the price of life and why doesn't it increase at the rate of inflation? Arch Internal Med 2003;163:1637-41.

⁶⁷² Elkin, 2004.

testing for HER-2/neu, recommended on every primary or recurrent breast cancer diagnosis,⁶⁷³ informs treatment decisions, as breast cancers that test positive for HER-2/neu are more likely to respond to the drug Herceptin. Targeting Herceptin treatment to those patients testing positive for HER-2/neu potentially can result in health care savings, because treating only susceptible patients limits the costs associated with adverse side effects of Herceptin in patients who would not respond.

G. Impact of Diagnostic Use on the Health Value Chain

Technological advancement has contributed to increased health care spending over the past several decades.^{674,675} Additional health spending arises in multiple ways, including when a more expensive technology replaces a less expensive one, when a technology is used in more people (due to population growth and aging), when a technology is used for additional clinical purposes and when technology becomes available to diagnose or treat diseases for which there were previously no such interventions. Such analyses often do not account for the value of health benefits or net savings from avoidable downstream costs. If a more costly technology results in the following types of net benefits, then it can be a sound investment.⁶⁷⁶

- **Comparable outcome benefits versus existing technologies, but offers other unique benefits such as:**
 - reduced processing or decision time/rapid results
 - ease of use/convenience
 - additional utility or flexibility/increased capacity
- **Superior benefits versus existing technologies:**
 - reduced mortality and morbidity
 - increased quality of life
 - greater procedural, operational, or other efficiencies that translate into health care quality improvements and/or cost savings

As do other health care interventions, diagnostic tests have benefits and risks.⁶⁷⁷ When diagnostics are overused, there is a higher risk of false positive results that can lead to unnecessary additional tests (e.g., prostate biopsy following a false positive PSA test) and treatments (e.g., removal of the prostate), patient discomfort and stress and unnecessary costs. When diagnostics are underused, diseases are not detected early or at all, which can result in greater patient suffering, adverse health outcomes and higher costs associated with treating advanced disease.

⁶⁷³ Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1865-78.

⁶⁷⁴ Baker L, Birnbaum H, Geppert J, et al. The relationship between technology availability and health care spending. *Health Affairs* 2003;W3-537.

⁶⁷⁵ Fuchs V. Economics, values, and health reform. *Am Econ Rev* 1996;86(1):1-24.

⁶⁷⁶ Cutler DM 2001.

⁶⁷⁷ Harris R 2001.

1. Implications of Diagnostic Overuse for Health Care Quality

Although the cost of diagnostic tests represents <5% of health care expenditures, frequent and sometimes redundant ordering of even inexpensive health services can result in significant health spending.⁶⁷⁸ As noted above, increased risks for false positive test results can translate into patient harms and unnecessary costs.

Several clinical laboratory audit studies have reported varying degrees of inappropriate laboratory utilization (e.g., redundant and/or untimely test ordering) relative to prevailing evidence-based guidelines. Utilization levels in these studies are gauged by physician ordering practices, with reported overuse ranging widely from 4.5-95%, depending on the particular test or group of tests being considered.^{679,680}

Some of the reasons for overuse of diagnostic tests include inadequate health care information systems that inhibit effective transfer of test information, concerns about malpractice litigation, financial incentives and other insufficient feedback or controls to guide or incentivize appropriate test ordering. A systematic review of more than 40 studies of physician test ordering indicated significant inconsistencies in study design and definitions of “inappropriate use,” including classification of a test request as inappropriate if a subsequent change in therapy did not follow or the result was abnormal. The study concluded that such factors make it difficult to draw generalizable conclusions about what volumes of diagnostic requests may be inappropriate in certain scenarios.⁶⁸¹ Even so, it is clear that there is extensive overuse of certain diagnostics.

A variety of physician feedback and educational models have proved effective in reducing inappropriate requests for diagnostic tests.^{682,683,684} These interventions primarily have included introduction of decision support systems, evidence-based prompts delivered via electronic medical records and development of internal review structures to evaluate levels of diagnostic and treatment services.

2. Implications of Diagnostic Underuse for Health Care Quality

A recent RAND Health study of 4,612 adults living in 12 metropolitan cities across the US evaluated the extent to which recommended medical care procedures, including certain ones pertaining to diagnostics, are delivered appropriately in the US.⁶⁸⁵ Performance was assessed for 439 quality of care indicators for 30 acute and chronic conditions, as well as preventive

⁶⁷⁸ Harris R 2001.

⁶⁷⁹ van Walraven C, Naylor D. Do we know what inappropriate laboratory utilization is?: a systematic review of clinical laboratory audits. *JAMA* 1998;280(6):550-7.

⁶⁸⁰ Solomon D, Hashimoto H, Daltroy L, Liang MH. Techniques to improve physician’s use of diagnostic tests: a new conceptual framework. *JAMA* 1998;280(23):2020-7.

⁶⁸¹ Ibid.

⁶⁸² Lewandrowski K. Managing utilization of new diagnostic tests. *Clin Leadership Manag Rev* 2003;17(6):318-24.

⁶⁸³ van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization: a time analysis series. *JAMA* 1998;280(23):2028-33.

⁶⁸⁴ Plapp F, Essmyer CE, Byrd AB, Zucker ML. How to successfully influence laboratory test utilization. *Clin Leadersh Manag Rev* 2000;14(6):253-60.

⁶⁸⁵ McGlynn E, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med* 2003;348(36):2635-45.

care.⁶⁸⁶ Selected quality indicators ranged broadly, from whether community acquired pneumonia patients over 65 received a white blood cell count on the day of presentation to whether patients admitted for acute heart attack received beta blockers within four hours of admission (unless contraindicated). Overall, this study found that only 54.9% of participants received recommended preventive care and treatment for the 439 indicators and 30 conditions.

Of the 439 quality indicators considered in this study, 102 (23%) involve direct measures of diagnostic use. Quality indicators used in this study were developed by RAND's Quality Assessment Tools System and percent underuse figures were calculated based on study appendix data for select indicators. Treated prevalence and total health spending figures were adapted from other sources identified in the **Figure 7.17** legend.

Underuse was found in every case for these diagnostics, at rates ranging from approximately 10% to 100%, with an average underuse of 51%. **Figure 7.17** lists a subset of the 30 preventive, acute and chronic condition areas included in the study for which diagnostics are relevant, the treated prevalence per 100,000, associated health expenditures and the percent underuse for select disease-specific indicators.⁶⁸⁷

In the categories selected for **Figure 7.17**, percent underuse (based on the RAND study) ranged broadly for individual indicators, but was high in most cases. Although reported underuse for certain RAND quality indicators was different than optimal baseline care levels reported in *The State of Health Care Quality 2004: Industry Trends and Analysis* report and in **Figure 7.7**, these metrics consider diagnostic use as a proxy for measuring different aspects of care for the same disease or disease category.⁶⁸⁸ For example, one RAND quality indicator reported that only 23.9% of diabetic patients were offered an HbA1c test every six months, while the NCQA report reflected a 79.8% national baseline of appropriate comprehensive diabetes care (as gauged by control of HbA1c levels). The latter measure uses HbA1c to gauge a range of diabetes care activities, including other testing (e.g., lipid levels, eye examinations) and treatment activities (e.g., medical and behavioral interventions). Thus, the RAND quality indicators reflect one of several factors that may be used in NCQA quality measures.

Consideration of these differences can illuminate means to help bridge gaps in health care quality. For instance, if only 23.9% of diabetic patients were offered a HbA1c test every 6 months, then this could, in part, contribute to the 20.2% of patients that the NCQA identifies as receiving inadequate comprehensive diabetes care. Identifying viable opportunities to correct this inadequate care can help reduce preventable adverse health outcomes and costs, particularly given that diabetes affects 30.2 million individuals and results in 18.2 million deaths and \$132 billion in health expenditures annually.⁶⁸⁹ Health practitioner education on the relationship between glycemic control and evidence-based electronic reminders to providers for HbA1c testing are among many solutions that can address this shortfall in quality.

⁶⁸⁶ A quality indicator only identifies whether a particular health care service is provided, whereas a quality measure also provides information on the degree to which a particular health service is provided per unit time.

⁶⁸⁷ Percent underuse figures are not adjusted for sampling distribution or other confidence variables.

⁶⁸⁸ The state of health care quality: industry trends and analysis. NCQA, 2004.

⁶⁸⁹ Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care* 2003;26:917-32.

Figure 7.17
Select Indicators of Diagnostic Underuse in the US (2004)

Disease*	Quality indicator*	Treated prevalence (per 100,000)^	Total health spending (billions)^+	Underuse (%)*
Asthma	Theophylline levels measured once per year for patients under constant medical management	4,610	\$11.3	100.0%
	Theophylline levels measured after an asthma attack			62.4%
Heart disease	Newly diagnosed atrial fibrillation patients that received a thyroid test	6,226	\$56.7	81.4%
	Newly diagnosed angina patients that receive hemoglobin test to detect diabetes			61.6%
	Newly diagnosed congestive heart failure patients offered standard blood panel within 1 month of diagnosis			65.9%
	Patients on ACE inhibitors with serum potassium checked annually			21.7%
Cancer	Colorectal cancer patients:	3,348	\$38.9	
	Patient offered colonoscopy within 3 months following positive FOBT result			72.1%
	Breast cancer patients:	13,290	\$42.6	
	Biopsy & cellular analysis performed within 6 weeks when mammography suggests malignancy			49.8%
	Biopsy & cellular analysis or mammography performed within 3 months following detection of a palpable mass			10.9%
Diabetes	Diabetic patients:	4,260	\$18.3	
	Offered a HbA1c test every 6 months			76.1%
	Urine protein test performed annually			76.4%
	With documented serum and HDL tests			42.1%
Prenatal care	African American or women with a history of sickle cell disease offered a sickle cell test	1,237	NA [§]	100.0%
	Rh factor/antibody screen following first prenatal visit			5.9%
	Women with abnormal glucose offered a glucose test			100.0%
Hip fracture	Initial laboratory tests include:	11,000	\$2.9	
	Preoperative coagulation test			57.3%
	Preoperative urinalysis			91.7%

Disease*	Quality indicator*	Treated prevalence (per 100,000)^	Total health spending (billions)^+	Underuse (%)*
Hypertension	Initial laboratory tests include:	11,382	\$23.4	
	Urinalysis			69.1%
	Serum cholesterol			39.9%
	Creatinine kinase			38.5%

*Adapted from: *The Quality of Health Care Delivered to Adults in the United States*. RAND Healthcare 2004.

^Adapted from: Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health care spending? *Health Affairs* 2004;W4-437.

+Additional sources: National Center for Health Statistics. *Centers for Disease Control and Prevention*.

§ Not available.

An additional example of diagnostic underuse arises from the Premier Hospital Quality Incentive Demonstration of CMS, noted above. This three-year project seeks to improve health care quality for the Medicare population by rewarding hospitals based on performance on 34 quality measures for five clinical conditions/procedures, including AMI, heart failure, coronary artery bypass grafting, community-acquired pneumonia and hip and knee replacement. While first-year data for this demonstration will be available in early 2005, some of the 278 participating hospitals already have provided historical data from October 2002 to September 2003 on these quality measures.⁶⁹⁰ Of these measures, 9% are direct measures of diagnostic test use and approximately 53% are informed by diagnostic tests (e.g., to determine eligibility for surgical procedures, treatments or to otherwise assess patient health status).

Figure 7.18 depicts percent underuse for three community-acquired pneumonia quality measures in a sample of four participating hospitals. Use of blood cultures and pneumococcal screening (to detect antibodies from prior vaccination) are two diagnostic quality measures that inform proper and timely treatment decisions (including proper antibiotic administration) for these patients. While underuse varies significantly across the sample hospitals, in many cases, it is quite high and has the potential to affect health outcomes (including mortality). As with the RAND study and NCQA data discussed above, such underuse of diagnostics translates into missed opportunities to inform treatment decisions, enhance overall quality of health care and prevent unnecessary health outcomes and costs.

⁶⁹⁰ Premier Hospital Quality Incentive Demonstration Project: historical data October 2002 – September 2003. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed October 28, 2004. <http://www.cms.hhs.gov/quality/hospital/capdetail.pdf>.

Figure 7.18
Diagnostic Utilization in the CMS Premier Hospital Quality Incentive Demonstration
Quality Measures for Community-acquired Pneumonia

Quality Measure	Percent Underuse Reported by Four Sample Hospitals			
	Hospital 1 (Oregon)	Hospital 2 (Florida)	Hospital 3 (New York)	Hospital 4 (Kansas)
Blood culture (prior to antibiotic administration)*	11.9%	6.4%	17.6%	61.2%
Pneumococcal screening and/or vaccination*	94.0	51.0	36.7	10.9
Antibiotic administration (within 4 hours of arrival)	18.7	37.2	35.1	13.4

* Direct measure of IVD test use

Sources:

1. Community-acquired pneumonia. Premier Hospital Quality Incentive Demonstration Project: historical data October 2002 – September 2003. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004.
2. The Premier Hospital Quality Incentive Demonstration: rewarding superior quality care. Fact sheet. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004.
3. The Premier Hospital Quality Incentive Demonstration: clinical conditions and measures for reporting. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004.

While some diagnostic tests (e.g., biopsy/mammography follow-up to breast mass detection) are well-utilized, these RAND, NCQA and CMS data document significant levels of diagnostic underuse in areas of high potential impact on patient outcomes. Certain diagnostic tests appear to be grossly underutilized, even in instances where harms and benefits are widely recognized (e.g., sickle cell and glucose testing for women with history/symptoms during prenatal care, annual measurement of theophylline for patients under medical care for asthma).

Use of diagnostics consistent with clinical practice guidelines and other evidence-based sources has substantial implications for improving outcomes (i.e., reduction of morbidity and mortality, improvement in quality of life) and reducing avoidable costs associated with many diseases. Considering that avoidable costs are in the tens and hundreds of millions of dollars for many conditions (**Figure 7.3**), even incremental improvements in diagnostic use may lead to tangible savings that can be redirected to improving other aspects of human health.

H. Optimizing the Impact and Value of Diagnostics

There are few aspects of conventional health care that are not influenced in some way by diagnostic testing. Information ranging from the most simple and fundamental health indicators to the most complex and multifaceted changes in health status, in many cases, are obtainable only through use of diagnostic technologies. Coupled with patient history and clinician experience, diagnostics objectively inform individual care decisions at all stages of care. The broader utility of this information in qualifying and quantifying care expands the value of diagnostics beyond the individual to the community, organizational and systemic aspects of health care.

Diagnostic tests face multiple barriers to development, including regulatory and reimbursement pathways that can be difficult to navigate and resource intensive. The rate of evolution for new diagnostic tests is mediated by regulatory and reimbursement mechanisms which, in some

cases, can be ambiguous, burdensome and inconsistently defined. Such development challenges can affect time-to-market and lengthen the timeframe for uptake of new technologies into patient care.

Reimbursement mechanisms that are structured inadequately or outdated not only may inappropriately cover, code and underpay for certain diagnostics, but create disincentives to innovation, adoption, diffusion and value optimization of these technologies. Reimbursement challenges also make it difficult for innovators to collect sufficient evidence to establish effectiveness outside investigational settings and fully characterize circumstances of use and clinical value in one or more aspects of patient care. These factors may be particularly relevant to novel diagnostics, such as many emerging gene-based and other molecular technologies, that do not neatly fit with existing regulatory/reimbursement definitions, processes and paradigms and also have unique associated benefits and harms. However, this also applies to incremental advancements in existing diagnostics, where a greater initial cost (than a previous model or version) can be justified via greater downstream health benefits and cost savings.

When barriers to innovation of new diagnostic tests, whether actual or perceived, become overly cumbersome for manufacturers and clinical laboratories, inhibition of diagnostic advancement and stagnation of patient health assessment and modalities of health services provision can result. Considering the significant downstream influence that diagnostic information has on other facets of health care and the growing need to balance quality and cost in provision of health services, it will be essential to address actionable areas, such as regulatory and reimbursement constraints. These efforts can translate into health care value at many levels, to improve health care delivery and the public's health.

Such emphasis will require dedication of time and resources, as well as clear and open communications among health stakeholders. Greater collaboration in the areas of: a) more predictable, transparent regulatory and reimbursement pathways; b) evidence-based applications of diagnostics across the health care continuum; and c) broader implications of how diagnostic information influences the quality and cost of care for health care stakeholders will benefit all stakeholders.

Appendix A: Glossary of Terms

Array

Diagnostic modality involving conduction of multiple unique tests for different biomarkers on the same testing medium (e.g., plate, glass slide, microfluid chip).

Bioinformatics

The use of computers in the analysis of biochemical and other biological information, including molecular genetics and genomics.

Coding

Alphanumeric nomenclature assigned to particular health conditions, services or products which also is used to designate payment levels for these.

Coverage

A decision or policy of a third-party payer to provide payment for a particular service or product under an insured benefit.

Diagnostic Kit

A term used to refer to an assembly of specific pre-packaged components necessary to conduct one or more diagnostic tests.

Deoxyribonucleic Acid (DNA)

The genetic instructions for making living organisms that exists inside the nucleus of a cell.

Genes

Composed of DNA, genes are the functional and physical unit of heredity and control the expression of traits.

Genetics

The study of single genes and their impact on health processes.

Genetic Susceptibility Tests

Diagnostics tests that measure an individual's genetically-based risk for developing a disease or health condition. Commonly referred to as predictive tests.

Genome

All of the DNA in an organism or a cell, including the DNA in the nucleus of a cell and the DNA in the cell mitochondria.

Genomics

The study of all of the genes in a person or an organism.

Glycomics

The study of carbohydrate(sugar)-protein interactions at the cellular level, particularly in cell-cell and cell-tissue interactions.

Human Genome

An individual's complete complement of DNA.

In vitro

A term used to refer to tests or procedures performed outside of the human body, or the bodies of other animals or plants, in an artificial environment.

In vivo

A term used to refer to tests or procedures performed inside the human body, or the bodies of other animals or plants.

Metabolites

Any substance that is either necessary for a metabolic process or is a product of metabolism.

Metabolomics

The study of the body's metabolic reactions to stress and/or disease.

Molecule

Composed of one or more atoms, molecules are the smallest particle of a substance.

Molecular Diagnostics

Diagnostic tests that detect certain specific molecules such as DNA, antibodies, proteins, etc.

Multiplex

A term used to describe the amplification of more than one primer pair in a single vial during the amplification of nucleic acid.

Nucleic Acid Amplification Test (NAT)

A technique in which segments of DNA are selectively replicated for either diagnostic or research purposes. One example of this type of test is polymerase chain reaction (PCR).

Pharmacogenetics

The study of the effects of genetic variation on differential efficacy and side effects of drugs.

Pharmacogenomics

The study of genetic variation in biomarkers, targets or target pathways, particularly the use of tests for these in conjunction with drug therapies.

Protein

Large complex molecules composed of one or more amino acid chains that perform a variety of functions in cells.

Proteomics

The study of the proteins produced by genes.

Reimbursement

The levels of payment for covered health services or products.

Ribonucleic Acid (RNA)

Chemically similar to DNA, RNA plays an important role in protein synthesis by transporting the genetic code from the DNA in the nucleus of the cell into the cytoplasm.

Theranostics

The use of diagnostic tests to detect disease/disease severity, to select the proper treatment and dosage and to monitor treatment response and/or therapeutic drug levels *in vivo*.

Third-party Payer

Any payer of health care services other than the person receiving the services. Third-party payers include private payers and the federal government.

Transcriptomics

The study of all RNA transcripts produced by human genes and translated into proteins.

Glossary terms were adapted from the following sources:

- CDC. Genomics and Population Health: United States 2003. Office of Genomics and Disease Prevention, 2003. Accessed November 23, 2004. <http://www.cdc.gov/genomics/activities/ogdp/2003.htm>.
- National Human Genome Research Institute. Talking Glossary of Genetic Terms. Accessed November 23, 2004. <http://www.genome.gov/10002096#d>.
- Roche. Genes and Health. 2004. Accessed November 23, 2004. http://www.roche.com/pages/facets/22/gene2_e.pdf.

Appendix B: Coverage During Clinical Trials

The considerable cost and time required to conduct clinical trials for FDA approval of many medical technologies continues to be a substantial hurdle to successful innovation and use. Resource constraints during clinical trials can have consequences for manufacturers. In the absence of sufficient revenue flow, the timing of trials sponsored by some companies may be delayed or their protocols may have to be restricted. Patient recruitment may be slowed or fail to reach magnitudes needed to determine the safety and effectiveness of devices; data collection may be curtailed by limiting patient follow-up or the number of clinical and economic endpoints assessed. To the extent that conditions for conducting clinical trials and gaining payment during trials are more favorable overseas, patient access in the US may be delayed in comparison. Aside from increasing the cost and risk of innovation, these factors can delay determination of the clinical and economic value of technologies and delay or reduce access to proven technologies.

Recognition of the potential benefits of at least partial payment during clinical trials of investigational devices led to an interagency agreement between FDA and CMS in 1995 establishing a system for determining eligibility of investigational devices for coverage by CMS.⁶⁹¹ The interagency agreement recognized that devices granted Investigational Device Exemptions (IDEs) by the FDA for clinical testing were, by designation as “investigational,” excluded from coverage. This applied, even though many of these devices represented only marginal changes to currently covered devices already demonstrated to be safe and effective. IDEs served as a de facto indication that such devices are not “reasonable and necessary,” and Medicare coverage was denied for devices with IDEs that had not received premarket 510(k) clearance or pre-market approval.

As negotiated by the FDA and CMS, the interagency agreement provides that certain devices used in clinical trials conducted under IDE protocols are eligible for payment. Under the agreement, the FDA classifies all approved IDEs as Category A (experimental/investigational) or Category B (non-experimental/investigational). Category B refers to Class I or Class II devices, or Class III devices for which underlying questions of the safety and effectiveness of the device type have been resolved. As of September 1995, IDEs that have been designated as Category B became eligible for Medicare coverage consideration during clinical trials.

Payment for Category B devices is not guaranteed under the agreement. Coverage is still at the discretion of the individual Medicare carriers and FIs. If a device meets the criteria for coverage during clinical trials (i.e., that the safety and effectiveness of the device type have been demonstrated), then the Medicare contractors will apply the standard criteria and procedures for making coverage decisions. For example, a device must be furnished in accordance with accepted standards of medical practice (in this case, in accordance with FDA-approved clinical trial standards). Other criteria include that the service is medically necessary and is furnished in an appropriate setting. Generally, this coverage is granted on a case-by-case basis.

⁶⁹¹ Payment for a non-experimental/investigational (Category B) device. 42 CFR Part 405.

In 2000, President Clinton issued a directive to CMS requiring that Medicare cover the routine costs of qualifying clinical trials, including costs associated with reasonable and necessary measures to deal with any related complications.⁶⁹² Routine costs are defined to include items and services necessary for investigational or control arms of a trial that are normally covered for Medicare beneficiaries. Per CMS, examples of these types of costs include:

- items or services that are typically provided absent a clinical trial
- items or services required solely for the provision of the investigational item or service, the clinically appropriate monitoring of the effects of the item or service or the prevention of complications
- items or services needed for reasonable and necessary care arising from the provision of an investigational item or service; in particular, for the diagnosis or treatment of complications.⁶⁹³

Services excluded from routine cost status include the investigational item or service, items or services for data collection purposes and items or services provided complementary of the sponsors of the trial. To qualify for coverage of routine costs, clinical trials are subject to certain requirements related to patient safety, scientific evidence and sponsorship.⁶⁹⁴ Clinical trials funded by the NIH, CDC, CMS, AHRQ, VA, Department of Defense (DOD) and trials exempt from or with FDA approved Investigational New Drug (IND) applications automatically have routine costs covered without demonstrating these requirements.⁶⁹⁵

As mandated by MMA 2003, CMS is to propose regulatory changes to allow for coverage of routine care services related to clinical trials of non-covered Category A devices. This policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies (LMRPs) or the regulations on Category B IDEs. MMA established additional criteria for trials initiated before January 1, 2010, to ensure that the devices involved in such trials would be intended, “for use in the diagnosis, monitoring, or treatment of an immediately life-threatening disease or condition.”⁶⁹⁶ The proposed rule states that CMS plans to provide guidelines for determining whether a device meets this standard through the NCD process.

⁶⁹² Medicare coverage: clinical trials. Final national coverage decision. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 1, 2004. <http://www.cms.hhs.gov/coverage/8d2.asp>.

⁶⁹³ Ibid.

⁶⁹⁴ Medicare coverage: routine costs of beneficiaries in clinical trials. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed November 1, 2004. <http://www.cms.hhs.gov/media/press/release.asp?Counter=383>.

⁶⁹⁵ Ibid.

⁶⁹⁶ Medicare Prescription Drug, Improvement and Modernization Act of 2003. Washington, DC, 108th Congress of the United States of America, 2003. Accessed December 9, 2004. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h1enr.txt.pdf.

Appendix C: Important Aspects of the CPT Application Process

Successfully navigating the CPT application process requires a substantial time and resource commitment on the part of diagnostics manufacturers. Applicants must demonstrate that a new test confers significant clinical benefit and is adopted widely by the appropriate medical communities. In addition, a new test must have support in the peer-reviewed literature, as well as from relevant specialty societies. If these criteria are not met, the likelihood increases that the CPT Editorial Panel may reject the coding application.

Specifically, applicants must consider the following questions, selected from those found on the AMA CPT Coding Change Request Form.⁶⁹⁷

- Does the procedure/service involve the use of a drug or device that requires approval from the FDA?
- If approval is necessary, has FDA approval been received for the device or drugs for the specific use that you are proposing?
- Is the procedure/service for which you are proposing a code change performed nationally?
- Is the procedure/service for which you are proposing a code change performed by a large number (as a proportion of practitioners within the specialty or subspecialty) of physician or non-physician health professionals?
- Has the clinical efficacy of the procedure/service for which you are requesting a code change been established and well documented?
- Is the procedure/service for which you are requesting a code change used as a performance or quality measure by any national organization? If yes please state the organization and name of measure.
- Indicate the specific reasons why this code change is necessary (rationale) (avoid non-rationales; reasons like “no code currently available” or “need new code” do not describe the clinical reason why you are requesting a coding revision)?
- How long (i.e., numbers of years) has this procedure/service been provided for patients (medical literature that indicates utilization of this procedure/service should be cited in and a hard copy of literature should be provided)?
- Do many physicians or non-physician health care professionals perform this service across the United States?

⁶⁹⁷ American Medical Association, Current Procedural Terminology (CPT) Coding Change Request Form. Chicago, IL: American Medical Association, 2003. Accessed February 25, 2005. <http://www.ama-assn.org/ama1/pub/upload/mm/362/changerequestform.doc>.

- How often do physicians or non-physician health care professionals perform this service?
- Please identify the specialties or subspecialties that might perform this procedure/ service.
- Did you contact any of these specialty groups? If yes, which one(s)?
- Please provide hard copy(s) (and internet addresses, if available) of literature to support your request (US PEER REVIEWED JOURNALS ONLY), and cite the author, title, journal, volume, page and year as necessary. For Category III codes please reference quality studies or research performed by national organizations.

Appendix D: Key Provisions of MMA for Diagnostics

Certain key MMA provisions affecting reimbursement for diagnostics include:

1. **Regulatory and Coverage Changes:** Section 942 of MMA addresses the method for determining the basis and payment amount for new clinical laboratory tests, provides criteria for evaluating whether a test should be cross-walked or gap-filled and addresses concerns that novel diagnostics will receive inadequate payment due to inappropriate mapping to existing CPT codes. This provision also encourages stakeholder participation and transparency in the payment determination process and acknowledges the recommendation to replace the 23-year-old ICD-9-CM coding system with ICD-10, as a potentially more effective system for determining medical necessity, accommodating codes for new technologies and easing administrative burden.^{698,699,700,701}

Implications: Due in part to this provision, CMS now is more openly engaging stakeholders in payment determinations. As such, this provision may help increase transparency of regulatory and reimbursement processes and encourage greater diagnostics industry involvement (e.g., monitoring the issuance of notices).

2. **Freeze of the Clinical Lab Fee Schedule (CLFS):** Effective January 1, 2004, Section 628 enacted a five-year freeze on the CPI update to the Medicare CLFS through 2008, extending the lack of updates to payments for tests. Imposing the CPI update freeze is an alternative to a 20% beneficiary co-payment requirement for lab tests, which the lab industry opposed on the grounds of the added billing costs for payments that have a low likelihood of being collected.⁷⁰²

Implications: Freezing the CPI update on the CLFS means that payment for diagnostics will continue to not keep pace with inflation. Therefore, payment levels will lag behind appropriate rates; providers will not receive adequate payment for use of diagnostic tests;

⁶⁹⁸ The National Committee on Vital and Health Statistics recommended that the ICD-10 system be implemented as quickly as possible, since it addresses important weaknesses of ICD-9-CM. ICD-9-CM Volumes 1, 2 and 3 have structural and space limitations that constrain their ability to accommodate scientific advances and limit the number of available codes for new technologies, placing unnecessary burden on laboratories to establish medical necessity. Authoritative groups, including the IOM in its 2000 report, have expressed that the ICD-9-CM system may not be appropriate for determining medical necessity. In particular, ICD-9-CM may be too outdated to respond adequately to the emerging needs of payers and providers in an environment of rapid technological evolution. Further, ICD-9-CM may not be able to meet increasing demands for accurate data for billing, quality assurance, public health reporting and health services research.

⁶⁹⁹ Wolman DM, Kalfoglou AL, LeRoy L (eds) 2000.

⁷⁰⁰ National Committee on Vital and Health Statistics recommendations to DHHS. November 5, 2003. Washington, DC: National Committee on Vital and Health Statistics, 2003. Accessed December 1, 2004. <http://www.ncvhs.hhs.gov/031105lt.htm>.

⁷⁰¹ Ibid.

⁷⁰² Ivor L 2004.

and adoption, diffusion and patient access may be adversely affected. In general, this freeze places further constraints on the financial outlook for the diagnostics industry.⁷⁰³

3. **Competitive Bidding Demonstration:** Competitive bidding is a process in which providers submit price bids and the lowest bid is selected as the payment rate for a particular service.⁷⁰⁴ Section 302(e) requires conducting a competitive bidding demonstration project to apply competitive acquisition for payment for certain clinical laboratory services (i.e., CLIA-compliant tests that do not require face-to-face encounters with patients), which would otherwise be made under the Medicare Part B fee schedule. Under this demonstration, contracts are to be re-competed every three years, with multiple winners in each competitive acquisition area. Interim reports from this demonstration are due to Congress by December 31, 2005.⁷⁰⁵

Implications: Total payment amounts for diagnostic tests are expected to be lower under this demonstration than total amounts that would be paid otherwise. This has financial implications for the diagnostics industry and also influences provider adoption and patient access. Depending on the outcome of this demonstration, Congress may consider competitive bidding in the future with the intent that it will result in cost savings without sacrificing quality.⁷⁰⁶ Certain stakeholders (e.g., the American Association for Clinical Chemistry) already have voiced concerns that competitive bidding may not capture the full value of laboratory tests, may inadvertently restrict access to laboratory services and may fail to account for differences in cost across laboratory facilities in different geographic areas (e.g., rural areas). Further, AACC recommends that once the winning bid has been accepted, all other interested, CLIA-certified laboratories should be allowed to provide laboratory services for Medicare beneficiaries at that payment level in the forthcoming competitive bidding demonstration.^{707,708}

4. **Coverage of Cardiovascular and Diabetic Screening:** Sections 612 and 613 establish coverage of cardiovascular and diabetic screening for at-risk individuals effective January 1, 2005 and specifies that coverage of cardiovascular screening tests is limited to those recommended by the USPSTF, which is administered in AHRQ. In addition, this provision establishes an accelerated path to payment for technologies involved in diabetes screening once regulatory review has been completed.

Implications: Certainly, the fast-track option for regulatory review to payment may have positive impacts on diabetes screening diagnostics, allowing more timely diffusion and patient access. However, for cardiovascular technologies, this provision may raise evidence

⁷⁰³ Ivor L 2004.

⁷⁰⁴ Competitive bidding: competitive bidding threatens laboratory services. Washington, DC: Clinical Laboratory Coalition, 2003. Accessed December 15, 2004. http://www.aacc.org/govt/images/comp_brief.pdf.

⁷⁰⁵ Demonstration Project for Competitive Acquisition of Clinical Laboratory Services. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 1, 2004. <http://www.cms.hhs.gov/researchers/demos/clinallabdemo.asp>.

⁷⁰⁶ Ivor L 2004.

⁷⁰⁷ Ibid.

⁷⁰⁸ CMS open forum on the clinical laboratory services demonstration project. Washington, DC: American Association for Clinical Chemistry, 2004. Accessed December 15, 2004. http://www.aacc.org/govt/2004/comp_bidding.doc.

hurdles to reimbursement, as the USPSTF is widely acknowledged as employing a high evidence threshold and typically provides recommendations to use only those technologies with well-established evidence bases (i.e., older technologies that have been on the market for many years). Diagnostics manufacturers and clinicians should understand the necessity for demonstrating the highest level of evidence possible and plan for these requirements, including communicating with USPSTF and CMS as appropriate. Manufacturers may anticipate the impacts of this process on the indications for coverage of these tests and the time that may be required to gain such coverage. Also, the USPSTF increasingly may need to adapt its work to accommodate rapid changes in the field in a timely manner.

5. **Creation of the CMS Council for Technology and Innovation:** In an effort to ensure timely access to new medical technologies for Medicare beneficiaries, Section 942 mandates the creation of a Council for Technology and Innovation (CTI) to coordinate Medicare coverage, coding and payment processes for new technologies whose CPT codes are assigned on or after January 1, 2005. Comprising senior-level CMS leaders and experts on clinical, coverage and payment issues, the CTI has two working groups: a) Effective Innovation; and b) Better Evidence.⁷⁰⁹ Initial developments include new Level II HCPCS coding changes to be phased in over an 18-month period beginning with the 2006 coding cycle. Among these are an earlier application deadline of January 3, which lengthens by two months the duration until new codes become effective on the subsequent January 1, yet enables greater time for the new provision for public comment on preliminary coding decisions.

Implications: The CTI is expected to provide CMS with evidence-based evaluation of the needs the safety, effectiveness, cost and utility of new technologies in order to promote the use of these technologies in the most effective manner.⁷¹⁰ The work of CTI may help ease the burden on diagnostics manufacturers of collecting data on new tests. For instance, it is possible that when these methods are employed, CMS could be more inclined to cover the costs associated with clinical studies of diagnostics, especially when studies are expected to accrue evidence regarding how to incorporate new technologies into clinical decisions.

6. **National Coverage Determination Process Changes:** MMA 2003 amended several aspects of the process for NCDs. Section 731 requires that factors used to determine NCDs are made public and that related guidance documents are developed similar to those available from the FDA.⁷¹¹ In addition, various changes specify that the total time required for an NCD should not exceed nine or 12 months, depending on the need for external technology

⁷⁰⁹ The Effective Innovation group is charged with improving the efficiency of coding, coverage and payment processes; considering ways for CMS to accommodate and anticipate technological advances; and engaging in “horizon scanning” to identify emerging interventions and prepare CMS to be more responsive to them. These goals are to be accomplished through a combination of approaches, including enhancement of stakeholder communication with CMS and using evidence-based approaches for evaluation of new technologies. The Better Evidence group is the clinical research priority-setting arm of CTI. Dedicated to developing methods for gathering reliable evidence about existing and emerging technologies, this group also seeks to streamline coding, coverage and payment.

⁷¹⁰ CMS launches council to improve timely access to new medical technologies. CMS press releases and facts sheets. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 1, 2004. <http://www.cms.hhs.gov/media/press/release.asp?Counter=1163>.

⁷¹¹ Medicare coverage guidance documents. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 1, 2004. <http://www.cms.hhs.gov/coverage/guidance.asp>.

assessment. In addition, effective July 1, 2004, revised procedures will allow the issuance of temporary national HCPCS codes.⁷¹²

Implications: The major changes in this provision include openness, standardization and interaction with CMS in an open process, representing a significant change over earlier procedures that have taken much longer to complete in many instances. Although NCD determinations are unlikely to be pursued for most diagnostics, the availability of guidance documents developed with the diagnostics industry will enable a more consistent and reliable process when NCDs are undertaken and the process and timeliness afforded by this statute may make this option more appealing.⁷¹³ In addition, if the authority for covering additional preventive and screening procedures shifts from Congress to DHHS, more diagnostics could be reviewed for national coverage.

Other Relevant Provisions: Provisions in the MMA also: a) establish increased control by CMS over the local coverage determination process by requiring the local coverage determinations (LCD) process to identify new technologies that may be more appropriate for review as NCDs; and b) provide a mediation approach for settling disputes between stakeholders and Medicare carrier medical directors, as a way of addressing systematic complaints regarding local coverage decisions.^{714,715,716}

⁷¹² Ivor 2004.

⁷¹³ Ibid.

⁷¹⁴ Ibid.

⁷¹⁵ Medicare coverage guidance documents. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 1, 2004. <http://www.cms.hhs.gov/coverage/guidance.asp>.

⁷¹⁶ Changes to the national coverage determination process. Baltimore, MD: Centers for Medicare & Medicaid Services, 2004. Accessed December 1, 2004. <http://www.cms.hhs.gov/coverage/8a4.asp>.