COVERAGE AND REIMBURSEMENT FOR PHARMACOGENOMIC TESTING

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ABSTRACT: Since the completion of the Human Genome Project there has been a great deal of publicity and discussion regarding genetic medicine. Genetic advances can be divided into two main categories: diagnostics and therapeutics. Although stem cell therapy and other genetic therapies have gotten most of the publicity relating to genetic advances, the diagnostic field in general and pharmacogenomic testing in particular are likely to have a greater impact on medicine in the near- to mid-term. The integration of pharmacogenomics into clinical practice is subject to several challenges, however, including the challenge of persuading government and commercial payors that they should provide reimbursement for pharmacogenomic testing and ensuring that the amount of reimbursement will make the development of these tests feasible.

This paper provides an overview of genetic testing and a brief discussion of pharmacogenomics. It also discusses the in vitro diagnostic test (IVD) industry, of which pharmacogenomic testing is a segment. Subsequent sections provide an overview of government and private payor coverage and reimbursement processes. The paper then identifies issues likely to influence coverage and reimbursement decisions for pharmacogenomic products and concludes with suggestions on how to improve the prospects for favorable coverage and reimbursement decisions.


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I. OVERVIEW OF GENETIC TESTING

The field of genetic testing is growing rapidly and the number of applications for genetic testing is increasing. These applications include neonatal screening to identify genes associated with “inborn errors of metabolism,” screening of adults thought to be at risk for single-gene diseases based on pedigree, screening to identify patients with a genetic predisposition to specified diseases, testing for genetic variations in disease for purposes of designing therapy, and individualization of drug therapies based on an individual’s genetic information.

An example of the first type of testing would be newborn screening to identify patients with phenylketonuria. Screening of presymptomatic adults includes testing for Huntington’s disease based on a family history. An example of genetic testing for predisposition to a disease would be testing for BRCA 1/2 mutations, which are associated with an increased risk of breast and ovarian cancer. A good example of the next application on the list, testing for genetic variations in disease, is testing for increased tumor expression of Her2/neu, to identify cancer patients who might benefit from therapy with Herceptin. The final application on the list involves testing to identify genetic variations that affect drug targets, drug transport or drug metabolism, to identify individuals for whom specific drugs might be unsafe or ineffective. This last application is called pharmacogenomics, and it is the focus of this paper.


3. Id. at 281–87.


7. Pharmacogenomics (or pharmacogenetics, as the terms are essentially interchangeable) is “the study of variability in drug response owing to heredity.” D.W. Neber & E. Bingham, Pharmacogenomics: Out of the Lab and into the Community, 19 TRENDS IN BIOTECHNOLOGY 519, 519 (2001).
The reason for this focus is that, for a variety of reasons, it appears likely that pharmacogenomics will be the first new* genetic testing technology to be widely incorporated into clinical practice.9

II. PHARMACOGENOMICS
IN A VERY SMALL NUTSHELL

Genetic variations that occur in more than 1% of the population are called polymorphisms, and mutations affecting a single nucleotide are known as single nucleotide polymorphisms, or SNPs.10 Genetic variations can affect drug receptors, drug transport mechanisms, and drug metabolism.11 Alone or in combination with other factors, such as environment, diet, and age, these variations can affect both the safety and effectiveness of pharmaceuticals.12

Because of these genetic variations, many patients experience adverse drug reactions (ADRs) from drugs that are relatively safe for others.13 ADRs are a significant cause of mortality and morbidity, which contribute to increased economic cost as well as human cost. In one study of the incidence of ADRs, the authors estimated that in 1994, 2,216,000 hospitalized patients had serious ADRs and 106,000 patients had fatal ADRs.14 Based on those estimates, ADRs are between the fourth and sixth most common causes of death in the United States.15 ADRs are estimated to result in $1.56 to $4.0 billion dollars in direct hospital costs each year.16
Regarding the effectiveness of drugs, "[t]he most striking feature of modern medicines is how often they fail to work."\textsuperscript{17} According to one estimate, "[m]ost major drugs are effective in only 25 to 60 per cent of patients."\textsuperscript{18}

Using pharmacogenomic testing, physicians will be able to select drugs and dosages based on a particular patient’s genetic makeup, or genotype. The use of pharmacogenomics as an aid to drug selection and dosing decisions will represent a major advance over the aptly named "trial and error" approach. Despite this advance, the incorporation of pharmacogenomics into clinical practice faces several challenges. These include scientific issues,\textsuperscript{19} societal issues,\textsuperscript{20} and physician attitudes.\textsuperscript{21} One of the biggest challenges may be economic. A group appointed by the Secretary of the Department of Health and Human Services "ranked coverage and reimbursement of genetic tests... as a high-priority issue warranting indepth [sic] deliberation and analysis."\textsuperscript{22} "Although advances in genetics and genomics are driving the development of new genetic tests and services, problems with coverage and reimbursement are limiting their accessibility and integration into the health care system."\textsuperscript{23}

\textsuperscript{17} David B. Goldstein, \textit{Pharmacogenomics in the Lab and the Clinic}, 348 NEW ENG. J. MED. 553, 553 (2003).
\textsuperscript{19} In some cases, pharmacogenomic testing may "give definitive answers about the probability... and effectiveness [of drugs] in subpopulations... However, this is unlikely to be the ordinary case. In most instances, a genotype or particular gene expression profile is likely to be one of a large number of factors that affects the probability of an adverse event or a favorable response." FDA, GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS 16 (March 2005), available at http://www.fda.gov/OHRMS/DOCKETS/98fr/2003d-0497-gd0002.pdf.
\textsuperscript{20} Because of concerns that genetic information may be used to make decisions about employment status and insurability, some people may refuse valuable genetic testing. Alan E. Guttmacher & Francis S. Collins, \textit{Realizing the Promise of Genomics in Biomedical Research}, 294 JAMA 1399.1401 (2005).
\textsuperscript{21} Many physicians have little or no knowledge about or experience with pharmacogenomics; one report states that few health care professionals have had "even one hour" of pharmacogenomic instruction as part of their formal training. Kathryn A. Phillips et al., Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review, 286 JAMA 2270, 2276 (2001); see also A.N. Freedman et al., US Physicians’ Attitudes Toward Genetic Testing for Cancer Susceptibility, 120 AM. J. MED. GENETICS 63 (2003).
\textsuperscript{23} \textit{Id.} at 3.
III. IVD INDUSTRY OVERVIEW

Pharmacogenomic testing involves the use of "in vitro diagnostic products," or IVDs. According to the Food and Drug Administration:

*In vitro* diagnostic products are those reagents, instruments, and systems intended for use in the 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 body.

Although most IVDs are not subject to FDA regulation, the quoted provision offers a good working definition. In addition, the emphasized portion of the definition distinguishes IVDs from other types of diagnostic equipment and devices which provide medical information without the taking of a sample.

IVDs range in complexity and cost from home pregnancy tests that cost a few dollars to genetic microarray tests that can cost thousands of dollars. While IVDs account for a small percentage of total health care costs—5% of hospital costs and 1.6% of Medicare expenditures—they are estimated to influence as much as 60% to 70% of health care decision making by providing diagnostic information that drives therapeutic decisions.

Diagnostics have been described as the "poor relation" of therapeutic drugs and devices, and diagnostic companies operate on smaller margins than

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25. 21 C.F.R. § 809.3 (emphasis added).
26. The FDA regulates test kits and systems, but most genetic tests are conducted by laboratories that use their own ialyte specific reagents or ASRs. Kathryn A. Phillips & Stephanie L. Van Bebber, Measuring the Value of Pharmacogenomics, 4 NATURE REVIEWS DRUG DISCOVERY 500, 501 (2005). These “home brews” are not regulated by the FDA. Id. The FDA may be seeking to extend its regulatory reach, id., and in 1997 it issued rules defining and regulating ASRs. Lewin Report, supra note 1, at 28 n.48. For the most part, however, clinical laboratories, and the “home brew” tests they develop and offer, are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). Lewin Report, supra note 1, at 4. CLIA was passed to “ensure the accuracy, reliability and timeliness of patient test results.” INSTITUTE OF MEDICINE, COMMITTEE ON MEDICARE PAYMENT METHODOLOGY FOR CLINICAL LABORATORY SERVICES, MEDICARE LABORATORY PAYMENT POLICY: NOW AND IN THE FUTURE 41 (Dianne Miller Wolman et al. eds., National Academy Press 2000) [hereinafter IOM Report], available at http://www.nap.edu/catalog.php?record_id=9997. CMS does not evaluate clinical validity or utility as part of assessing CLIA compliance. Phillips et al., supra note 4, at 430. For a detailed discussion of FDA and CLIA regulation of diagnostics, see Lewin Report, supra note 1, at 72-91.
27. Devices such as medical imaging devices and blood pressure monitors, which measure, image or assess health status inside the body, may be referred to as in vivo devices. Lewin Report, supra note 1, at 14.
28. Id. at 147.
drug companies. Diagnostic companies also tend to be relatively small: nearly half of all diagnostic companies have fewer than fifty employees. As a result of being smaller and less profitable, diagnostic companies may be less able to withstand cash flow problems resulting from delays or denials in coverage determinations made by Medicare and other payors. On the positive side, as compared to the United States diagnostics industry as a whole, the molecular diagnostics segment may enjoy higher margins, and may be growing at a faster rate.

There clearly is an increase in the number of laboratories performing genetic tests, and in the number of diseases for which genetic tests are available. As of August, 2000, there were 1300 facilities performing tests relating to more than 700 genetic conditions, compared to 116 facilities and 111 conditions in 1993.

IV. MEDICARE COVERAGE AND REIMBURSEMENT

Medicare is a federally funded health insurance program for people over age sixty-five, people under sixty-five who have certain disabilities, and people with end stage renal disease. Medicare includes Part A hospital coverage, Part B medical coverage, Part C Medicare Advantage, and Part D

29. Kerry A. Dolan, Good Genes, FORBES, June 6, 2005, at 106. According to this article, which estimates that diagnostics account for 4% of health care spending, diagnostic companies operate on 50% margins as compared to 80% margins for drug companies. Id. The author also estimates that the United States market for diagnostics is $30 billion. Id. The Lewin Report puts the worldwide market at $28.6 billion (to $39 billion in four years) and the United States market at $11.2 billion. Lewin Report, supra note 1, at 3, 131.

30. Lewin Report, supra note 1, at 3.

31. Id. at 25. According to another report, companies in the $2.5 billion molecular diagnostic segment have margins in the 75% range, and that the segment is growing at 15% annually, while the diagnostic market as a whole is only growing at a 4% rate. Dolan, supra note 29, at 106. The author of the article believes that the mapping of the human genome has contributed to the higher margins and faster growth experienced by the molecular diagnostics segment. Id. Another author reports that the molecular diagnostics industry, which includes genetic testing, is growing at a 25% rate. Michelle M. Schoonmaker, Reimbursement for Molecular Diagnostics, IVD Tech., Jan.-Feb. 2007, http://www.devicelink.com/ivdt/Archive/07/01/011.html.

32. IOM Report, supra note 26, at 65.


34. Part A covers inpatient hospital care and some skilled nursing care, hospice care and home health. Id. The Part A benefit is funded through payroll taxes; beneficiaries are not required to pay premiums for the coverage. Id.

35. Part B covers physician services and certain types of outpatient care, including laboratory testing. Id. Most beneficiaries pay a premium for Part B coverage. Id.

36. Part C is a program under which Part A and Part B services are provided to beneficiaries through private managed care plans. IOM Report, supra note 26, at 25. As of 2000, approximately 16% of Medicare beneficiaries participated in these types of plans. Id.
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prescription drug coverage.\(^{37}\) The program is managed by the Centers for Medicare and Medicaid Services (CMS).\(^{38}\)

Medicare covers more than forty-one million Americans at an estimated cost of $295 billion annually.\(^{39}\) Medicare expenditures make up approximately 16.5% of total health care expenditures in the United States, making Medicare the single largest purchaser of health care services in the United States.\(^{40}\) Because of its size, and because Medicaid and commercial payors follow Medicare’s lead in many circumstances,\(^{41}\) Medicare has a great deal of influence on health care financing in the United States.\(^{42}\)

The Medicare program was created in 1965 with the passage of the Social Security Act.\(^{43}\) During the debate that led to the passage of the Act, some hospital and physician groups expressed concern that the Medicare program would interfere with the practice of medicine.\(^{44}\) To help alleviate that concern and enlist support from health care providers, Congress created a structure in which private companies would serve as a “buffer” between the federal government and providers.\(^{45}\) Under Part A, hospitals nominated “fiscal intermediaries,” or FIs, to manage hospital relations, reimbursement, utilization review and related services.\(^{46}\) For Part B services, the government contracted with regional or local “carriers,”\(^{47}\) who performed similar functions.\(^{48}\)

This approach resulted in a system in which a large number of private companies were involved in making coverage policy and carrying out policy established by the Health Care Financing Administration (HCFA). For example, as of 1966 there were forty-nine carriers in the Part B program.\(^{49}\) The decentralized nature of the Medicare program has had significant repercussion...
sions for the development of Medicare coverage policy: approximately 90% of Medicare’s coverage determinations are made at the local level.  

The Social Security Act does not contain a list of all of the items or services that are eligible for Medicare Coverage. Rather, the Act specifies benefit categories and authorizes the Secretary of the Department of Health and Human Services to make determinations about which items or services are covered. The basic coverage algorithm involves a determination that the item or service in question falls within a covered benefit category, that it is not specifically excluded from coverage, and that it is “reasonable and necessary for the diagnosis or treatment of illness or injury, or to improve the functioning of a malformed body member.”

The requirement that an item or service be “reasonable and necessary” for the diagnosis or treatment of disease has particular relevance for pharmacogenomic tests because it means that, with certain statutory exceptions, Medicare does not pay for screening tests. Therefore, absent some indication that a person has a genetic variant that would make a particular drug unsafe or ineffective for him, Medicare would not cover a pharmacogenomic test.


52. Id. Historically, the Secretary has delegated this function to the administrator of CMS (or its predecessor, HCFA), and in practice, the vast majority of these decisions have been made by carriers and FIs. Muriel R. Gillick, Medicare Coverage for New Technologies—Time for New Criteria?, 350 NEW ENG. J. MED. 2199, 2199 (2004).


54. § 1395y (“Notwithstanding any other provision of this chapter, no payment may be made under Part A or Part B of this chapter for any expenses incurred for items or services—(1)(A) which, except for items or services described in a succeeding paragraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”). The “succeeding paragraph” allows certain types of screening, with specified limitations. Id. The covered screening exams include, subject to specified limitations: mammography; pap smears and screening pelvic exams; glaucoma exams; prostate cancer screening; colorectal cancer screening exams; cardiovascular screening exams; and diabetes screening exams. Id. The exceptions to the exclusion also permit payment for an initial preventive physical examination, certain home health services and drugs and biologicals furnished under certain conditions. Id.

55. Medicare Program: Negotiated Rulemaking: Coverage and Administrative Policies for Clinical Diagnostic Laboratory Services, 66 Fed. Reg. 58,788, 58,813 (Nov. 23, 2001) (“Tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute.”).

56. Personal history might play a role in establishing coverage in several ways. For example, if a patient has had an adverse reaction to a particular drug, or if the drug does not appear to be having the desired or expected result, that history might support the use of a pharmacogenomic test. Interestingly, some Medicare carriers have approved coverage for the BRCA 1/2 test “in the
The Part A benefit categories include inpatient hospital services, posthospital extended care services, home health services (for beneficiaries not enrolled in Part B) and hospice benefits. The Part B benefit categories include physician services, other services and supplies (including certain drugs and biologicals such as serums, antitoxins and vaccines), outpatient hospital services and diagnostic services. Because diagnostic tests may be provided in the inpatient or outpatient settings, both Part A and Part B are relevant to coverage determinations for such tests.

There is no statutory or regulatory guidance for the meaning of "reasonable and necessary," but CMS has interpreted the term to require "that the item or service should, at a minimum, improve net health outcome for Medicare beneficiaries." Stated differently, the coverage determination involves an analysis of the clinical effectiveness of the item or service in question. Depending on a variety of factors, discussed below, the analysis may be conducted—and the coverage determination made—by CMS, or by individual FIs and carriers.

CMS makes coverage determinations through the development and issuance of National Coverage Determinations, or NCDs. NCDs apply to all absence of signs, symptoms, or personal history of the disease." SACGHS Report, supra note 22, at 28. Similarly, a minority of Medicare contractors provide coverage for the test that determines whether a breast cancer patient's tumor overexpresses Her-2/neu, which would be an indication for Herceptin. Id. at 30. Coverage for the test for Her-2/neu may be based on the fact that the test is used to diagnose a subtype of a disease, cancer, which has manifested "signs and symptoms." Pharmacogenomic testing microarrays pose an interesting coverage question: if the array tests for dozens, hundreds or thousands of SNPs, only one of which is relevant based on the patient's signs, symptoms or personal history, would the cost of the test be covered?

57. 42 U.S.C. § 1395d.
58. § 1395x(s) (providing coverage for "services and supplies (including drugs and biologicals which are not usually self-administered by the patient) furnished as an incident to a physician's professional service"). Before implementation of the prescription drug benefit under the MMA, approximately 75% of Medicare reimbursement for prescription drugs was paid to physicians for chemotherapy and other infusion drugs. Patricia M. Danzon, et al., Alternative Strategies for Medicare Payment of Outpatient Prescription Drugs—Part B and Beyond, 11 AM. J. MANAGED CARE 173, 174 (2005).
59. § 1395k (specifying that Part B covers "medical and other health services" and other types of services); § 1395x(s) (defining "medical and other health services").
60. Given the prevalence of prospective payment systems (PPSs), such as the "diagnostic-related group" or "DRG" reimbursement system common in the hospital setting, and the fact that this type of reimbursement puts the hospital at financial risk for the services provided, it may be the hospital, as opposed to the FI, that determines which diagnostic tests will be provided in the inpatient setting. Gregory J. Tsongalis, A Reality Check for Molecular Diagnostics in Clinical Practice, PHARMACOGENOMICS 667, 667-68 (2003); MEDICARE PAYMENT ADVISORY COMMISSION (MEDPAC) REPORT TO CONGRESS: ISSUES IN A MODERNIZED MEDICARE PROGRAM 187 (June, 2005) [hereinafter MedPac Report], available at http://www.medpac.gov/documents/June05_Entire_report.pdf ("For services paid through PPSs, providers serve as the purchaser and make decisions about which services to furnish to beneficiaries."). Because approximately half of all laboratory services are provided by hospital laboratories, IOM Report, supra note 26, at 31, hospitals are an important target market for IVD manufacturers.
61. SACGHS Report, supra note 22, at 29.
beneficiaries.\textsuperscript{64} FIs and carriers.\textsuperscript{65} An NCD review may be initiated by CMS where, inter alia, there are conflicting coverage determinations at the local level, a new technology represents a significant advance, there is a question about the effectiveness or administration of a particular item or service, a covered service is suspected to be obsolete or ineffective, or CMS has concerns regarding over- or under-utilization of an item or service.\textsuperscript{66} An NCD also may be requested by Medicare beneficiaries or by manufacturers, suppliers or health care providers.\textsuperscript{67}

In the past, CMS was criticized because its process for making coverage determinations was viewed as arbitrary, inconsistent, and opaque.\textsuperscript{68} The Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA) addressed concerns about lack of transparency by requiring CMS to publish guidance documents regarding factors it considers in making those determinations.\textsuperscript{69} Since that time, CMS has published guidance documents describing several aspects of its process.\textsuperscript{70}

To determine whether a new item or service is clinically effective, for coverage determination purposes, CMS evaluates the evidence relating to the technology. This evaluation uses “standard principles of evidence-based medicine, which require a thorough evaluation of relevant clinical evidence to determine whether the evidence is of sufficient quality.”\textsuperscript{71} In conducting this assessment, CMS evaluates the quality of the available evidence, its application to the Medicare population, and any conclusions that can be drawn regarding the technology’s risks and benefits.\textsuperscript{72}

In recent years, CMS has developed new tools to assess whether a new technology is clinically effective. In December, 1998, CMS established the Medicare Coverage Advisory Committee (MCAC), to provide external input

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\item Beneficiaries can challenge NCDs and LCDs under a final rule published at Medicare Program: Review of National Coverage Determinations and Local Coverage Determinations, 68 Fed. Reg. 63,692 (Nov. 7, 2003).
\item SACGHS Report, supra note 22, at 27.
\item Id. at 2; see also Lewin Report, supra note 1, at 99.
\item Paul Barr, Declassifying Coverage: New Guidance Documents Issued by the CMS May Clarify the Great Unknown of Medicare Coverage Determination, MOD. HEALTHCARE, Mar. 21, 2005, at 6.
\item SACGHS Report, supra note 22, at 29.
\item Id.
and guidance on coverage determinations. The MCAC is comprised of up to 120 members appointed from disciplines including clinical and administrative medicine, public health, health information management, basic science, health care economics, and ethics. Questions delegated to the MCAC are assigned to smaller groups selected for their expertise. These groups review literature and data and make recommendations regarding coverage.

CMS may also request a technology assessment (TA) either before or as a part of the NCD process. A TA includes a review of the medical literature with respect to a particular intervention to assess the validity of the evidence regarding the intervention, its clinical relevance, and its importance to patients or beneficiaries. CMS may request a TA in a variety of circumstances, including where there is an extensive body of literature regarding the item or service in question, the literature is complex or conflicting, or where an understanding of the literature requires “unique technical and/or clinical expertise” that CMS staff does not possess. TAs may be conducted by any entity “with the requisite experience in TA methods and evidence-based medicine to ensure technical competence and fairness.”

The use of MCAC or a TA as part of the coverage determination results can result in a delay in the determination. The statutorily mandated timeframe for releasing an NCD in response to an external request is six months after receipt of a completed request. That timeframe is increased to nine months where CMS requests a TA or MCAC review, or both.

One new aspect of the coverage determination process that may be of particular interest to IVD manufacturers and others involved in the development of innovative technology is the Council on Technology and Innovation (CTI). The CTI, established by Section 942(a) of the MMA, is charged with

73. Medicare Program: Establishment of the Medicare Coverage Advisory Committee and Request for Nominations for Members, 63 Fed. Reg. 68,780 (Dec. 14, 1998); Neumann et al., supra note 50. at 244.
75. Id.
76. Id. Between 1999 and 2003, CMS referred 22 percent of NCD requests to the MCAC. Neumann et al., supra note 50. at 246.
77. CMS Technology Guidance, supra note 70.
78. Id.
79. Id.
80. Id. Currently, CMS has a contract with the Agency for Healthcare Research and Quality to conduct TAs and provide reports. Id.
82. 42 U.S.C. § 1395yy(t) (2006). In either case, these deadlines may be more of a goal than a standard, as completion of the process often takes more time than is allowed under the specified timeframes. Neumann et al., supra note 50. at 248–49. According to the Lewin Report, it can take 14 to 26 months or more for a new code to become effective for a new laboratory test. Lewin Report, supra note 1, at 5.
83. § 1395ee.
"coordinating coverage, coding and payment processes for Medicare with respect to new technologies and procedures, including new drug therapies."\(^{84}\)

The Food and Drug Administration also plays a role in CMS coverage determinations. Drugs or devices that are subject to FDA pre-market approval must be approved by the FDA for at least one indication to be eligible for Medicare coverage.\(^{85}\) Currently, the vast majority of laboratory tests that do require FDA approval qualify for a less rigorous review under the 510K Premarket Notification,\(^{86}\) and the FDA will clear these tests for marketing if the sponsors can demonstrate that the tests are "substantially equivalent" to previously approved devices.\(^{87}\)

Although the FDA and CMS may review the same evidence in making their decisions, the focus of those decisions differs. The FDA determines that a drug or device is "safe and effective," CMS then decides whether the drug or device is "reasonable and necessary" for the Medicare population.\(^{88}\) Consequently, while FDA approval is a necessary condition of Medicare coverage in most cases, it is not sufficient to ensure Medicare coverage.\(^{89}\)

Based on its evaluation of the clinical effectiveness of the item or service under review, CMS may take any of the following actions: (1) issue an NCD, with or without limitations, providing coverage (that is, requiring FIs and carriers to cover the item or service); (2) issue an NCD precluding coverage (that is, precluding FIs and carriers from covering the item or service); or (3) decline to issue an NCD, leaving the coverage determination to FIs and carriers.\(^{91}\)

The types of coverage limitations CMS might impose include clinical or demographic limitations, facility-specific limitations (for example, services might be covered only if provided in facilities that meet certain requirements),

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85. Medicare Program; Revised Process for Making Medicare National Coverage Determinations, 68 Fed. Reg. 55,634, 55,636 (Sept. 26, 2003). The one exception to this rule is that Category B devices subject to the investigational device exemption (IDE) may be approved for Medicare coverage. Id. See 42 C.F.R. § 201–215 (regarding Medicare coverage and payment for Category B IDE devices).

86. This may be changing, at least with respect to a class of IVDs known as "multivariate index assays" or IVDMIAs. FDA, Draft Guidance for Industry, Clinical Laboratories and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (July 26, 2007), available at http://www.fda.gov/cdrh/ivd/guidance/1610.pdf. The FDA has defined IVDMIA in their guidance document. Id. at 3–4. According to this Guidance, FDA believes that certain IVDMIAs will be Class III devices, which will require Premarket Approval. Id. at 8.

87. SACGHS Report, supra note 22, at 29.


90. Id.

91. SACGHS Report, supra note 22, at 29.
or limitations that allow coverage only for beneficiaries participating in "coverage with evidence development" or CED programs.

The CED process was initiated in April, 2005 as a way of providing coverage for a particular technology, but only for patients enrolled in a "protocol-specified prospective data collection" process. Basically, the CED process allows CMS to make a coverage determination regarding a new technology contingent upon the enrollment of beneficiaries into a clinical trial designed to assess the effectiveness of the technology. In the press release announcing the release of the draft CED guidance, CMS Administrator Mark B. McClellan, M.D., Ph.D., stated: "As health care becomes more personalized, better evidence can help doctors and patients use the treatments that Medicare covers more effectively." Because the CED process occurs only in the context of an NCD, and because few NCDs are issued per year, the CED process is not likely to be used frequently.

If CMS does not issue an NCD, it leaves the field open for carriers and FIs to make coverage-related determinations through Local Coverage Determinations (LCDs) and Local Medical Review Policies (LMRPs). LCDs represent a determination "respecting whether or not a particular item or service is covered on an intermediary- or carrier-wide basis." They do not address coding decisions or establish the amount of payment CMS will make for the item or service in question. An LMRP may relate to benefit categories, coverage, application of exclusions from coverage, or coding. Neither LCDs nor LMRPs are binding on administrative law judges, who are charged with resolving coverage disputes.

As noted above, the vast majority of Medicare coverage determinations are made at the local level. As a result, there are many, varied and some-
times conflicting coverage policies for the same technology, depending on the region in which the technology is provided. This is particularly true for laboratory tests, because most of the requests for NCDs relate to medical devices, surgical procedures and other relatively expensive items. This situation is particularly problematic for companies that distribute test kits to users across the country, as they must face the choice of seeking LCDs from each carrier or seeking an NCD (and risking an adverse decision at a national level). This has resulted in calls for more centralization in the coverage determination process and more consistency in the coverage determination outcomes.

A favorable coverage determination, even at the national level, is only the first hurdle facing a manufacturer who wishes to profit from selling products or services to Medicare beneficiaries. Once Medicare decides to provide coverage, the next step is to assign a code to the technology. The code then determines how much Medicare will pay for the item or service.

Most diagnostic services are assigned a code under the Current Procedural Terminology (CPT) coding system created by the American Medical Association in 1966. Typically, the CPT code is a five digit number that is assigned to an item or service, with genetic tests billed using CPT laboratory and pathology codes.

In 1984, Congress authorized the creation of the Medicare Clinical Laboratory Fee Schedule (CLFS) for clinical laboratory services. The CLFS is, in reality, many fee schedules, as each carrier is required to establish its own schedule. Payments allowable under the CLFS were to be adjusted annually based on the Consumer Price Index, an index that grew at a rate be-

104. Foote, supra note 44, at 137-38. For example, there are more than 35 policies addressing coverage for deep brain stimulation. Id. at 138; see also Barr, supra note 68.
105. CMS Fact Sheet, supra note 50, at 1-4; Barr, supra note 68.
106. Foote, supra note 44, at 138.
107. Or, more precisely, how much Medicare will “allow” for the item or service: with deductibles and copay amounts applicable to some items and services, Medicare beneficiaries remain responsible for payment of a portion of the amount due. Beneficiaries are not required to make co-payments for diagnostics billed under the Clinical Laboratory Fee Schedule. G. Gregory Raab & L. Joan Logue, Medicare Coverage of New Clinical Diagnostic Laboratory Tests: The Need for Coding and Payment Reforms, 15 CLINICAL LEADERSHIP & MGMT. REV. 376, 377 (2000).
108. See SACGHS Report, supra note 22, at 36. Some items or services that do not have an assigned CPT code, but that may be covered by Medicare, are given a Healthcare Common Procedural Coding System (HCPCS) code. Id. at 38.
109. Id.
110. IOM Report, supra note 26, at 26. The CLFS provides the payment for the technical component of the laboratory studies. Id. Physician services, for example, patient visits and interpretation of test results, are covered under the physician fee schedule. Id. at 27 n.18. Interestingly, laboratory reimbursement and physician reimbursement are something of a zero sum game. Laboratory expenses are included in the measure of physician expenditures for purposes of calculating the Medicare “sustainable growth rate,” which updates the annual Medicare budget for these services; as a result, a significant increase in laboratory expenses could result in a decrease in the amount of money available to pay for physician services. Id. at 98.
111. Raab & Logue, supra note 107, at 377.
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low the rate of inflation for medical goods and services.\footnote{112} One year later, Congress established a National Limitation Amount (NLA) to establish a cap on fees for laboratory services.\footnote{113} Following establishment of the NLA, the maximum allowable charge for laboratory services covered by Medicare was the lesser of the provider’s charge for the service, the applicable carrier’s fee schedule amount, or the NLA.\footnote{114}

When the AMA updates its laboratory CPT codes, which it does on an annual basis, CMS must incorporate the new codes (and the tests they represent) into the CLFS.\footnote{115} This is accomplished in one of two ways, cross-walking or gap-filling.\footnote{116} Cross-walking is used when a new test is clinically or technologically similar to an existing test.\footnote{117} In that circumstance, the new test is assigned the same CLFS payment amount for CLFS and NLA.\footnote{118}

When there is no comparable test available, CMS employs gap-filling.\footnote{119} Each carrier is instructed to establish a payment amount for the new test for the first year after a coverage determination is made.\footnote{120} The payment amounts of the carriers are then used to determine an NLA for the following years.\footnote{121} Both of these rate-setting processes have been criticized for being unpredictable\footnote{122} and for setting reimbursement rates for laboratory services at unreasonably low levels.\footnote{123} Some of these complaints may be addressed by the issuance of new regulations, required under Section 942(b) of the MMA, which will articulate “procedures for determining the basis for, amount of, payment” for new diagnostic laboratory tests.\footnote{124}

Notably absent from a discussion about Medicare’s coverage and payment processes is any reference to a consideration of the economic impact of those

\footnote{112} Id. To provide further pressure on laboratory service providers, Congress froze the fee schedule for a five year period ending in 2002, and again for the period from 2003–2009. SACGHS Report, supra note 22, at 43.
\footnote{113} Raab & Logue, supra note 107, at 377. Initially, the NLA was 115% of the median amount of all carriers’ fee schedules for the specified item or service; as of 2001, it was 74% of the median. Id.
\footnote{114} Id.
\footnote{115} Id. at 378.
\footnote{116} Lewin Report, supra note 1, at 111.
\footnote{117} Through this process, Medicare could employ an evaluation of the clinical effectiveness of an item or service to determine the amount of reimbursement, as well as the decision of whether to provide coverage in the first instance. MedPac Report, supra note 60, at 181–82.
\footnote{118} Raab & Logue, supra note 107, at 379.
\footnote{119} Lewin Report, supra note 1, at 111.
\footnote{120} Id.
\footnote{121} Id.
\footnote{122} Id. “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 uncertain, the poorly delineated pathway for gap-filling may pose even more uncertainty for marketed tests.” Id.
\footnote{123} IOM Report, supra note 26, at 94; Raab & Logue, supra note 107, at 383–85. Testimony provided to the SACGHS indicated that “Medicare payment rates were significantly lower than the actual costs incurred by laboratories to provide genetic testing.” SACGHS Report, supra note 22, at 46.
\footnote{124} SACGHS Report, supra note 22, at 45.
processes on the federal Treasury. Although CMS has tried to incorporate economic considerations into coverage determinations, they have had virtually no success in doing so to date. Reasons for this lack of success include resistance from beneficiaries and policymakers who fear that this approach might lead to rationing, concerns that economic analysis might slow the pace of innovation, and uncertainty about whether CMS has the authority to consider costs in making coverage determinations. It appears that CMS is trying to overcome the resistance to use of cost-effectiveness analyses (CEA) as a continuing failure to consider cost effectiveness could have significant economic consequences.

In recent years, there have been renewed calls for Medicare to employ CEA in its coverage determinations and to provide criteria that it will consider in those analyses. The MMA, which created an expanded prescription drug benefit for Medicare beneficiaries, provided an excellent opportunity to add CEA to coverage and reimbursement processes; however, the Act does not require participating plans to make use of the analysis.

125. MedPac Report, supra note 60, at 179. "Medicare does not explicitly consider the cost effectiveness of a service in either the coverage or payment process." Id.; see also Neumann et al., supra note 94, at 1516. "The Medicare program has been a notable holdout in the global movement toward the use of cost-effectiveness analysis to inform health care decisions." Id.


127. Neumann et al., supra note 94, at 1516. In 1990, the Oregon Health Service tried to implement a coverage and reimbursement arrangement under which conditions and their treatments were ranked in accordance with their cost-effectiveness. MedPac Report, supra note 60, at 187. Treatments that fell below a specified line were not covered. Id. Following objections about rationing, this approach was abandoned in favor of a process in which cost-effectiveness was one of thirteen factors considered in making coverage determinations.

128. MedPac Report, supra note 60, at 186-87; see also Neumann et al., supra note 94, at 1517-19.

129. Neumann et al., supra note 94, at 1516. In 2003, CMS approved three high-cost procedures (lung reduction surgery, implantable defibrillators and left ventricular assist devices) that could cost the program between $1.3 billion to $11.4 billion per year, or figures equaling between 3% and 20% of the new Medicare drug benefit. Gillick, supra note 52, at 2199. The cost of the left ventricular assist device per "quality-adjusted life-year," (QALY) is estimated to range between $500,000 and $1.4 million. Id. at 2202.

130. See Gillick, supra note 52, at 2202. In response to the Gillick article, Sean Tunis of the CMS Office of Clinical Standards and Quality pointed out some of the difficulties associated with setting explicit coverage criteria, including cost-effectiveness. Tunis, supra note 42. These include: lack of public confidence in the coverage determination process; a reluctance to interfere with the physician-patient relationship; and concerns about how explicit coverage criteria might impact health care innovation. Id. at 2196-97.

131. Neumann et al., supra note 94, at 1516. The MMA does not preclude plans from using CEA to establish their formularies, and "the plans’ use of cost-effectiveness information to guide
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The fact that Medicare does not formally conduct CEA in making coverage determinations does not mean that money is no object in coverage and reimbursement decisions. As a threshold matter, expensive items or services are likely to be subject to greater scrutiny.\(^\text{132}\) Also, for expensive new procedures, CMS may require participation in a “coverage with evidence development” program as a condition of coverage,\(^\text{133}\) or limit coverage to procedures performed in facilities with demonstrated expertise.\(^\text{134}\) In addition, there is some suspicion that Medicare’s determination of the amount it will pay for a service reflects economic considerations. For example, the decision to reimburse implantation of left ventricular assist devices at an amount less than cost may have resulted from a determination of an acceptable cost-threshold for the device.\(^\text{135}\) Finally, the cross-walking process discussed above and Medicare’s “least costly alternative” approach to setting payment may allow Medicare to fix reimbursement for new technology at a level low enough to assure that the technology is cost-effective.\(^\text{136}\)

V. MEDICAID COVERAGE AND REIMBURSEMENT

The Medicaid program is a joint state-federal medical assistance program established and governed by Title XIX of the Social Security Act.\(^\text{137}\) The program provides assistance to more than fifty million Americans,\(^\text{138}\) approximately half of whom are children.\(^\text{139}\)

The federal government establishes broad guidelines for the program. Within those guidelines, states are free to administer their programs and to establish their own eligibility standards, type and scope of services, and pay-
ment rates.\textsuperscript{140} Regarding eligibility, states must provide Medicaid benefits to certain individuals who are deemed “categorically needy”; most of these individuals are indigent women and children, and people receiving Social Security disability benefits.\textsuperscript{141}

States may, and most states do, provide benefits to individuals who are not “categorically needy” but who are deemed to be in need of assistance.\textsuperscript{142} In addition, children who do not qualify for benefits under Medicaid may be eligible to participate in the State Children’s Health Insurance Program (SCHIP) under Title XIX of the Social Security Act.\textsuperscript{143} Medicaid programs also are substantial payors for care provided in skilled nursing facilities.\textsuperscript{144} Given this mix of beneficiaries, Medicaid programs are important payors for items and services that are needed by women, children and nursing home residents.

Regarding benefits, states that participate in the Medicaid program are required to cover inpatient and outpatient hospital services, physician services, childhood vaccines, and certain laboratory and imaging services.\textsuperscript{145} Also, in contrast to Medicare’s historic reluctance to provide preventive care, states participating in the Medicaid program must provide “early and periodic screening, diagnostic and treatment services” (EPSDT) for children under the age of twenty-one.\textsuperscript{146} In addition to these mandated services, many states also cover a broader range of diagnostic services and prescription drugs.\textsuperscript{147}

States also have a great deal of flexibility with respect to the process for and amount of payment for covered services. Some states, such as Arizona, operate a system in which the state makes prepayments to health maintenance organizations, which then administer claims and make payments to providers; other states pay providers directly.\textsuperscript{148} The primary constraint in setting the amount of payment is that the amount must be sufficient to ensure that there are enough providers willing to accept the payment.\textsuperscript{149}

\textsuperscript{140} Id. at Overview of Medicaid.
\textsuperscript{141} Id. at Basis of Eligibility and Maintenance Assistance Status.
\textsuperscript{142} Id.
\textsuperscript{143} Id.
\textsuperscript{144} Lewin Report, supra note 1, at 118. According to CMS data, Medicaid programs paid 41% of the total cost of care for individuals in nursing homes and home health care programs. CMS Medicaid Summary, supra note 137, at Medicaid Summary and Trends.
\textsuperscript{145} CMS Medicaid Summary, supra note 137, at Scope of Medicaid Services.
\textsuperscript{146} Id. The current EPSDT requirements include: a comprehensive health and developmental history; a comprehensive physical exam; immunizations; screening laboratory services (of a type deemed age-appropriate for children by providers in the state); lead toxicity screening; vision, hearing and dental evaluations; and health education. CMS, Medicaid Early & Periodic Screening & Diagnostic Treatment Benefits: EPSDT Benefits, http://www.cms.hhs.gov/MedicaidEarlyPeriodicSern/02_Benefits.asp (last visited Apr. 20, 2008).
\textsuperscript{147} CMS Medicaid Summary, supra note 137, at Scope of Medicaid Services.
\textsuperscript{148} Id. at Payment for Medicaid Services. From 1993 to 2003, the percentage of Medicaid beneficiaries enrolled in some type of managed care program rose from 14% to 59%. Id. at Medicaid Summary and Trends.
\textsuperscript{149} Id. at Payment for Medicaid Services.
Low income Medicare beneficiaries may qualify for Medicaid benefits. These “dual eligible” individuals may receive Medicaid benefits that are not covered by Medicare, such as extended stay nursing facility care, eyeglasses, and hearing aids. Where an item or service is covered by both Medicare and Medicaid, Medicare makes payment for the item, as the Medicaid program is always the secondary payer.

VI. COMMERCIAL PAYOR OVERVIEW

Commercial payors offer two basic types of health insurance coverage: indemnity insurance and managed care plans. Indemnity insurance plans, which were predominant in the early years of health insurance, provide members with unrestricted access to covered services and pay providers on a fee-for-service basis. As a result of the relative absence of any care management or utilization management features, these plans tend to charge higher premiums and they have become less common as healthcare costs have risen.

Managed care plans involve varying degrees of utilization and cost controls, ranging from the most restrictive staff model health maintenance organizations (HMOs), with physician gatekeepers and limited access to non-staff providers, to preferred provider organizations (PPOs), which attempt to direct members to lower cost contract providers via reimbursement incentives and disincentives. Managed care plans insure approximately 200 million Americans, most of whom obtain insurance through their (or their family members’) employers. In terms of the challenges associated with understanding and working with a variety of coverage systems and processes, the private sector makes Medicare and Medicaid look easy: according to one report there are more than 700 HMO plans and 1,000 PPO plans in the United States.

Adding to the uncertainty and confusion is the fact that there is little easily accessible data about coverage policies employed by private insurers. Publicly available information suggests that private payors are likely to consider the following in making coverage decisions regarding genetic tests: current signs and symptoms of the disease the test is intended to diagnose or rule out; personal or family history or risk factors for the disease; whether the test is considered to be investigational or experimental; the site at which the test will

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150. Id. at The Medicare-Medicaid Relationship.
151. Id.
152. Lewin Report, supra note 1, at 120.
153. Id.
154. Id.
155. Id. This figure includes approximately 15 million Medicaid members and seven million Medicare members in managed care plans. Id.
156. Id.
157. SACGHS Report, supra note 22, at 17; Lewin Report, supra note 1, at 123.
be performed (for example, is it CLIA certified?); and whether the test will influence management or treatment of the disease. 158

Like Medicare, private insurers are beginning to show interest in the use of scientific or medical evidence as a basis for coverage decisions. 159 In addition, some private payors are using a formalized technology assessment process to evaluate new tests and treatments. 160 For example, Blue Cross Blue Shield employs a Technology Evaluation Center, the function and goals of which closely resemble Medicare’s Technology Assessment process, which is described above. 161

Regarding payment processes, many private payors have adopted the use of CPT codes and a laboratory fee schedule, making their processes similar to what Medicare employs. 162 In fact, some payors adopt the Medicare approach on an almost wholesale basis, 163 agreeing to pay providers, for example, “95% of the Medicare Fee Schedule.”

Although the available information suggests that the coverage and payment processes employed by private payors are similar to what Medicare employs, there are at least two areas in which the two systems appear to differ. The first difference is that while most Medicare beneficiaries stay in the Medicare program for life, private plan enrollees, or their employer-sponsors, change insurance plans with some frequency. 164 The second difference is that private payors do consider cost-effectiveness as part of their coverage determination process, at least in some circumstances. 165

Turnover among private plan members has some relevance to those who wish to obtain private plan coverage for IVDs because it affects a payor’s willingness to pay for preventive medicine or to incur any other short-term costs that might yield long-term benefits. 166 This attitude may be particularly

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158. SACGHS Report, supra note 22, at 18. Private payors are not likely to receive coverage for population screening (except for certain conditions); testing for informational purposes; or testing of minors for adult-onset diseases. Id.
159. Id. at 4, 18.
160. Id. at 18.
161. Id.; Lewin Report, supra note 1, at 121–23.
162. Lewin Report, supra note 1, at 123.
163. SACGHS Report, supra note 22, at 46.
164. Id. at 21.
165. MedPac Report, supra note 50, at 185; Mitchell K. Higashi & David L. Veenstra, Managed Care in the Genomics Era: Assessing the Cost Effectiveness of Genetic Tests, 9 AM. J. MANAGED CARE 493, 494 (2003). Although CEA may be the most common method of analyzing the economic effect of health care interventions, there are a number of other approaches: cost of illness analysis; cost minimization analysis; cost consequence analysis; cost utility analysis and cost benefit analysis. Phillips & Van Bebber, supra note 26, at 501; see also Veenstra et al., supra note 6, at 2.
166. SACGHS Report, supra note 22, at 21. “Because plan members change plans at fairly frequent intervals, private health insurance coverage for preventive services may be difficult to rationalize from an economic standpoint since the cost savings may not accrue to the plan that paid for the service.” Id.; see also Patricia Danson & Adrian Towse, The Economics of Gene Therapy and of Pharmacogenomics, 5 VALUE HEALTH 5, 5–12 (2002). One author suggests that “[g]iven that many current HMOs themselves have limited independent lifespans as large plans rapidly acquire smaller plans, most managed care executives do not consider the long-term impact of their plans’ diagnostic strategies and are often unwilling to reimburse for tests that promote wellness.
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acute with respect to tests that are not widely covered by other plans; in this situation, Company A’s payment for a test performed on a member today yields a savings for the member’s next insurer, Company B, tomorrow. 167

VII. COST EFFECTIVENESS ANALYSIS

Basically, cost effectiveness analysis (CEA) compares the costs and outcomes of one health care intervention with the costs and outcomes associated with another intervention (or with no intervention). 168 CEA has been increasingly popular since the time of its early application in health care, beginning in the 1970s. 169 The analysis can be applied to all types of health care interventions, including drugs, preventive services, screening exams, diagnostics, and procedures. 170

One of the early challenges to the use of CEA was the fact that different studies used different approaches to the analyses, making it difficult to make meaningful comparisons. 171 To address this concern, in 1993 the United States Public Health Service convened the Panel on Cost-Effectiveness in Health and Medicine, to make recommendations on the quality and comparability of CEA studies. 172

In 1996, the Panel published a summary of its efforts and recommendations in a series of articles in the Journal of the American Medical Association. 173 Basically, the Panel recommended the use of a “reference case” for every CEA study “intended to contribute to decisions about the broad allocation of health care resources.” 174


167. SACGHS Report, supra note 22, at 21; see also Ridge, supra note 41, at 346.


169. MedPac Report, supra note 60, at 183. According to one report, more than one hundred CEA studies are published yearly in medical and health care related journals. Id.

170. Id.

171. Russell et al., supra note 168, at 1173. “Studies vary widely in the health effects and costs included and in the way these are valued and combined, so that studies of the same intervention can produce very different cost-effectiveness ratios; potential users may be confused and suspicious that CEA can be manipulated to support almost any conclusion.” Id.

172. Id.


174. Russell et al., supra note 168, at 1173.
The Panel’s recommendations for the standardized elements that make up the reference case include choices relating to the perspective from which costs and effects should be measured and the appropriate measure of health effects resulting from the interventions being compared. On the first issue, the Panel recommended a societal perspective for all CEAs. Perspective is critical in CEA because in some circumstances, one person’s loss can be another’s gain.

One example of how this might happen would be an employee with a chronic condition that requires expensive treatment. The employee’s physician recommends a diagnostic test that might help assess possible complications relating to the chronic condition. The insurer refuses to authorize the test, and the test is not performed. As a result, the employee suffers a serious illness and loses his job. From the insurer’s perspective, this might be a positive economic outcome, as the insurer has shed its obligation to pay for the employee’s expensive care. This economic benefit to the insurer comes at a cost to the employee, society (if the employee becomes dependant on government assistance), and the employer. Because of these types of concerns, the Panel recommended use of the societal perspective in the reference case of all CEAs.

With this perspective, all costs and benefits associated with a health care intervention are measured, regardless of who sustains them.

Regarding the standard measure for health outcomes, the Panel recommended the “quality adjusted life year,” or QALY. The QALY is a measure that assigns a value (ranging from 0 to 1) corresponding to the quality of life associated with a particular state of health, and then multiplies that value by the number of years the health condition is expected to endure (or life expectancy, for chronic conditions). Expressed as a formula, a QALY is “the arithmetic product of life expectancy and a measure of the quality of the remaining life years.” The quality element of the equation comes from research establishing measurements for health-related quality of life associated with particular medical conditions, ranging on a continuum from least to most desirable; using this approach, optimum health would be ranked as a 1 and death would be ranked as a 0.
At the risk of dangerous oversimplification, if a person with a life expectancy of ten years spends $10,000 for an intervention that improves his or her quality of life from 0.5 to 1.0, assuming no other costs or benefits associated with the intervention, the cost per QALY for the intervention would be $2,000 (a $10,000 cost divided by the product of a 0.5 improvement in quality and a ten year life expectancy, or $[10,000/(0.5 x 10)]).

Interestingly enough, there is a suggested retail price, or price range, for QALYs: $50,000 to $100,000. An article that reviewed three studies published between February and June of 2000 noted that all three studies referenced a commonly used threshold for assessing the cost-effectiveness of medical interventions: "those interventions that produce a QALY for $50,000 or less are a bargain, whereas those that require $100,000 or more are considered unaffordable." Applying those cut-points, retinal screening exams for low risk diabetics and extended hospital stays for patients with uncomplicated myocardial infarctions were borderline investments ($100,000 and $105,000 per QALY, respectively), while Viagra was a bargain at $11,000 per QALY.

The $50,000–$100,000 cost per QALY range has been subject to criticism by physicians and others, including criticism based on the fact that it has not kept pace with inflation in the twenty-plus years since it was established. Despite that fact, it is in common use in CEA studies.

VIII. IF YOU BUILD IT, WILL THEY PAY?

Presumably, one of the primary goals of companies involved in development of pharmacogenomic tests is to see the tests incorporated into clinical practice. Whether that goal is motivated by economic or philanthropic interests, reimbursement for the tests will drive clinical use of the test. Consequently, it is never too early to start thinking about whether and under what circumstances payors might pay for a test, and to consider how to maximize the prospects for both coverage and a reasonable level of reimbursement.

For pharmacogenomic test manufacturers who wish to see their products in use in the Medicare population, the threshold hurdle is the fact that Medicare does not pay for screening services, except for certain screening services specified by statute. Congress appears to be increasingly receptive to argu-
ments about the benefits of screening examinations. In addition, CMS and the FDA recognize that pharmacogenomic tests offer "significant, tremendous opportunity both in terms of economic savings and therapeutic outcomes." Pharmacogenomic tests that both decrease morbidity and reduce net health care costs would seem to be the best candidates for a lobbying effort regarding an expansion of the benefit categories to include at least some types of pharmacogenomic screening tests. Also, where there is clinical evidence to suggest that a particular drug might be unsafe or ineffective in a particular patient, a pharmacogenomic test to confirm or rule out that concern probably would not be deemed a screening exam.

If the limitation on coverage for screening services can be addressed, the factors driving coverage and reimbursement will be clinical effectiveness and cost-effectiveness. Although Medicare does not currently use cost-effectiveness as a factor in making coverage determinations, there is continuing pressure in that direction. Also, even under the current Medicare system, cost-effectiveness may affect whether there are limitations on coverage, and it may influence the level of reimbursement.

Questions of clinical effectiveness involve technical issues that are beyond the scope of this paper. There are, however, some factors relating to clinical effectiveness that are discussed in literature and address reimbursement issues. These factors include: prevalence of the polymorphism the test is designed to identify; test characteristics, including analytical validity, sensitivity, specificity, ease of use, and turnaround times for results; and clinical utility (that is, whether identification of the polymorphism influences treatment decisions).

189. See id. "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 screening." Id.


191. See Neumann et al., supra note 94, at 1516. "Medicare's policy of paying for any medical advance that has positive benefits, regardless of its costs, is unsustainable." Id.; see also Louise B. Russell, Prevention and Medicare Costs, 339 NEW ENG. J. MED. 1158, 1158-59 (1998). The author calls for CEA in Medicare coverage determinations and compares a drug that costs $520,000 per year of life saved, with smoking cessation programs, that cost $5,000 per life saved (meaning a one million dollar investment could yield two years of life or two hundred years). Russell, supra at 1158.


193. Analytical validity means "the test measures the property... it is intended to measure," producing "the same results repeatedly and in different laboratories." SACGHS Report, supra note 22, at 15.

194. "Genetic tests for detection of variant genes are typically quite accurate, with sensitivities and specificities near 99% when direct sequencing or restriction site assays are used." Veenstra et al., supra note 6, at 3.

195. A test for a drug typically given, for example, in a trauma setting, would not be of much value if the results of the test took days to deliver; Phillips et al., supra note 192, at 134

196. See Phillips et al., supra note 192, at 132-34
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Regarding cost-effectiveness, there is a growing body of literature addressing CEA for genetic tests in general and CEA for pharmacogenomics in particular. These articles include reasonably formal CEA studies for specific genetic tests, discussions of factors that are likely to drive favorable CEA conclusions, and surveys and summaries of the available literature. 197

Several of the articles suggest factors that are likely to drive CEAs for pharmacogenetic tests. 198 The suggested factors include: 199 the prevalence of the genetic variance in question; 200 the strength of the association between the genetic variance and an adverse reaction to a particular drug; 201 the “clinical outcome characteristics;” 202 the cost of the therapy that a test might show to be

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197. Obviously there is a fair amount of overlap, but some of the articles can be categorized as follows:


(2) Discussions of factors likely to drive favorable CEA conclusions: Higashi & Veenstra, supra note 165; Phillips et al., supra note 8; Jay B. Lichter & Janice H. Kurth, The Impact of Pharmacogenetics on the Future of Healthcare, 8 CURRENT OPINION IN BIOTECHNOLOGY 692 (1997); Ross, supra note 166; see also Veenstra et al., supra note 6.

(3) CEA of specific genetic tests: Dunson & Touwe, supra note 166, at 5, 12; Elkin, supra note 5, at 854; Wen Hwei Chou et al., Extension of a Pilot Study: Impact from Cytochrome P450 2D6 Polymorphism on Outcome and Costs Associated with Severe Mental Illness, 20 J. CLINICAL PSYCHOPHARMACOLOGY 246 (2000).

198. Higashi & Veenstra, supra note 165, at 496; Veenstra et al., supra note 6, at 1; Carlo A. Marra et al., Practical Pharmacogenetics: The Cost Effectiveness of Screening for Thiopurine s-Methyltransferase Polymorphisms in Patients with Rheumatological Conditions Treated with Azathioprine, 29 J. RHEUMATOLOGY 2507, 2508 (2002).

199. Because clinical effectiveness is a component of cost-effectiveness, a CEA must include any factors relevant to the question of whether the test in question is clinically effective, in addition to these factors.

200. This factor looks at the percentage of the relevant population that will have the subject variant. Higashi & Veenstra, supra note 165, at 496. A prevalence of .01% means that only one person in ten thousand who are tested will have the variant. See id. at 497. The more prevalent an SNP is in the relevant population, the more cost-effective the test for that SNP will be, all other things being equal. See id. at 496.

201. Also called the “genotype-phenotype association,” this measure looks at the likelihood that a person with a specific SNP will have a “clinically relevant outcome.” See id. at 495. If there is only a weak association between the genotype and the phenotype, genetic testing for the genotype will be less cost-effective. See id. at 495-96.

202. This measure looks at the consequences of giving the drug in question to a person who has the genetic variant that makes the drug unsafe or ineffective for them. Id. at 497. For example, giving warfarin to a patient who has the CYP2C9 gene variant can result in major bleeding problems. Id. at 498.
ineffective and therefore unnecessary; the availability and cost of alternative measures of safety and effectiveness; and the cost of the test.

Combining these factors, from a CEA perspective, the “perfect” pharmacogenomic test would be inexpensive; it would identify a common SNP; there would be a strong correlation between the SNP in question and a significant, adverse, expensive clinical outcome; and there would not be any easier, cheaper way to predict or monitor the adverse reaction. In this best case scenario, the total cost of testing the population in general would be less than the cost of dealing with the adverse consequences of a failure to give the test. In this situation, where testing is both cheaper and more clinically effective than not testing, the testing alternative is said to be “dominant” for CEA purposes. Where a test is a dominant alternative, a payor’s failure to provide coverage is irrational from an economic perspective.

Another scenario in which a pharmacogenomic test might easily be deemed cost-effective would be if the test could predict that an expensive therapy would not be effective on patients with a particular genotype or patients with a subtype of disease characterized by a particular molecular pattern. One example of this type of test is the test for tumors that overexpress HER-2/neu. Heceptin is a drug that targets these tumors, and patients are given the test before they are considered as candidates for Heceptin. Also, there are reports that one payor is working with a genetics company to develop a test that will predict whether patients with rheumatoid arthritis are likely to respond to an expensive drug therapy for that condition.

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203. Lichter & Kurth, supra note 197, at 694.
204. See also Veenstra et al., supra note 6, at 4. For example, a pharmacogenomic drug to test whether a particular drug is likely to be effective in controlling a patient’s hypertension might be less cost-effective given the cheap and available alternative of measuring the patient’s blood pressure after administering the drug. In a similar situation, BCBS decided not to cover a $500.00 genetic test that screens for colon cancer because it concluded that the test was little better than a $5.00 test for blood in the stool. Pollack, supra note 5. At the other end of the spectrum, the benefits of psychiatric drugs are extremely difficult to assess, so a test that predicts effectiveness might save significant amounts of money by avoiding the use of ineffective drugs. Veenstra et al., supra note 6, at 9.
205. Veenstra et al., supra note 6, at 1. From a cost standpoint, “one of the benefits of genetic testing to predict drug response is that the information can be used throughout the lifetime of the patient. Thus, other potential uses of the genetic information obtained from a test may further offset the cost of the test. This is most likely to occur when the genetic variation affects more than one drug, as with the P450 metabolic enzymes, for example.” Id. at 3.
206. MedPac Report, supra note 60, at 183.
207. See CMS, Medicare Coverage Database, Drugs & Biologicals: Heceptin (Trastuzamab), http://www.cms.hhs.gov/medicviewarticle.asp?article_id=9166&article_version=5 &show=all (click on “Accept” at bottom of screen to access article), Apr. 11, 2000. In 1998, the FDA approved Heceptin for women whose breast cancer tumors overexpress Her-2/neu, and AdminStar Federal Medicare Part B considered providing coverage for that indication. Id. at 70, 74, available at http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=727966&pageID=1. In most cases, the coverage question is whether a patient who is going to get a particular drug should be tested beforehand; in the case of Heceptin and the rheumatoid arthritis drug, pharmacogenomic testing is or might be used defensively, that is, unless a patient gets the “right” result on the test, the payor will deny coverage for the drug. A few payers are conducting
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The more difficult situations involve tests in which the cost of offering the test to the relevant patient population exceeds the cost of caring for an adverse outcome that results from a failure to offer the test. For example, assume the availability of a pharmacogenomic test that will identify individuals who will have an immediate, fatal reaction to a particular drug. If the SNP that is associated with the reaction is rare and the cost of the test is high, the purely economic costs of giving the drug might well exceed the purely economic cost of dealing with the consequences, to the payor, of the complication (in this case, a brief hospitalization followed by death). In this situation, the test is not dominant and the focus of the analysis shifts to the question of how much the payor should be willing to pay for the increased QALYs associated with saving the life of the rare individual with the fatal variant.

At the risk of stating the obvious, coverage and reimbursement issues need to be factored into product design and development from the outset. In addition to clinical effectiveness, CEA, and related issues, there are some other strategic or tactical considerations that might improve a product’s prospect for coverage and reimbursement at a reasonable rate.

For products that might be considered for Medicare coverage, a careful review of recent guidance from CMS and an understanding of the tools CMS uses to make coverage decisions should increase the likelihood of a favorable decision. From a tactical standpoint, the manufacturers of these products need to analyze and decide on the pros and cons of seeking a coverage determination at the national level or, in the alternative, approaching the issue locally.

For private payor coverage, at least one payor has articulated a process that its vendors should follow if they hope to get their products approved for coverage. This payor requires submission of a “dossier” that includes specified information regarding the product’s clinical effectiveness and economic features. Although the specific requirements apply only to a single payor, they probably provide a good roadmap of what types of information other
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... payors might deem persuasive. In addition to using this type of guidance to organize data to be presented to payors, proactive CEA can help manufacturers determine the price a payor might set for a particular test, thereby helping to determine whether the likely revenue from the test will cover its development costs.

Direct to consumer advertising is a strategy that might drive coverage and reimbursement decisions. Information gathered to date suggests that patients would be very interested in a test that could tell them whether a particular drug might be unsafe or ineffective for them. Patient demand influences coverage decisions, both for government payors and private payors, so anything that increases patient demand will improve a product’s prospects for coverage. Similarly, patient education about the differences between pharmacogenomic testing and other types of genetic testing could help dispel patient concerns about privacy and discrimination, thereby helping to build demand.

Another strategic consideration is whether to collaborate with pharmaceutical companies in the development of tests that will predict the safety and efficacy of drugs based on patients' genotypes. There is some reason to believe that pharmaceutical companies might resist pharmacogenomic testing. At least in some situations, however, drug companies may want or need pharmacogenomic tests for their products.

213. “Providers of molecular-based testing must develop programs to educate third-party payers so that the tests that have proven impact on patient outcomes are accepted for reimbursement.” Ross, supra note 166, at 1071.

214. One approach would be the types of advertisements that invite consumers to “ask your doctor about . . . .” A more direct approach, which is already in use, is to market genetic tests directly to consumers. Phillips et al., supra note 4, at 427.

215. According to one survey, “two thirds of respondents would pay extra for a ‘genetically customized drug that you knew would work for you.’” Phillips et al., supra note 8, at 278.

216. SACGHS Report, supra note 22, at 23–24. For example, some payors acceded to public pressure for coverage for high dose chemotherapy combined with autologous bone marrow transplants, despite the fact that “evidence to support coverage was weak or nonexistent.” Id. at 23–24.

217. See Phillips et al., supra note 192, at 135–37. According to one survey, “nearly seven in ten Americans are somewhat or very concerned that genetic information may be used against them by either their employer or insurer.” Id. at 135. “[P]rivacy concerns and fears of insurance discrimination that discourage patient demand for genetic testing for risk prediction, are less likely to be as important of factors in determining demand for pharmacogenomics, because the use of genetic information is immediate and specific.” Phillips et al., supra note 8, at 278.

218. In Person: Pursuing a Common Goal, IVD TECH., Jan. 2006; http://www.devicelink.com/wdt/archive/06/01/005.html. “Pharmacogenomics presents challenges for the pharmaceutical and diagnostics industries, but also presents opportunities for the two to work together.” Id.

219. By identifying patients who will not benefit from, or will be harmed by, a particular drug, pharmacogenomics has the potential to shrink markets for some drugs, a fact that is not pleasing to some pharmaceutical companies. See Abbott, supra note 14, at 762. “Our general philosophy is not to initiate a drug-development programme that would limit the group of patients a drug could treat.” Id. (quoting Brian Spear of Abbott Laboratories).

220. Payors may reimburse “targeted” drugs at higher rates, making a test/drug combination more profitable. Danzon & Trowse, supra note 165, at 10.

221. Some payors may not cover a drug unless the patient has had molecular testing indicating that the drug will be effective. Bernard, supra note 208, at 74.
Clearly, in vitro diagnostic test manufacturers must be able to demonstrate that their products are clinically effective. Just as clearly, however, clinical effectiveness is not likely to ensure a favorable decision. Early on and continuously, manufacturers need to focus on efforts to demonstrate that their products are cost-effective as well as clinically effective.