

Coverage and Reimbursement for Molecular Diagnostics: Current Issues and Options

by Bruce Quinn MD PhD



Biography

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Before serving in the Medicare Part B program, Bruce was a physician executive in the Health & Life Sciences division of Accenture and was a clinician-scientist at Northwestern University School of Medicine, leading pathology research for Northwestern's NIH-funded Alzheimer Research Center. He also held academic positions at New York University School of Medicine and UCLA Center for Health Sciences.

The Committee on Medicare Payment Methodology for Clinical Laboratory Services studied many aspects of the current payment system...From the perspective of the committee, the current system contains irrationalities, which could exacerbate current problems and jeopardize beneficiary access in the future.

Institute of Medicine (2000)

Medicare Medical Laboratory Policy

The American health care system is in need of major restructuring. This will not be an easy task, but the potential benefits are great. To cross the divide between today's system and the possibilities of tomorrow, strong leadership and clear direction will be necessary.

Institute of Medicine (2001)

Crossing the Chasm

The fields of political science, public administration, law, and policy analysis have a common mission of rescuing public policy from the irrationalities and indignities of politics, hoping to make policy instead with rational, analytical, and scientific methods.... People do not always perceive a goal first....Often, they see a problem first, which triggers a search for solutions and a statement of goals.

Deborah Stone (2002)

Policy Paradox

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Executive Summary

Personalized medicine – getting the right treatment to the right patient at the right time – will be a major pillar of efforts to bring increased effectiveness and efficiency to healthcare. Today, we know far more about the molecular heterogeneity of major diseases, including cancer. It is clear that targeted and more effective medical treatments will often be unattainable unless physicians have precise molecular information about the patient’s disease. In short, it is a priority that our healthcare system (both private payors and Medicare) facilitates the adoption of new molecular technologies when they are shown to be efficient and effective.

In 2000, the Institute of Medicine published a comprehensive monograph entitled “Medicare Laboratory Payment Policy, Now and in the Future.” This report described a number of substantial difficulties created by the legacy U.S. system for coding and payment of laboratory tests in an era of substantial advances for test technology. Few of these difficulties have been resolved. However, the pace of technologic change has risen and today complex gene panel tests for cancer and other sophisticated diagnostics are rapidly becoming reality. Remarkably, an increasing number of stakeholders now raise concerns that legacy administrative conventions may be on par with scientific challenges in bringing molecular diagnostics to patient

care. Normally, the development of new medical technology proceeds through stages that are deliberately designed to yield progressive reduction of uncertainty, allowing rational investment in the next stage of research for the product. Innovation is discouraged if innovators perceive that a high and irreducible level of uncertainty is caused by payor issues (unrelated to the actual clinical value of the product) that will occur at the final stage of product development (market entry). It follows that more transparency and rationality in payor processes will encourage cost-effective innovation in molecular diagnostics.

In June 2008, the Department of Health and Human Services commissioned this white paper to overview the current status of payor systems for coverage and reimbursement of complex molecular tests, and brought together an expert panel to discuss present difficulties and possibilities for change. The workshop focused on benefit classification, billing processes, coding systems, payment systems, and coverage decision processes. The goal of the workshop was not to choose single solutions, but to articulate the most pressing issues and discuss options for system change. Participants felt that the legacy coding system was the most pressing problem in the overall reimbursement system, but other parts of the payor process offer opportunities for improvement as well.

1. Introduction

1.1 Administrative barriers should not surpass technological barriers

The Institute of Medicine monograph “Crossing the Chasm: A New Health System for the 21st Century” has been frequently cited across the broad efforts to bring transformational change to the American healthcare system. Published in 2001, the report describes a “chasm” between the circumstances of today and the possibilities of the future.

At the Department of Health and Human Services, Secretary Leavitt has emphasized the Department’s interest in shifting our healthcare system toward effective, personalized healthcare.¹ *Personalized medicine* – getting the right treatment to the right patient at the right time – will be a major pillar of efforts to bring increased effectiveness and efficiency to patient care. In 2001, when “Crossing the Chasm” was published, the emergence of molecular personalized medicine lay mostly in the future. Today, we know far more about the molecular heterogeneity of major diseases, including cancer. And today, it is clear that targeted and more effective medical treatments will often be unattainable unless physicians have precise molecular information about the patient’s disease. In short, it is a priority that our healthcare system (both private payors and Medicare) facilitates the adoption of new molecular technologies when they are shown to be efficient and effective.

To create this “new generation” of clinically important and cost-effective molecular diagnostics, each test will be developed in the face of considerable technological challenges and development risks. Personalized medicine diagnostics are developed through clinical trials not unlike those for drugs, using the concepts and paradigms of evidence-based medicine (Feero et al., 2008; Joshi & Kucherlapati, 2008).

Of course, all drugs and devices emerge through such a process. But the lynchpin of this study of personalized medicine diagnostics is the discovery that, to a degree rarely found so near the surface, a considerable number of

purely administrative and process-based challenges exist as well. These can be framed as challenges that laboratory innovators, physicians, and private and government payors face together to craft good rules for billing and payment, and processes for sound but timely coverage decisions. Unlike scientific or technological barriers, purely administrative or process-based barriers can be discussed objectively – including payor goals and the pro’s and con’s of alternatives – with confidence that improvement is possible. Legacy administrative conventions, at least when better solutions are possible, ought never present a greater barrier to progress than do natural scientific challenges.

1.2 This survey canvasses five basic operations of payors

This background document will briefly survey current processes and models for change in five areas:

- Benefits eligibility
- Billing processes
- Coding systems (CPT-4, ICD-9/10)
- Pricing processes
- Guidelines for coverage decision-making

This approach expands on that taken by Billings (2006). As much as possible, we will *frame issues similarly* for both private payors and Medicare. However, although we preserved that as a major goal, our study found that there are currently some fundamental ways in which private insurer processes and Medicare processes differ. One straightforward example is *pricing*, where federal statutes and regulation tightly channel and enumerate Medicare’s administrative practice for what is otherwise a flexible and strategic business capability. That is, private payors have flexibility to negotiate and contract as they find best and to establish a market price based on value and competition. After surveying the five issue areas, we present alternate models which are briefly described and then framed in terms of major pro’s and con’s.

Scope of “Complex Molecular Tests”

What is the scope of tests we are concerned with? We focus on problems facing “personalized medicine” tests for disease-specific uses, such as gene panel tests for cancer prognosis. But we emphasize that we do not limit “molecular tests” to DNA/RNA tests. The tests studied here are complex tests that may be based on either tissue samples or blood samples, and the tests may measure nucleic acids, proteins, or other metabolites. As we will see, these tests often defy the historical segregation of “chemistry” tests and “pathology” tests, whether in the laboratory itself or in the domain of policy.

We also note that the term “diagnostic” laboratory tests is interpreted broadly. The immediate use of the test may be diagnostic (does the patient have disease X, e.g. recurrent ovarian cancer?), prognostic (e.g. what will be this patient’s disease course?), or predictive (e.g. will this patient respond to Drug X?). Just to list these factors hints at problems the tests may face with the current reimbursement system. Are the tests prognostic, or diagnostic? Do they have a CPT code – likely not, they are too new. Are they billed by inpatient or outpatient rules? Are they found on a fee schedule? Are they covered? The provider of the test will likely ask a high price, due to high development costs, while the payor may question the price and also have difficulty with coverage decisions. These questions outline the range of our report.

1.3 Concerns with the present system have been raised in diverse forums

Concerns with the present reimbursement processes (and/or options for alternative systems) have been presented in diverse forums since 2000:

Source		Representative Examples
Government-sponsored research		<p>Institute of Medicine (2000) Medicare Laboratory Payment Policy, Now and in the Future. 241pp.</p> <p>Medicare Payment Advisory Commission. (2002) Annual Report to Congress.</p> <p>Secretary’s Advisory Commission on Genetics, Health, and Society (2006) Coverage and Reimbursement of Genetic Tests and Services.</p> <p>Department of Health & Human Services (2007). Personalized Healthcare: Opportunities, Pathways, Resources.</p> <p>Agency for Healthcare Research & Quality (AHRQ; 2008) Infrastructure to monitor utilization and outcomes of gene-based applications: An assessment.</p> <p>Centers for Disease Control (2008) Laboratory Medicine: National Status Report [Lewin Group].</p> <p>Institute of Medicine (2008) Diffusion and Use of Genomic Innovations in Health and Medicine.</p> <p>President’s Council of Advisors on Science and Technology (2008) Priorities for Personalized Medicine.</p>
Industry associations		<p>Advamed (2005) The Value of Diagnostics Innovation.</p> <p>American Clinical Laboratory Association (position statements)</p>
Congress	Past Legislation	<p>Social Security Act/Medicare: 1833(h)(2)(B)</p> <p>BBA (Section 531)</p> <p>MMA (Section 942)</p>
	Proposed Legislation	<p>H.R.5369 (Medicare Clinical Laboratory Fee Schedule Improvement Act of 2006)</p> <p>H.R.1321/S.2404 (Medicare Advanced Laboratory Diagnostics Act)</p> <p>S.736 (Laboratory Test Improvement Act)</p> <p>S.976 (Genomics and Personalized Medicine Act)</p>

The most comprehensive study of the American laboratory payment system is “Medicare Laboratory Payment Policy” (IOM, 2000, 240 pp.) We cite this report as “IOM 2000.” The “IOM 2000” report focuses on Medicare billing, coding, coverage, and pricing processes across all laboratory tests. However, as a reference source its value is broader because IOM 2000 frequently compared Medicare’s processes to the status quo for the private insurers. Some processes were found to be very similar, such as coding, where national regulations enhance uniformity of this process (42 CFR 160/162 specifies the CPT-4 and the ICD-9 code sets for all U.S. payor/provider interactions.) The IOM’s report, now eight years old, contains far more detail than the update we present here, and IOM 2000 explored topics outside the scope of the present document. However, in Section Two we will overview the recommendations found in the IOM 2000 report and salient changes between 2000 and 2008.

1.4 Our presentation follows two organizing premises:

- (i) Legacy processes met certain needs.**
- (ii) Options can be presented with pro’s and con’s.**

The first premise we used in approaching the topics is that current (legacy) processes are usually rational, insofar as they reflect a good response to some historical demand. For example, a largely fixed system of procedure codes (e.g. CPT-4 codes) are an excellent means to deal with provider/payor coding of medical services that change rarely. After seeing what good purpose legacy rules serve, we can distinguish clearly why some aspects of these processes appear irrational or dysfunctional with reference to the expected expansion in very complex molecular tests. We survey alternative processes which better address the new issues.

The second organizing premise is that pro’s and con’s can be laid out – notwithstanding that different parties may hold sharply contrasting views regarding the proper weight accorded to different pro’s and con’s, or indeed the net feasibility of different solutions to improve the system. For example, *fixed fee schedules* (like the Medicare clinical laboratory fee schedule, set in 1984) have the *advantage* of yielding highly predictable annual expenditures for the

payor. In addition, fixed fee schedules have the *advantage* of strongly encouraging innovations which drop the cost of production below the fixed and stable price (either through technologic innovation or through economies of scale gained by industry consolidation). At the same time, the fixed fee schedule *discourages or prevents* other important types of innovation which have high healthcare value and may even be cost-saving for the healthcare system:

Consider a hypothetical molecular test which replaces \$800 of imaging, or a \$1500 biopsy, or redirects \$20,000 of chemotherapy. The lab test required substantial clinical research, which can be amortized over 5 years, 10,000 tests per year. The marginal test cost including amortized research is \$200, but the legacy fee schedule for the relevant CPT code is locked at \$15.

No one will ever develop or supply the test, although both net healthcare dollar savings and improved patient care would result.

Following our second premise, whether a frozen and fixed fee schedule is “good” or “bad” depends on balancing its pro’s and con’s. Whether at the end we favor the status quo or favor change, the pro’s and con’s are still there and can be articulated. At its best, the “brainstorming” effort which enunciates these pro’s and con’s also can point toward new strategic options, such as a fixed fee schedule for some tests and some kind of negotiated or de novo price for others.

We note that literature citations in the present report are selective and not comprehensive.

2. IOM 2000 As A Departure Point

2.1 IOM (2000) is the most detailed survey of the present U.S. system

The Balanced Budget Act of 1997 commissioned a report by the Institute of Medicine on the U.S. laboratory reimbursement system, and asked CMS to report on those findings to Congress, along with any recommended legislative changes.ⁱⁱ As a result, in 2000, the IOM published a comprehensive 240-page report entitled “Medicare Laboratory Payment Policy: Now and in the Future.”

Key features of the IOM 2000 recommendations are shown in the table below. One sees that most of the recommendations made by the IOM committee (particularly recommendations with the most radical implications, such as a *de novo* basis for the Medicare laboratory fee schedule) were not implemented. This could be due to any of several factors:

- The IOM committee might have been overly concerned that the system had many problems, but such concern has not been shared by most regulators, the majority of the industry, or by Congress;
- A balance of forces has existed between:
 - pro’s and con’s of the existing systems and the pro’s and con’s of novel systems;
 - different parties benefiting from the existing system and/or being disadvantaged by it;
- There is a general tendency of a regulatory system to stasis in the absence of crisis;
- High barriers to disruptive change, not fully foreseen by the committee; or
- Any combination of the above.

	Recommendation for Medicare (2000)	Interval Events (2000-2008)
1	Single national fee schedule, eliminating variant local Medicare lab schedules.	No change.
2	Set all payments at “NLA” (National Limitation Amount)	No change.
3	Alternate basis for the fee schedule (e.g. competitive bidding)	No change, but a demonstration local competitive bidding system is in development. New codes, selectively, can be priced by methods not based on the legacy schedule (gap-fill).
4	Geographic adjustments (weights) to a single national fee schedule (variant on recommendation 1)	No change. Would occur only after Recommendation 1.
5	Open, timely process, with appeal.	Substantially changed, as required by Medicare Modernization Act (2003, S. 942). CMS established procedures by regulation for determining the basis for and the amount of payments for clinical laboratory tests with new or substantially revised codes “assigned after January 1, 2005. CMS implemented a novel public meetings each summer and an appeal step. The legacy process of “cross-walk” and “gap-fill” were unchanged, but are now defined by regulation (42 CFR 414.514).
6	Process to periodically update the Clinical Laboratory Fee Schedule.	No change. The update remains depending on irregular legislative actions (e.g. update 2% in year X).
7	Review alternatives to the coding system.	No change at CMS. However, since IOM 2000, the AMA CPT has implemented a temporary code system called Category III codes.
8	Do not begin to impose a co-pay for laboratory tests.	No change requested; the status quo was recommended. However, in the interim, the introduction of much more complex and costly tests (>\$1000) changes the assumptions of the IOM committee (most legacy tests range from \$5-\$30).

	Recommendation for Medicare (2000)	Interval Events (2000-2008)
9	CMS should discontinue use of ICD-9 codes to determine medical necessity.	No change. The recommended change would require regulatory change at 45 CFR 160, 162. IOM 2000 perceived fundamental flaws in using the ICD-9 system as a basis for medical necessity decisions.
10	CMS should formulate laboratory policy after stakeholder input, increased communication with its own contractors.	No specific change. However, both annual rulemaking and ad hoc rulemaking allow considerable public comment to be reviewed.
11	CMS should consolidate the number of contractors processing laboratory claims.	Change via MMA, 2003. The IOM request in 2000 seems to be concordant with the 1997 BBA (S. 4554(a) would have reduced laboratory test contractors to four regional contractors.) This change did not occur. The 2003 MMA reduces national Part A/B contractors to 15 or less by 2010, however.
12	Collect data to manage the performance of the clinical laboratory payment system. Trends in the existing program, or trends following change (such as competitive bidding) to be monitored for impact on access, responsiveness (e.g. of the coding system), value (quality/cost.)	The MMA created a Council on Technology and Innovation at CMS to evaluate and reduce any problems caused by coding and reimbursement systems, which meets this end, but is not specific to clinical laboratory tests. Data collection & payor databases reviewed by AHRQ (2008), "Infrastructure to Monitor...Gene Based Applications."

See also Weiss (2007), Aspinall & Hamermesh (2007). The full IOM 2000 report is readable online, and may be purchased as a PDF at: http://www.nap.edu/catalog.php?record_id=9997

3. Five Basic Operations of Payors

- Benefits categories
- Billing processes which avoid discontinuity of services
- Coding systems (CPT-4, ICD-9/10) to describe tests and diagnostic conditions
- Pricing processes
- Guidelines for coverage decision-making

The summaries below are relatively short and highlight certain aspects of particular interest. This should provide the general reader with a background and vocabulary to understand features of several major payor business processes which are relevant this report.

3.1 Benefits Categories

Benefits: Meaning. An individual is enrolled in a health plan (either a private plan or Medicare). A healthcare service, such as a laboratory test, must fall within a “*benefit category*” of the plan. Health plans have “exclusions,” meaning services that are never eligible for coverage. Medicare may exclude screening tests; a private plan might exclude chiropractic benefits; payors may exclude “experimental” services.

Workshop participants noted that there is direct relationship between the benefit category and billing rules. Copays vary based on whether a service falls into categories for “screening,” “preventative,” or “diagnostic” tests. Under Medicare, we will see that billing jurisdiction currently shifts drastically depending on whether a test is classified as a “clinical laboratory” (chemistry) or “pathology” test although there is sometimes no simple hallmark for the difference.

Note that where “experimental” services are excluded by a contractual statement, identifying *whether* a specific service the patient encounters in the future is “experimental” is a process, a medical policy or medical review function. Therefore, the “coverage” aspect of this categorical decision is found in section 3.5, guidelines for coverage decision-making.

Benefits: Medicare perspective. Medicare covers a broad range of healthcare, but each service must fit into a specific “statutory” category. These include physician services, hospital inpatient services, hospital outpatient services, ambulance services, diagnostic tests, and other categories. Diagnostic tests encompass all tests, from PET scans to a blood glucose test.

Diagnostic tests under Medicare must contribute to the diagnosis or the management of disease [the patient shows evidence of a disease] except for a short list of “screening tests.” Some Medicare screening tests span the entire Medicare population. Others are covered in an “at risk” subpopulation. A periodic stool-guaiac test to screen for colon cancer is covered for all beneficiaries, but periodic glucose tests are covered only in patients pre-defined “at risk” for the appearance of diabetes.

Paradoxes can occur. A screening test that is directed toward a new disease that is occult, that has no apparent symptoms, is *not* covered by Medicare (except for the short list of pre-approved screening tests.) But tests that screen for occult *secondary* conditions are covered: consider a hematocrit test in a cancer patient on chemotherapy, which is a test for anemia, although the patient lacks any *specific* symptom of anemia. Pre-test risk, in the Bayesian sense, is not determinative. If the patient has a known condition with a 5% association with a second problem, the second problem may be tested-for, but if his familial history gives him a 25% or 50% risk of an even more serious problem, that test is not covered. This demonstrates a Medicare principle that family history *per se* is never considered a personal “sign or symptom,” although in the presence of one actual sign or symptom, family history would govern the choice of tests.ⁱⁱⁱ Prognostic tests are also problematic; Medicare’s coverage documents include examples where Medicare has specifically stated it cannot cover prognostic tests.^{iv} The principles for covering tests for occult or secondary disorders are difficult to enumerate, opening up a gray zone where some personalized medicine tests may fall.

The Medicare Improvements for Patients and Providers Act of 2008 allows CMS to offer coverage for preventive tests approved by the U.S. Preventive Services Task Force.

Benefits: Private payor perspective. Two broad categories of private payor are usually differentiated. The first category of private payor is subject to state benefit mandates for screening tests, the second is not.

- “Health insurers” Private payor plans may offer health insurance in exchange for premiums; the payor bears risk and is usually regulated as a state insurance entity. The state may legislate various coverage requirements include screening tests (CAHI, 2008). Outside of these requirements, benefit breadth typically starts (and may finish) with a carte of options offered by the private plan.
- “ASO organizations” Alternately, private payors may manage benefits (i.e. claims processing; “administrative services only” or ASO) for a large employer. ASO plans generally fall under ERISA and are exempt from state-based insurance mandates. In ASO plans, benefit breadth is established by contracting between the employer and the ASO plan. A large proportion of US employer-based insurance falls under ASO plans.

As mentioned earlier, private insurers vary co-pays based on benefit categories such as screening, preventive, and diagnostic services. For diagnostic test benefits, insurers under state regulation face variable, state-to-state requirements. All states require private insured plans to cover mammography while only 2/3 require coverage of PSA and colorectal cancer screening. No state mandates were identified which relate directly related to any complex diagnostics for personalized medicine (e.g., internet search for BRCA + “state mandate”; 5/2008). Privacy regarding use of mutation information is now regulated by Genetic Information Nondiscrimination Act (GINA, 2008), but this law does not deal with coverage (payment) for genetic testing.

Key similarities and differences (Medicare, private payor). Assuming molecular laboratory tests are not excluded as “experimental,” new molecular tests that manage “disease” are medical benefits which can be covered by U.S. payors. Tests which are purely “preventive” in the absence of signs and symptoms of disease are not

covered by Medicare unless they are specifically enumerated by law or regulation. In contrast, private insurers may be somewhat more flexible about “preventive” services but will usually enumerate preventive services in advance, such as an annual physical or mammography.

In practice, both government and private payors may be *unable* to actually distinguish between preventive and diagnostic tests during routine claims processing.

3.2 Billing Processes

Billing: Meaning. *Billing processes* means the pathway that leads from the medical care event to payment for that service. Although a part of the billing process, *coding systems* themselves are considered separately in the next section, Section 3.3. What remains of the billing process after the exclusion of coding systems are the processes of provider enrollment, determining who will bill the service, where a claim will be submitted, and who will be paid for the service. Medicare and many states have laws requiring laboratories to direct-bill the payor (e.g. a physician may not “purchase” the lab test for \$10 and “re-sell” it to a payor for \$20.)

Billing: Medicare perspective. Medicare regulations for billing laboratory tests are strikingly complex, and have ramified into new categories and exceptions over time, with unusual new layers of rules added in 2006 and 2007. The rules distinguish among (a) multiple locations of specimen collection, (c) test-performing entity (hospital lab, independent lab), (d) type of test performed (“pathology” versus “chemistry” tests), (e) whether the specimen entered an archive, (f) the date the test was ordered, and (g) time between specimen collection and test order. These billing rules for a specimen defy condensed description.

(i) Hospital inpatient. Both “pathology” and “clinical laboratory” (chemistry) tests are “bundled” with Medicare’s inpatient DRG inpatient payment. This means that molecular tests based on blood or tissue samples of inpatient origin must be paid by the hospital from its DRG reimbursement *while* the patient is an inpatient, *and* up to 14 days after discharge *or* 30 days after the biopsy, whichever comes first.

But, due to BIPA 542(c), if the test is a pathology test and performed by an *outside* lab for the inpatient, *and* fits under certain additional conditions, *and* it is billed before 12/31/2009, it *must* be billed by the non-hospital lab, *whether inside or outside* the 14 day rule.^v

(ii) Physician office patient. Tests are billed by the physician if his office performs the test. But if the specimen is sent to the independent lab, that lab must bill it.

(iii) Independent laboratory. Tests taken at an independent laboratory's local blood draw center: the laboratory bills Medicare directly.

(iv) Hospital outpatients. The most complex intersection of specimen, test, location, and date rules occurs for Medicare hospital outpatients. The patient was in a hospital-based outpatient clinic at the time of blood draw or biopsy, and registered as an outpatient.

(iv-a, Test performed on-site by hospital)

The hospital has bills Medicare as a line-item for each test it performs itself.

(iv-b, Test sent to outside reference lab)

The rules here continue to shift and in some cases are poorly defined. In 1999, Medicare stated that an outpatient's lab tests, if transferred for outside lab pathology tests, should be billed by the outside lab unless re-purchased by the hospital, which would then bill Medicare (64 FR 39623, 59408). In 2001, Medicare revised this position (65 FR 55285), asking the outside lab to bill the hospital, rather than Medicare. But thereafter, Congress required an outside pathology lab to bill Medicare directly for pathology tests on both hospital outpatient and inpatient specimens, a rule set to expire on 12/31/2009 (BIPA 542(c); footnote (iv).) If a clinical chemistry test is *ordered* during the hospital outpatient encounter, but the blood is *drawn* off the hospital grounds on the same day, the reference lab bills (65 FR 18440ff). If the test is drawn by the hospital for its outpatient and sent to a reference lab, the hospital bills. Various policy statements were formalized in regulations in 2005 and 2006 (42 CFR 414.510). Corresponding instructions to Medicare's contractors implement the clinical chemistry rule effective either 1/1/2007 or 1/1/2008 (interpretations vary), and 1/1/2009 for outpatient

pathology specimens except for those covered by BIPA 542 until 12/31/2009. Rules change if the specimen is stored 14 days before the day the physician orders the test. Additional issues are discussed in an endnote.^{vi}

(iv-c, Hospital "non-patient" & on-site hospital lab)

If the patient is *not* formally registered as an outpatient (CMS calls him/her a "non-patient") and the test is performed at the hospital lab, the hospital bills. For example, the specimen may be triaged to the hospital from an independent blood draw site.

(iv-d, Hospital non-patient, unrelated reference lab)

If the patient is *not* registered as a "hospital outpatient" *and* receives only a blood draw from the hospital, and the test referred elsewhere for processing, the service appears to be classifiable as a non-patient service but several complexities can occur.^{vii}

Billing: Private payor perspective. Generally, the performing entity (private payor, hospital, or independent laboratory) bills the insurer for the laboratory test. The plan may contract with a limited network of laboratories at preferred prices.

Key similarities and differences (Medicare, private payor). The most obvious difference is that Medicare's rules for billing jurisdiction spill over two pages, while private payors' rules fit within a sentence. This violates the spirit, if not the letter, of HIPAA legislation which required CMS to superintend a nationwide consolidation and standardization of efficient billing processes between providers and *all* payors (e.g. see 45 CFR 160, 162).

The rising discrepancies between Medicare and national private payor billing processes require laboratories to make complex distinctions not only among services for non-Medicare and Medicare patients but also between subtypes of Medicare lab samples, tracking location of collection date of collection, date of physician order, interval between these dates and hospital discharge, and other factors. A specialty molecular lab that directly bills private payors may need to establish a payment contract with each national private payor plan whose patients it is likely to serve. In the case of a specialty molecular lab that bills for Medicare patients, it may need to establish one contract with its local

carrier (for physician-origin or independent lab-origin specimens) and *also* establish contracts with each hospital in the U.S. (circa 5000 hospitals; AHA, 2008) to invoice each hospital, after which the hospital bills its fiscal intermediary. A deeper problem is that for Medicare, billing jurisdiction whipsaws among providers based on the uncertain definition of a “covered hospital” and covered service under BIPA 542, and the ambiguous nature of a “pathology” versus “clinical laboratory” test, which has become blurred by the advent of modern complex diagnostics that intimately merge the two laboratory disciplines within one final test product.

3.3 Coding systems (CPT-4, ICD-9/10)

Coding systems: Meaning. The HIPAA act required the Secretary of Health and Human Services to establish standard code sets for transmitting healthcare services data between providers and payors (HIPAA, 1996, section 1173). Regulations were finalized in 2000^{viii} and establish the AMA’s CPT-4 as the U.S. code set for physician services and laboratory tests, and the ICD-9-CM code set for diseases. In choosing the code sets, HHS followed ten guiding principles including:

- ease of use,
- flexibility,
- minimize burdens on users, and
- encouragement of innovation.^{ix}

For procedures, the CPT-4 describes thousands of physician services and some 9000 laboratory tests using a five-digit code for each service (e.g. 12345). CPT-4 laboratory test codes fall in the 80000 series. Molecular tests are described in three different ways. The molecular test may be identified by a single unique code (e.g. HIV RNA quantitation). Molecular tests may also be described by a series or “stack” of generic chemical test steps (e.g. DNA extraction, DNA amplification). Finally, test may be described by “not otherwise classified” codes (84999, unspecified chemistry procedure.)

For diagnoses, codes in the ICD-9-CM describe conditions such as appendicitis or acute leukemia, and symptoms such as abdominal pain or cough. The basic format for ICD-9 codes is 5 digits, of which two are decimals (e.g. 555.12). Generally, providers submit a procedure code and

one or more related diagnosis codes on their insurance claims. Payors may edit to “procedure + diagnosis” in order to autopay or autodenial a claim. For example:

- hematocrit test + anemia diagnosis = pay; and
- appendectomy service + schizophrenia [+ no other diagnosis] = deny.

Issuance of a new AMA CPT code requires widespread use of the test, acceptance of the test as medically necessary by an multispecialty review panel, and a timeline of roughly 18 months between proposal of the test (e.g. by the manufacturer) and activation of a new code.^x ICD-9-CM is also updated annually, but updates are typically modest in scope. In 2005, the AMA added an Appendix “I” which lists 83 two-place modifiers for types of genetic tests (e.g. 2B, BCR/ABL genes associated with 9:22 translocation in chronic leukemia.)

Formally, all codes for items and services are HCPCS codes, of which the CPT-4 code set are “Level I” codes. In common usage, many average users call Level I codes “CPT” and Level II “HCPCS” codes. “Level II” codes begin with letters (A1234) and typically indicate disposable supplies, durable medical equipment, and injectable drugs. Medicare and private payors differ in the use of alphanumeric HCPCS Level II “G codes” for Medicare and “S codes” for private payors only (see below).

In the past five years (2004-2008) there have been approximately 90 new codes in the “80000” section of the CPT manual. However, nearly all of these “new codes” can be accounted for by divisions of existing codes (e.g. flow cytometry 88180) into a family of codes, or addition of new named tests within a category (e.g. microbiology). Only a few codes represent a substantially new technology (such as 88380, laser microdissection; or 88384-86, or array-based molecular probes with 11-50, 51-250, and 251-500 probes). Note that the technology codes represent a newly accepted process and not a specific test which insurers can evaluate based on the code alone.

Coding systems: Medicare. Medicare contractors are required to follow all rules in the AMA CPT manual plus additional rules released from time to time by Medicare. CPT requires that codes used must “precisely, not approximately, match the service rendered” and that when

a precise code is not found, a not-otherwise-classified code should be used. Sometimes Medicare uses Level II “G” codes which define a service covered by Medicare in lieu of any code other available in the CPT system.^{xi}

Coding systems: Private insurers. Due to HIPAA and federal regulations which apply to all provider:payor transactions for “healthcare services” CPT-4 and ICD-9-CM code sets are also used by private insurers. Private insurers may also use a set of HCPCS Level II codes beginning with “S”. Nominally proposed to CMS by Blue Cross Blue Shield plans for addition in the S-code list, the S-codes can be used by any private payor, but are not recognized by Medicare. Of 593 “S” codes current in 2007, about 40 represented laboratory tests (ICD9data.com, 2007) about 30 of those were molecular tests (S38nn: S3818, complete gene analysis, BRCA1; S3854, gene panel for managing breast cancer). Private insurers may establish a new “S” code either to pay specifically for a test or to flag the test for denial.

Key similarities and differences (Medicare, private payor). Most complex molecular tests have no specific code, although private payors have created about 30 “S” codes which do not exist in the standard CPT-4 system, including S3854, gene panel test for breast cancer management. This suggests that private payors see a need to call out more molecular tests in a specific way (either for payment or for denial purposes), but the regular CPT system fails this function, so the private insurer institutes S-codes on a one-off basis.

There are no clear guidelines as to the scope of existing CPT codes; only the text of the code is binding on the providers/payors under HIPAA regulations (implemented at 45 CFR 160, 162). No entity is designated as the final arbiter of CPT code ambiguities. For example, parties may differ on whether the code 83898 (amplification of nucleic acid), established in 1993, includes high-sensitivity quantitative PCR or not. Proper use of CPT codes that are only a few words long requires a certain depth of content knowledge about the underlying services. For example, in the 83XXX series the adjective “molecular” refers only to nucleic acid tests – although any protein or metabolite is also a “molecule” – because the original authors *intended* that “molecular” referred only to nucleic acids (DNA, RNA).

Otherwise, a reader could not guess whether or not:

88384 Array-based evaluation of multiple molecular probes; 11 through 50 probes

includes protein marker arrays as well as DNA arrays, since both proteins and DNA are “molecules.”

The addition of the CPT’s “Appendix I” molecular test modifiers provides some additional information (“2B” = BCR/ABL gene translocation) but is focused on gene tests of longstanding interest and it is unclear how often this Appendix will be updated to reflect novel personalized medicine molecular tests.

3.4 Pricing process

Pricing process: Meaning. Pricing sets the payment transferred between payor and laboratory. This is usually a flat per-item reimbursement. Recently, new reimbursement models contractually encompass risk-sharing arrangements between the provider and the payor (in the U.K.: NHS re bortezomib/Velcade; for a U.S. molecular test, United Healthcare, Genomic Health/Oncotype DX; see Pollack, 2007). Not all parts of the US healthcare system follow a granular administered pricing scheme, see e.g. the Kaiser and Veterans Administration healthcare systems.

Pricing process: Medicare. Medicare prices most laboratory tests based on a clinical laboratory fee schedule set in 1983 and occasionally revised upward or downward en masse by legislation (IOM, 2000; Raab & Logue, 2001; Young, 2002; Weiss, 2007).

A public and Medicare-specific pricing process is triggered when the AMA CPT panel issues a new laboratory CPT code. To set prices for new codes entering the Clinical Laboratory Fee Schedule, Medicare “crosswalks” the price from an existing, similar laboratory service, or else “gap-fills,” that is, interpolates a price (e.g. 30% above Code X, 20% below Code Y). Through legislation, Congress asked CMS to refine its policy to assure appropriate pricing of new tests (BBA 531, MMA 942). CMS now holds public meetings each summer to solicit public comment on the appropriate pricing of new laboratory CPT codes. In brief, if most commenters recommend the same crosswalk price, CMS will assign that crosswalk price. If commentators

differ, or CMS believes a crosswalk price is of inaccurate, a “gap-fill” process begins. For one year, regional carriers price the test and submit their chosen price to CMS. Carriers consider a number of disparate pricing tools (e.g. invoiced charges; prices paid by other insurers; resources required to perform the test; resources required by related services; or other data.) At the end of the gap-fill year, current regulations require CMS to then assign a price which is the median of prices submitted by its contractors (each contractor having equal weight, regardless of the number of claims reviewed; see 42 CFR 414.514.)

CMS may adjust prices by up to 15% per year based on an “inherent reasonableness” authority (Health Law Alert, 2006) and has been given authority in the laboratory pricing section of the Social Security Act at 1833(h)(2)(b)^{xii} to set prices of tests with unusual complexity.

So far, most novel molecular tests such as Oncotype DX have been billed with “unlisted codes” in the Medicare system. Medicare carriers must follow gap-fill rules for new CPT codes but are not required to for “unlisted” codes. Tests with “unlisted codes” may be treated very harshly in the *hospital outpatient* system: unlisted laboratory codes such as 84999 and 89240 were until recently assigned to APC 0342 at circa \$10 (e.g. 72 FR 66937) and code 89240 still is. Now 84999 in the hospital outpatient setting is priced through a series of steps different than the gap-fill process (see CMS, 2007).

Some of the molecular CPT codes are priced a great deal lower in several states, e.g. 83902-83912. In a handful of states (e.g. Massachusetts; Georgia) these molecular steps are paid at only 20% of the levels in most other states.

Most of the issues also apply to *proteomics tests*; there are very few historical codes for proteomics tests and payment rates are fixed (\$10-20). Depending on the Medicare carrier, a new proteomics test could be variably classified under 83950 (oncoprotein assay) versus 86316 (immuno assay for tumor) versus 84166 (quantitative protein assay) versus 84999 (unlisted chemistry test) or 89240 (unlisted pathology test) with 10X price variation across these “coding” alternatives.

Pricing process: Private payors. Most private payors pay for laboratory tests in some proportion to the Medicare Clinical Laboratory Fee Schedule, although they are not required to do so (IOM, 2000). As of the IOM 2000 study, most private payors paid rates roughly similar to the Clinical Laboratory Fee Schedule (IOM, 2000, Tables C1-C11), particularly at the private payor median. No similarly comprehensive but more recent survey of private payor pricing was identified. The IOM surveyed a sampling of CPT codes but none in the “molecular diagnostics” series. As noted earlier (Section 3.3) private insurers may use “S” codes for some molecular diagnostic tests, but pricing schedules for these codes are not publicly available. One company, Genomic Health, has a single marketed test (Oncotype DX) in the \$3000 range. Publicly available SEC reports indicate that this test is paid near its list price by both private payors and Medicare.

Some payors have proposed innovative risk-sharing coverage and payment for at least one complex molecular test (Pollack, 2007). Specific details of a reported contract between United Healthcare and Genomic Health for reimbursement of the Oncotype DX test have not been released. However, the cited report (Pollack, 2007) compared the arrangement to the UK NHS reimbursement of bortezomib/Velcade, in which payment is tied to the drug’s observed effects in individual patients.

Key similarities and differences (Medicare, private payor). Medicare is required to follow a fixed fee schedule when pricing complex molecular diagnostics, by “code-stacking” individual steps in the test process. This is based on a principle that when CPT codes (or a combination of codes) exist to code a test, it must be so coded. And once it is so coded, the resulting price is read out from the Medicare Clinical Laboratory Fee Schedule. However, it can be ambiguous whether existing CPT codes do or do not describe proprietary steps in new-generation diagnostic tests. When “code-stacking” is not feasible, and the claim is submitted with an “unlisted” code, Medicare provides no defined pricing algorithm, although most contractors are likely to elect to apply the gap-filling guidelines they would use for a specific new, but unpriced, CPT code.

Some question whether the legacy Medicare fee laboratory fee schedules covers costs for molecular tests

(e.g. Raab & Logue, 2000; IOM 2000) and this problem would be accentuated if a personalized molecular medicine laboratory was located in states with very low molecular reimbursement (e.g. Georgia; Massachusetts), and if the laboratory's test was reimbursed through "code-stacking." Medicare's pricing guidance for "gap-filling" asks contractors to compare a range of price references (e.g. median of invoiced priced; prices paid by other payors; resources required to "perform" the test) which could span a very wide range of price benchmarks. The resulting uncertainty in test payment could discourage investment in new complex molecular tests, because of the difficulty of making reliable projections for early decision-making (see "a note on economics", below).

Private payors have considerably more discretion to negotiate pricing with providers, for example, to depart from the published Clinical Laboratory Fee Schedule and negotiate "value-based pricing" using pharmacoeconomic models or other reimbursement models, such as more complex risk-sharing agreements.

A note on economics of pricing

Note 1. "Value-based pricing," by reference to a pharmacoeconomic or similar model, is problematic in practice. Imagine a test costs \$1 to run but saves \$1000 in health-care costs. If many competitors can produce the test, economics suggests that the price will tend toward \$1. If there is one seller and one rational buyer, the price may tend toward \$1000 (but behavioral economics suggests there may be a face-off until the price is near \$500). Where the price actually settles will include factors like the availability of alternatives or work-arounds, and market segmentation of purchasers (by their available funds, negotiating power, or their perceived test value), as well as buyer uncertainty about the real value of the test (will it really save \$1000? Maybe one-fourth that?). Value-based pricing will not establish a single price without the interplay of many other marketplace factors.

Note 2. Medicare's "crosswalk" and "gap-fill" rules have considerable ramifications. Clinical laboratory fee schedule prices, as described in IOM 2000, were set for mature, commodity tests in the 1980s and thus economics suggests they reflect marginal-cost pricing. If in fact they allow little room for "producer surplus" over the marginal cost of

the test, it will be impossible for the producer to run clinical trials to develop new tests. By contrast, Medicare's four "gap-fill" rules yield a wide but unpredictable range of solutions, from which the Medicare carrier will set one single price for the test. For example, one "gap-fill" metric is median price paid by other insurers (say, \$1000) while another "gap-fill" metric is "resources to perform the test" which the Medicare carrier might estimate at \$50, that is, the bare cost of chemicals, tubes, minutes of technician time.^{xiii} While Medicare (and any other payor) will aim for the lowest price possible, attempting to reimburse a service with high development costs at marginal cost could simply yield a "null" marketplace. Both classical and recent economists have argued cogently that some market "inefficiency" – that is, prices floating above marginal costs – is a critical factor for technologic progress (McKenzie & Lee, 2008, and references therein). In addition, one would predict that the extremely high variance under the gap-fill rules would lead to under-investment due to the wide uncertainty of future returns.^{xiv}

3.5 Guidelines for Coverage Decision-Making.

Meaning. Both public and private payors want to pay for only medically necessary services. However, ruling whether a given procedure or service is "medically necessary" is subjective and the border between "investigational" and "medically necessary" care is difficult to define. There is an enormous amount of literature on the validation of biological and medical concepts (Schaffner, 1993; Thagard, 1999; Haack, 2007) and on what should constitute "evidence-based medicine" (EBM; CEBM, 2008; Jenicek & Hitchcock, 2005; Riegelman, 2004). But much less known about exactly how payors make coverage decisions, or better stated, exactly how individuals making coverage decisions, or how individuals or teams weigh the diverse components of coverage decisions. Coverage decisions rely more strongly on data from trials high in the "levels of evidence" hierarchy (e.g. U.S. Preventive Services Task Force; randomized clinical trials rank above cohort studies, etc.) The Blue Cross Blue Shield "TEC" criteria list five questions which are used to structure reviews of the evidentiary support for a new technology, although TEC reviews are labeled as not being coverage decisions (BCBS, 2008). Very specific thought capital regarding analysis of prognostic cancer gene panels is available in the academic literature (e.g. Ioannidis, 2006).

Principles for the validation of therapeutics are better developed than for the validation of diagnostic tests (Hernandez-Aguado, 2001; Feinstein, 2001; Moons et al., 1997; Moons & Harrell, 2003). This may seem quite paradoxical, if one assumes that “diagnostic tests” are at bottom described by simple and easily grasped metrics such as sensitivity and specificity. There is a large literature on the problems with “sensitivity and specificity” (e.g. Moons et al., 1997; Feinstein, 2001).^{xvi} Evaluation of which test is “better” is actually quite difficult (Bossuyt et al., 2006) as is calculating the net value of additive tests or of staged-testing protocols. These issues are rarely voiced in everyday technology analyses or coverage policies. In theory, a much better approach to valuation of clinical utility would be to assess the uncertainty in diagnosis (or therapeutics) before and after the test in question and value the “delta” of the uncertainty reduction (Benish, 1999). However, this cannot be done without both detailed performance metrics for the test *and* a working scenario for the clinical context. The required scenario-building becomes unwieldy when multiple therapies and multiple test choices or sequences of tests are in play and there is no well-accepted clinical path for using them. In addition, dollarizing or otherwise valuing the “uncertainty reduction” is difficult.

Coverage guidelines: Medicare. Medicare coverage decisions may be published National Coverage Decisions (NCDs), published Local Coverage Decisions (LCDs), or unpublished contractor coverage decisions applied during claims processing (claims are paid or are denied, but there is no published explanation). All of these decisions follow from a statutory requirement that Medicare not pay for coverage that is not reasonable and necessary to diagnose or treat disease.

Medicare has published general guidance to be used during local coverage decisions (CMS, 2008b). For national decisions, Medicare has published several regulatory approaches to defining medical necessity; the last of these was published in draft in 2000 and never finalized (65 FR 31124; Foote, 2002; Tunis, 2004). Medicare’s national coverage decisions (NCDs) are reached in the conclusion of a national coverage analysis (NCA), which contains an extensive discussion of the published literature on the technology or service in question (CMS, 2008c). These discussions provide a comprehensive review of the relevant

literature and are usually framed around a series of questions (such as, Is the evidence sufficient to establish X?). However, other than review of the “case law” of diverse decisions, exactly how different factors are weighed together is uncertain (Giacomini, 2005).

Medicare’s LCDs vary greatly in how (or whether) they present a reasoning process behind the coverage position. Not infrequently, Medicare LCDs may state tersely that a given service was reviewed and found to be “not reasonable and necessary.” Almost no LCDs provide a critical *discussion* of the literature, although either few or many journal articles may be *cited* in an LCD (Foote & Town, 2007).

Coverage guidelines: private payors. Private payors vary in the number of coverage decisions available on their websites. Among private payors, Aetna and Cigna maintain large websites with regularly updated coverage policies, as do some Blues plans. Aetna (2008), for example, lists some 500 medical policies. Most include several pages of literature review. Like Medicare NCDs, private payor coverage policies review and discuss the available literature. Typically, in private payor systems, non-covered devices or procedures are described as “experimental” or “investigational.” This description foreshadows contractual statements that experimental or investigational devices and procedures are not covered in the insurance policy.

Key similarities and differences (Medicare, private payor). Both Medicare and private payors prefer to base coverage decisions on large, double-blind randomized controlled trials. However, coverage decisions must give equal weight to the internal validity and external validity of studies. Undertaking a double blinded trial may be impossible (e.g. the surgeon knows his type of surgical procedure, or the drug has distinct adverse effects compared to placebo). The more precisely the study population is defined, the greater may be its differences from the general population in whom the procedure or test may be used. It is difficult to lay out procedures in advance for balancing conflicting data or balancing conflicting clinical needs (Braddick et al., 1999), yet these clinical counter-forces may be at the heart of coverage decisions. There is a general interest for encouraging adoption of medically useful innovation, but this is balanced by the concern that early positive results are not always replicated (Ioannidis, 2005). In some

circumstances, enough may be known about a test (e.g. it categorizes high- and low-risk patients accurately) that randomized clinical trials are unethical (e.g. known low-risk patients will not be ethically randomized to chemotherapy.) This raises a dilemma if an insurer requires a prospective randomized controlled trial for its coverage decision.^{xvii}

Key Processes

4.1 Benefits Categories

Problems to be solved.

- Health insurance would be impractical without defined benefits; for example, actuarial calculations would be disrupted.
- Services should be readily identified as part of a covered versus excluded category.
- States may require specific test benefits.
- Medicare statute excludes “screening” services unless previously enumerated, but the border between screening & diagnostic services is sometimes problematic.

4. Alternative Approaches to

Current Benefit Approach	Pro	Con
<ul style="list-style-type: none"> • Coverage benefits are broadly (telegraphically) defined. • Excluded categories may contain enumerated exceptions (Medicare excludes “screening tests” as a category, but then lists enumerated exceptions.) • Benefit category distinctions for laboratory tests categorize “screening”, “preventive”, and “diagnostic” tests. 	<ul style="list-style-type: none"> • Economy of contracting. • Meaning of benefit categories have been established by time and by convention. Relatively few tests raise uncertainty as to their classification. • Additional tests may be specifically excluded or included by name. 	<ul style="list-style-type: none"> • Gray zone between categories.
Benefit Proposal 1		
<ul style="list-style-type: none"> • CMS, AHIP, or other entities produce a consensus reference document defining “screening”, “preventative” and “diagnostic” tests in more detail. 	<ul style="list-style-type: none"> • This will reduce uncertainty. • There will be closer compliance for different payments or co-payments in the “screening” and “preventive” categories 	<ul style="list-style-type: none"> • Consensus definitions may be difficult to achieve. Even if consensus is difficult, the process could elevate key problems in the current definitions.

4.2 Billing Processes

Problems to be solved.

- Billing processes are administratively efficient for payor.
- Billing processes are administratively efficient for laboratory or physician/hospital.

- Double-billing to different entities is avoided.
- All entities are properly verified (enrolled lab, enrolled patient, enrolled doctor, etc)

Current Billing Approach	Pro	Con
<ul style="list-style-type: none"> • Medicare and state laws generally require direct-bill to payor by performing laboratory. • Medicare exceptions for hospital outpatients (see next row) • Labs enroll with payor. • Medicare has additional complex rules for the hospital outpatient setting. 	<ul style="list-style-type: none"> • States have flexibility to set regional requirements. Few lab tests fall under state mandates. • Set pathway of bill submission reduces double payments to two entities (e.g. physician office and performing lab.) • Although complex, the rules aim to implement the statute that the hospital bill for hospital services, via additional regulations and evolving agency interpretation of statutory language. 	<ul style="list-style-type: none"> • Multi-state insurers must vary lab test benefit plans by states. • Processes change despite no intervening statutory update. • Hospitals become responsible for costs and medical necessity of later lab tests ordered by distant, unaffiliated physicians and performed by distant labs. • Complex rules generate more opportunities for gray zones. • Basic events such as the “date of service” of a lab test vary depending on what payor the provider is submitting to (Medicare, private, etc).
Billing Proposal 1		
<ul style="list-style-type: none"> • Private plans: No change suggested. 		
Billing Proposal 2		
<ul style="list-style-type: none"> • Medicare: Revisit recent billing rules for outpatient-origin specimens. Replace existing complex rules with simpler rule. For example, to identify a hospital-origin specimen, add modifier “HS” to indicate a hospital specimen but allow performing lab to bill at the same price as the hospital. 	<ul style="list-style-type: none"> • If the laboratory bills, responsibility for repayment on later audit is held by the laboratory • Just one contractor audits and controls most of laboratory’s payments. • Redesign could be cost-neutral for CMS. 	<ul style="list-style-type: none"> • Regulatory change required.

4.3 Coding

Problems to be solved.

- Define services performed, in uniform exchanges between provider and payor.
- Most services are well served by fixed codes which change rarely.
- Interfaces between codes may be complex and require specialty or subspecialty understanding of current & proposed codes.
- The coding system should adapt to changing technology.

- The coding system should support needs of coverage decisions, since they are specifically interchanges between provider and payor.
 - Provider and payor exchange information to adjudicate reimbursement.
 - Payors need to distinguish among specific molecular medicine tests (e.g. prostate gene panel X is acceptable; prostate gene panel Y is not.) In contrast, CPT codes do not distinguish manufacturer-specific services.

Current Coding Approach	Pro	Con
<ul style="list-style-type: none"> • Coding system changes rarely. • New codes are carefully scrutinized for necessity & for conflicts or “interface” with existing codes. • Infinite range of genomic tests can be coded by a small number of fixed codes (e.g. “gene amplification”) 	<ul style="list-style-type: none"> • System is stable and uniform nationally. 	<ul style="list-style-type: none"> • Payor need to distinguish among services (panel X, panel Y) is unmet. Recent two-places modifiers fail to meet this need. • Timeline to new code is lengthy. • Uncertainty about so-called “politics” of code creation. • Delay in new codes increases the payor’s administrative costs due to manual processing of “unclassified” codes.
Coding Proposal 1		
Increase use of Category III codes (“temporary tracking codes”) for molecular tests.	The proposed process is already in place; revisions occur annually; barrier to obtaining a Category III code is not high.	Codes are by definition temporary, so this is not a long-term solution. Reports of payor bias against paying Category III codes. Following CPT principles, the resulting codes would be non-specific to vendor (e.g. “Breast cancer gene panel test;” “Prostate cancer gene panel test”).
Coding Proposal 2		
Increase use of Level II (HCPCS) codes for molecular tests.	Codes could be updated outside the CPT process.	Level II codes (except S codes) are managed by CMS, which has limited administrative resources. CMS issues Level II procedure codes sparingly and only for clear programmatic need, e.g. to edit services under a specific NCD where CPT codes are not specific enough for CMS claims processing.
Coding Proposal 3		
Establish new code set, more similar to NCD codes for specific drugs.	<p>Rapid and specific identification of new test.</p> <p>System works well for drugs (NCD system) and consumer products (UPC system.)</p> <p>Five-place codes using letters (LWXYZ) allows 12 million codes.</p>	<p>Would require new national process; but some Congressional proposals have proposed a national multi-stakeholder committee to issue codes (and set prices).</p> <p>Drug codes are tied to specific drug approvals and drug names (e.g. “bevacizumab”). There is no such fixed nomenclature for lab-developed molecular tests.</p>

4.4 Pricing

Problems to be solved.

- Maximize overall economic efficiency (e.g. if U.S. healthcare spending is \$2T, distribute among an optimal array of services.)
- Definition of economic efficiency of healthcare services is uncertain and overall allotment of resources very difficult to control and monitor.
- Encourage value-creating innovation. *De minimus*, cost-saving to cost-neutral technological innovations should be promoted.
- Definition of value in healthcare is uncertain.
- Administrative efficiency.
- Transparency (particularly government payors).

Current Pricing Approach	Pro	Con
<ul style="list-style-type: none"> • Private payors – free hand to contract at market prices; more often than not, payments near CMS fee schedule (IOM, 2000). • Rarely (so far), use of risk-sharing contracts (see white paper) • Medicare – gives priority to pricing molecular diagnostics by “code-stacking” • If Medicare finds code-stacking is not possible, entirely different rules appear (e.g. median of invoiced charges) 	<ul style="list-style-type: none"> • Market forces define prices • Innovative pricing systems are possible • Total costs for lab tests highly predictable across CMS • Administratively efficient 	<ul style="list-style-type: none"> • Insurers have limited resources to thoroughly negotiate one-off prices for each molecular test • Fee schedules for some molecular lab steps vary sharply (5X) among states • Novel tests may use steps that have no CPT code and are difficult to price-set administratively • “Gap fill” rules may point to widely varying prices and have poorly defined options (price to “resources needed”) • Unpredictability of price-setting creates irreducible risk at the end of development, after all investments are sunk costs
Pricing Proposal 1		
<ul style="list-style-type: none"> • Competitive bidding 	<ul style="list-style-type: none"> • Natural market process for private payor (e.g. Megalab X and Y compete for the business of Insurer X) • Some experience with competitive bidding in the Medicare system; Congress already has launched demo projects in Medicare system 	<ul style="list-style-type: none"> • Coding system does not allow precise specification of molecular tests, making the definition for competitive bidding vague • “Competitive bidding” fails to work well for sole-source (e.g. monopoly) products
Pricing Proposal 2		
<ul style="list-style-type: none"> • Medicare – price by market surveys (similar to drugs/ASP) 	<ul style="list-style-type: none"> • Assumes market prices are fair and competitive 	<ul style="list-style-type: none"> • Administratively cumbersome • Does not leverage “pricing power” of government vis a vis sole source products
Pricing Proposal 3		
<ul style="list-style-type: none"> • Medicare – set “code-stack” price and adjust upward to account for development costs 	<ul style="list-style-type: none"> • Avoids marginal pricing which could prevent new product development 	<ul style="list-style-type: none"> • Administratively cumbersome • Assumes a “fair” composite price can be established • Requires rules for choice of “add-on” value above “code-stack” price
Pricing Proposal 4		
<ul style="list-style-type: none"> • Creative contracting 	<ul style="list-style-type: none"> • Optimize incentives for both lab and payor 	<ul style="list-style-type: none"> • Little experience with this process in US healthcare; U.K. has tried to implement in the NHS. • Administratively cumbersome

4.5 Coverage decisions

Problems to be solved.

- Pay for care that is “reasonable and necessary” and “not experimental”
- Terms not clearly defined
- Timelines are long
 - Genuine uncertainty with replicability of new publications
 - Review period is long (4-8 months)
 - Concern about “Type 2 error”, that is, withholding high-value services from member patients
- Developers/investors have high uncertainty about requirements and judgment processes used

Current Coverage Approach	Pro	Con
<ul style="list-style-type: none"> • Primarily technology assessments which leverage principles of critical thinking in experimental design and the “principles of evidence-based medicine” 	<ul style="list-style-type: none"> • Numerous US payors and tech assessment groups (govt/non-profit/commercial) “compete” for credibility and probably collate toward consensus over time • Congress may propose a new evidence-based medicine institute or agency 	<ul style="list-style-type: none"> • Less than optimal understanding of how “incommensurate” factors are weighed: • (a) a blinded RCT is good because it has high internal validity, but use of restricted test population during the RCT limits external validity) versus • (b) a “practical trial” or registry documents events in a natural population, but lacks clear controls • Differences between “EBM” decisions and “coverage decisions” not well articulated
Coverage Proposal 1		
<ul style="list-style-type: none"> • Use of focused guidelines, similar to FDA guidelines for narrow product categories 	<ul style="list-style-type: none"> • Works well for FDA • Maximizes predictability for industry • Natural categories have been suggested, e.g. “a test which replaced another service” (Feinstein, 2001) 	<ul style="list-style-type: none"> • Difficult-to-articulate factors may play variably large role, depending on the coverage decision. It may be hard to produce a useful step-by-step template for a future decision.
Coverage Proposal 2		
<ul style="list-style-type: none"> • Produce book or thorough white paper of “case studies” of natural coverage decisions 	<ul style="list-style-type: none"> • Raise visibility of issues for future work • Other fields, such as judicial decision-making, have enormous literature of this type (e.g. Posner, 2008) • A few examples exist (e.g. Giacommini, 2004) 	<ul style="list-style-type: none"> • Unclear who would ever do this

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ⁱ See the Department's report, "Personalized Healthcare: Opportunities, Pathways, Resources" (75pp) at:
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ⁱⁱ The BBA is identified as PL105-33. Section 4553(c) requested the IOM issue a comprehensive study of laboratory test reimbursement, known as the IOM 2000 report. 4554(b) required the creation of uniform national policies for laboratory tests through "negotiated rulemaking". This included a date of service rule (for example, to bill a 24-hour collection, would the claims date-of-service be: [a] the first day, when the test is ordered, [b] the second day, when the sample is taken, [c] the third day when the test is completed, or [d] the fourth day, on which the test is reported). The effort created 23 national coverage decisions for common laboratory tests, with precise coding instructions. The committee met nine times between July 1998 and August 1999. For results of 4554(b) see 65 FR 13082ff, 3/10/2000 and 66 FR 58788ff, 11/23/2001. Of historical interest, the subsequent section of this law, 4554(a), created four laboratory test regional carriers who would handle all laboratory test claims. Exactly this four-carrier system was in fact established for DME carriers (Regions A-D). But no "laboratory test carriers" were never created.

ⁱⁱⁱ *Incongruous coverage* can result. For example, a screening test for glaucoma is covered for asymptomatic patients with a racial heritage of being African-American or Hispanics (the status of the benefit for multi-racial individuals are undefined). Some individuals who had one or more parents with glaucoma actually have a *higher* risk of glaucoma than an African-American or Hispanic individual. Since "family history" does not count as a personal sign or symptom nor as a category for screening, in the end some higher-risk individuals are not covered for glaucoma screening while some lower-risk individuals are.

^{iv} In 2000, CMS stated that, in general, under some circumstances prognostic cancer tests were necessary in the care of disease: "Prognostic information, even if it did not affect a treatment decision, *could be considered* to improve health outcomes." See Decision Memo CAG-00065N. However, in 2003, CMS stated it could not undertake a request for a prognostic clinical test in cancer patients. After receiving a request to at review published data on prognostic accuracy of PET scans for thyroid cancer patients, CMS answered concisely, "[The proposed clinical scenario, cancer prognosis] is not reasonable and necessary and was not addressed." See Decision Memo, CAG-00095N.

^v BIPA 2000, Section 242(c), requires that *only* the outside laboratory can bill for "physician pathology services" on inpatient or outpatient specimens, if the specimen is taken at a "covered hospital." A "covered hospital" is a hospital which

sent some pathology tests to an outside lab before 1999. The law is challenging to implement because there is no bright line between “chemistry” and “pathology” tests in the CPT manual, and many newer laboratory steps are not found in the manual at all. Like rules of Latin grammar, CMS’s classifications of “chemistry” and “pathology” tests must be memorized one by one. Essentially chemical tests such as flow cytometry and gene panel (microarray) tests are classed by CMS as “pathology tests.” Complex personalized medicine tests now in the marketplace torture the historical but ill-defined border between “clinical laboratory” and “pathology” tests. For example, a modern tumor analysis test may use tumor tissue, even paraffin blocks, laser microdissection, and a gene panel microarray (defined as pathology tests) and also include steps such as DNA separation and amplification (defined as chemistry tests). Variability is real: one contractor (NHIC) classifies cancer chemosensitivity tests as a form of chemistry test (84999) while another (HGSA) classifies them as a form of pathology test (89240).

^{vi} The chemistry test date of service rule entered regulation on 1/1/2007 but CMS gave the “implantation date” as 1/1/2008. The pathology test rule entered regulation on 1/1/2008 but in 05/2008 CMS stated the effective date would be 1/1/2009. These are referred to as “date of service” or “DOS” regulations because they administratively fix the “date of service” of the future laboratory test as *during* the hospital outpatient encounter (42 CFR 414.510)

^{vii} For Medicare, a hospital outpatient is defined as one who receives services (as opposed to supplies) from the hospital, AND is not an inpatient, AND is registered as an outpatient (thus, there are three separate conditions to be an outpatient; 42 CFR 410.42 and 410.2.)

^{viii} 65 FR 50312; creating 45 CFR 160, 162.

^{ix} 65 FR 50351 (8/17/2000). The ten guiding principles were: (i) Improve efficiency and effectiveness of the health care system re: electronic transactions. (ii) Meet the needs of users, e.g. providers, health plans. (iii) Consistency with other regulatory standards. (iv) Low implementation costs. (v) Codes are updated by accredited or [reliable] private or publications; continuity and efficient updating over time. (vi) Timely implementation and updating standards. (vii) Technically platform-independent. (viii) Precise and unambiguous and as simple as possible. (ix) Burdens on users as low as possible. (x) Incorporate flexibility to adapt to new services and information technology; encouragement of innovation.

^x AMA, CPT Code Process: <http://www.ama-assn.org/ama/pub/category/3866.html>

^{xi} As hypothetical examples, the main AMA CPT system might have a code 12345 for wound care, and Medicare might require use of a special Medicare code G1001 for small wound care and G1002 for large wound care.

^{xii} SSA 1833(h)(2)(B). The Secretary may make further adjustments or exceptions to the fee schedules to assure adequate reimbursement of... (ii) certain low volume high-cost tests where highly sophisticated equipment or extremely skilled personnel are necessary to assure quality.

^{xiii} In other contexts Medicare administered pricing includes development costs. For example, the practice expense of the RVU system prices physician services at the physician’s cost. However, that cost is build from inputs (such as a \$1000 disposable surgical device) into which a development cost is already packaged.

^{xiv} High variance ties to risk and volatility in financial valuation theory; see e.g. Boer, 1999. One set of risk-narrowing tools, real options analysis, e.g. Mun, 2006, will be unhelpful here because of the volume of variability stored in the final step in product development, the Medicare gap-fill process. Rational product development normally produced a series of staged and rising investments following progressive reduction of uncertainty, as in the Phase 1, 2, 3 trials of drug development.

When very high uncertainty looms at the final step, Medicare's gap-fill pricing, investing for progressive risk reduction is unsuccessful.

^{xv} “Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized...[the principle] must be sufficiently established to have gained general acceptance in the particular field in which it belongs.” *Frye v United States*, 293 F. 1013 (DC Cir 1923)

^{xvi} For example, it is usually taught that sensitivity and specificity are fixed features of a test, while true- and false-positive rates depend on a population base rate for the disease. However, sensitivity and specificity are set by arbitrary cut-off values. Sometimes they will be set so that one-sided result is obtained (e.g. very low false negatives), sometimes not. Sensitivity and specificity also vary by complicated factors such as “spectrum” effects (see e.g. Feinstein, 2001; Moons et al., 1997, for more detailed discussion).

^{xvii} The general point, that strong but not definitive data may make future randomized trials unethical, has been made before, e.g. Ioannidis J et al. (2001) *JAMA* 286:821-30. A classic older paper on problems with RCTs is “An additional basic science for clinical medicine: The limitations of randomized clinical trials”, A.R. Feinstein (1983) *Ann Intern Med* 99:544-50. Some participants in the June 2008 workgroup felt that no insurer would require a double-blind trial when this appeared unethical based on existing information. Others felt that this sometimes occurs. One example of the dilemma is found in CMS Coverage Analysis CAG-0018N, PET coverage for women with cervical cancer. CMS found that “with respect to FDG PET compared to conventional imaging in detecting pre-treatment metastasis that ‘there is fair to good evidence that PET is more sensitive than CT or MRI for detection of retroperitoneal nodal metastasis in patients with newly diagnosed cervical cancer.’ Data suggest that PET is more sensitive than conventional imaging and has the potential to improve the early diagnosis of recurrent cervical cancer. [But] it is unclear whether improved early diagnosis of extra-pelvic recurrent cervical cancer leads to improved patient outcomes except in the setting of patients who have not previously received radiation.” One approach to resolving this issue would be to identify 100 patients who have *known* recurrent cervical cancer, and enroll them in a randomized controlled trial, 50 to treatment upon diagnosis of recurrence, and 50 to a control group who agree to receive treatment after a substantial delay. Such a study would probably be very difficult to enroll, making it hard to resolve the question at issue.

