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A Pay-For-Value, Data-Driven Approach for the Coverage of Innovative Genetic Tests

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SUMMARY

The Coverage with Evidence Determination (CED) methodology is necessary for treatments and appropriate for traditional diagnostics. However, when applied to innovations in personalized medicine and molecular diagnostics, CED (in its current form and with proposed modifications) fails to capture the benefits of improved health care and decreased costs that are possible from the new technology and the data generated from these services. Given the speed of innovation in this important clinical area, CED methods may make new tests obsolete before they are commercialized, hindering investment in their development. Current registry systems have demonstrated promising concepts for an alternative to CED, but have also uncovered additional challenges, as would be expected by pioneering new ideas.

This paper proposes an alternative model for coverage determination that builds upon programs like MolDx by Palmetto and capitalizes on the knowledge gleaned from early registries, addresses the key underlying financial motivations that drive coverage determinations, and advocates for a shift to a Pay-For-Value (PFV) model based on risk sharing between parties. This proposed model is intended to move forward the discussion on a design for coverage determination that encourages innovation in the agile environment of molecular diagnostics. Changes are urgently needed to allow health care to meet the new demands posed by increased medical personalization and for accountability of all parties in the US healthcare system. A technology-enabled coverage determination process presents a unique opportunity for a self-regulating system that inherently optimizes patient outcomes, payor costs, and developer profits.

INTRODUCTION

Centers for Medicare & Medicaid Services (CMS) Recognizes the Need for Change

One in four Americans receives benefits through CMS.[1] Thus CMS is in a unique position to not only make coverage determinations and negotiate low pricing for its beneficiaries, but also to establish the coverage and pricing precedents most other payors follow. The mission of CMS is to "ensure effective, up-to-date health care coverage and to promote quality care for beneficiaries."[2] In 2000, CMS (then known as the Health Care Financing Administration) needed to develop coverage policies for procedures "where we believed that the enthusiasm of interested parties was disproportionate to the persuasiveness of the then-current evidence base."[3] Put more bluntly, diagnostic providers held out higher hope for certain diagnostics and therapies and therefore recommended their prescription even when there was no direct evidence of benefit. In 2000, CMS recognized several key shortcomings[4] that are still at issue today:

> CMS is one of the largest purchasers of health care in the world, covering one in four Americans

1) For many emerging technologies, seemingly insufficient utilization evidence had been collected to support a coverage policy; a clear definition of "sufficient evidence" has yet to be seen in 2013.
2) In many cases CMS beneficiaries could benefit from early access to an emerging technology, and by covering an emerging technology CMS could itself expedite the collection of the necessary data to support a coverage decision; this is still true in 2013.
3) Randomized Controlled Trials (RCTs), previously considered the gold standard, are neither a good fit, nor are feasible, for the rapid pace of development of some medical innovations. Applied to molecular diagnostics, it may increase the cost of development substantially. In 2013, retrospective data, not garnered from RCTs, is becoming more acceptable as illustrated by a recent reference from Novitas Draft LCD DL33138 (see Figure 1).[5]

The Rise of Coverage with Evidence Development (CED)

In 2006, the Coverage with Evidence Development (CED) program[6] formalized a control mechanism to allow CMS to provide cutting-edge health care coverage

while still evaluating the clinical utility of new procedures. The CED process, with its classically designed studies and data collection techniques, was created for drugs and biologics and is not well suited to molecular diagnostics.

> Comparative cohort designs are critical for assessing predictive ability, and randomization is highly desirable, although nonconcurrent randomized cohorts can speed the evaluation process. The sufficiency of nonrandomized cohorts must be very carefully scrutinized, on a case by case basis. This is a reflection of the fact that alternative approaches to more conventional randomized prospective controlled trials—such as prospective-retrospective study designs—may be able to support predictive biomarker CVU, as long as they are appropriately conducted. Per above, there are currently NO standardized thresholds and/or benchmarks for evaluating the CVU/medical necessity of emerging biomarkers.
>
> Novitas Draft LCD
> DL33138

Figure 1: This draft LCD from Novitas indicates alternatives to randomized controlled trials are viable, if appropriately conducted.[5]

CED approaches fit best in a medical system akin to an assembly line stage-gate supply chain model:

01 Validation of diagnostic

02 Clinical utility

03 Reimbursement determination

04 If additional indications, go to stage 01

Not only is this stage-gate process not optimal for molecular diagnostics, but it negates (by providing no incentive or collection mechanism for) the vast amount of data the tests can produce and must freely flow between the stages.

In early 2012, CMS solicited feedback about updating the program and at about the same time the President released the National Bioeconomy Blueprint that specifically stated, "Expanding the Coverage with Evidence Development program to drive innovation: reimbursement for medical treatments is a powerful driver of industry investment."[7] The draft guidance for CED[8], the review of which ended in January 2013, makes recommendations that are based on the feedback from the existing CED program, and are in alignment with the Blueprint. While these recommendations provide some minor tweaks to the current CED program, they do not address the unique considerations and opportunities of molecular diagnostics (outlined below). This results in molecular diagnostics developers being saddled with untenable returns on investment delaying potentially life-saving (and cost-saving) diagnostics.[9]

Food and Drug Administration Regulation Could Add Additional Burden

The role of the Food and Drug Administration (FDA) should also be considered. Currently through a trial parallel review program, parts of the clinical trial process can be run in parallel with early validity studies. While this may help accelerate the FDA-approval path, it further codifies a path that the majority of molecular diagnostics do not currently follow. Laboratory Developed Tests (LDTs), subject to more industry appropriate, agile regulations and oversight by CLIA have, and for the foreseeable future will (due to the structure of the industry), provide a rich source of new diagnostics. LDTs, regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1998, have historically been able to deliver critical tests of public health importance before FDA approval is received. An LDT diagnostic for HIV viral load testing was available six years before an FDA approved kit was available. Similarly, an LDT diagnostic for KRAS to determine which patients would respond to cancer treatments was available years before the FDA kit. A recent ACLA petition stated that "FDA's regulation of LDTs as devices would adversely affect patient care in the US."[10]

CED and Molecular Diagnostics

The CED process, in efforts to ensure correct utilization, can unnecessarily stifle innovation for smaller, venture-backed companies that do not have the resources to survive the extended period of data-gathering and potential non-coverage dictated by the CED process. Given that a great deal of innovation in the molecular diagnostic space is done by these venture-backed companies, the CED process has the effect of dampening the entire molecular diagnostics industry. CED—by design—can take years, and the diagnostics going through the process may be saddled with an unrecoverable cost burden, private insurer non-coverage, and be eclipsed by another technology before reaching market (similar to why labs oppose the FDA process in favor of the more agile Clinical Laboratory Improvement Act (CLIA) process for Laboratory Developed Test (LDT) oversight). The proposed CED process requires the services of a protocol "expert," such as the independent Center for Medical Technology Policy (CMTP)[11] further increasing the cost. With these burdens imposed by CED protocols, the risk-adjusted ROI for developing new diagnostics such as NexGen Sequencing may not be favorable to produce desirable rapid development and deployment.

Finally, there is growing recognition of the value of longitudinal studies, which can capture real world clinical practice, outside of a sometimes "artificial" study environment. Another system (not CED) that embraces broader data collection and analysis capabilities and delivers a revamped incentive system is needed. It should be parsimonious and let research physicians explore how new diagnostics can be most valuable and allow producers to be innovative and agile.

Molecular Diagnostics: Unique Considerations and Unique Opportunities

Genetic testing, molecular diagnostics, genomic testing, and personalized medicine are fundamentally different from, and will change, traditional diagnostics and medicine. The difference

between traditional and molecular diagnostics is comparable to that between devices and “smart” devices; a room “knows” when someone enters and turns on the lights, a car knows when it is skidding and applies the anti-locking break system. Very specific technology-provided information (motion detection, skid recognition) alters outcomes in a manner completely impossible without the added information. Similarly, very specific information provided by molecular diagnostics for specific patients, can alter the course of medical treatment in a manner completely impossible without the added information.

Molecular diagnostics presents unique **financial**, **timetable**, and **scientific** benefits relative to other diagnostics, which are not leveraged by the CED process:

1. **Financial – molecular diagnostics target small markets with high development costs**
    - **Unit costs are higher** – The development costs for molecular diagnostics and treatments are commonly on par with, or higher than, non-molecular tests and treatments, but generally are only given to a relatively small number of patients exhibiting very specific indicators.
    - **Benefits are greater** – Molecular diagnostics can be more precise than traditional diagnostics, allowing appropriate therapies to be delivered sooner, resulting in better outcomes and less waste.
    - **Relative value is greater** – As treatments and diagnostics evolve (Figure 2), their costs generally increase, as does the value of knowing when to utilize a treatment. In other words, a $20 test to determine if $50 worth

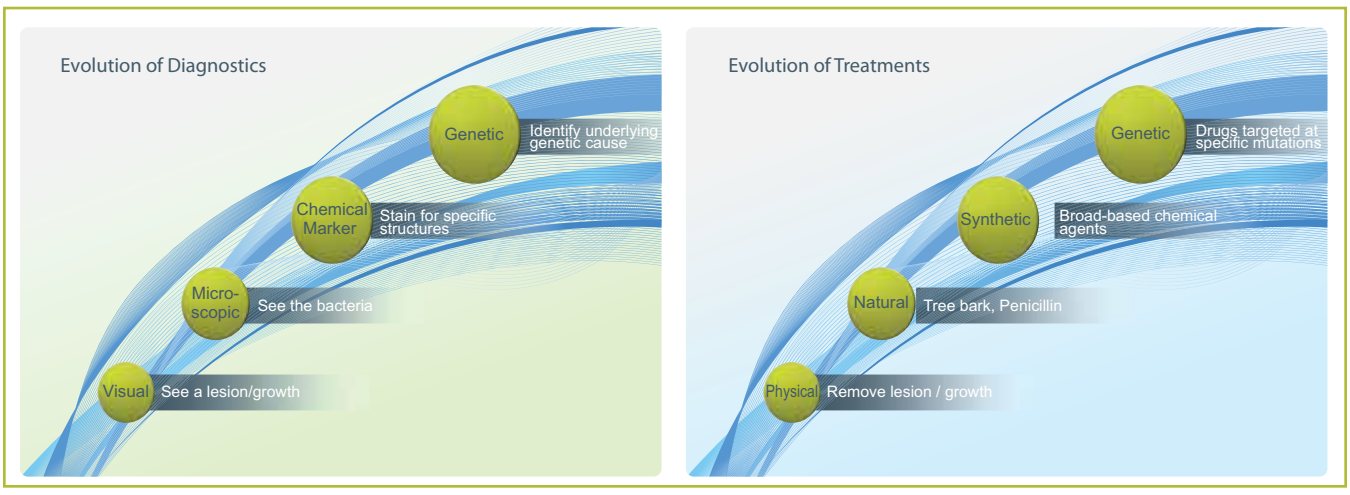

Figure 2: Both diagnostics and treatments continue to evolve to higher-cost, more complex protocols that also possess higher potential value to the patient.

of antibiotics should be prescribed is a beneficial test; a $3,000 test to determine if $100,000 worth of a cancer therapy should be prescribed is a more beneficial one. This results in the personalized test being more valuable from a purely financial perspective.

The CED process does not take into account the increased development costs to the developer, the improved health outcomes for the patient, the potential for waste reduction or cost control, or the decreased costs for payors. It additionally assumes that costs will be offset in the long run when the diagnostic is disseminated for usage by the general public. The entire point and value of genetics is that they will never be broadly disseminated. Markets will be smaller and even more personalized.

2. Timetable of molecular diagnostics – studies are slow, trials need not be slow

- **Conducting studies is more difficult –** Because molecular diagnostics are narrowly targeted, the group of patients who have the correct set of highly specific risk factors that indicate appropriate use of a diagnostic is necessarily small. Identifying a patient population large enough to support statistically significant results can prove time-consuming and difficult, and could delay access. The challenge of finding suitable patients increases the value of data from each patient and speaks directly to the need for increased data federation through electronic health records.
- **Trial periods –** While studies can be slow, trials, and the inception of data gathering, can happen more quickly. It is beneficial and preferred to begin gathering data immediately rather than in a drawn out trial process. Unlike treatment trials, diagnostic trials can, by appropriate weighting of the results, present no health risk to patients. It is important to note that in the absence of decision support tools to help physicians determine the weight that should be applied to diagnostics results, the diagnostics may not be used in an efficacious manner.[12]

The CED process makes no allowance for the rapidity with which molecular diagnostics evolve or the dearth of test subjects who can contribute to the knowledge pool (and the data these test subjects can provide).

3. **Scientific – molecular diagnostics involves huge numbers of variables**

   Because of the virtually limitless combinations of genetic markers possible, it is likely that during the course of evaluating a specific molecular diagnostic, useful variations will be identified. These variations are far more numerous than could be reasonably addressed by sequential independent studies. The variations may:

   - Increase the accuracy or specificity of a diagnostic
   - Identify new applications in test subjects (e.g., identifying the presence of HER2 in colon cancer patients who subsequently respond to Herceptin)

   The CED process does not allow tests to evolve dynamically based on the cornucopia of data that can be provided by slight biomarker variations, or newly-discovered indications.

CRITICAL CONCEPTS FOR COVERAGE

Clinical Utility

The core element to determining appropriate coverage centers on clinical utility. There is little dispute that for analytic or clinical validity, measurements should be done accurately and be reproducible in varying clinical environments.[13] The disputes arise around the concept of utility or clinical utility—what does it mean? How is it measured? Who pays to measure it? How is it used as both a yardstick and gate for payment?

A study done by McKinsey & Co for the Personalized Medicine Coalition revealed that of $292B spent on medications in 2008, approximately $145B went to drugs that were ineffective for the patients who took them. Further findings estimate the cost of adverse drug events to range between $45 to $135B per year. An estimated 25% of these costs could be averted through the use of diagnostic tests for the appropriate biomarkers.

All parties have slightly varying definitions of utility; utility can have different meanings when applied to inherited conditions vs. reproductive decision-making vs. public health, and there is uncertainty around when an appropriate quantity of data has been accumulated to measure utility. In the context of CED, the payors' definition that a clinically useful result is one that alters the course of treatment (e.g., identifying the right type of intervention or changes in monitoring methods or frequency), is probably most relevant.

Measuring clinical utility, or determining when it needs to be measured through the CED process, is not clearly defined. The historical code-stacking

reimbursement methodology (the use of which we are not advocating) largely circumvented the need to define clinical utility by allowing diagnostics, still lacking complete clinical utility studies, to be reimbursed. In fact, under the code-stack methodology, tests were frequently reimbursed before much, if any, clinical utility data were generated—allowing information to be collected after commercialization. Since diagnostics are ordered by physicians, adoption of new diagnostics is generally driven by expert specialty physicians or key opinion leaders integral to the research process and the generation of data for more widespread publication. The end of code-stacking at the beginning of 2013, and the concomitant introduction of specific codes for various diagnostics, resulted in limiting the scope of use of some diagnostics (e.g., EGFR) and requiring new tests to be coded as miscellaneous requiring appeals. Without reimbursement for new tests, physicians may be unnecessarily constrained in using their best judgment for medical care. Additionally, under the code-stacking model, slight variations of tests could be used and reimbursed. Code-stacking, while far from ideal, provided a mechanism by which patients could benefit from innovative diagnostics.

Clinical utility is in the eye of the beholder

For **patients**, relief or cure is a shared goal with the provider. But utility might be the end of wasteful payments, palliative care provision, or estate planning.

For **providers**, utility may be a simple change of guidelines or atrophied standards of care but could also mean changes in office or hospital workflows, simpler and more targeted test ordering or less iatrogenic illness.

For **hospitals,** utility is better Diagnosis related group management and facility optimization as well as potentials for marketing and differentiation.

For **payors,** utility is cost saving, improved outcomes and more informed management of groups.

An increased reliance on cost-prohibitive, fixed CED utilization studies, when combined with the discontinuation of code-stacking provides impediments to: investment in new molecular diagnostics (costs are higher and revenue is delayed); the collection of data so new diagnostics can be approved; and most importantly, providing the best care. Diagnostics that fulfill unmet medical needs are not properly incented or financed.

Prognostic Rather Than Predictive Results

There is an important distinction between predictive and prognostic factors in relation to the utilization of diagnostics.[14] Prognostic factors speak to the probable course and outcome of a disease, while predictive factors address

the likely effectiveness of a therapy. The coverage decision for a diagnostic should be based on the test's ability to provide prognostic guidance that impacts patient care, (a so called "actionable result"), not on the predicted (or realized) effectiveness of the resultant therapy. The prognostic guidance is realized as soon as the physician sees the results. The results could range from the avoidance of an unnecessary therapeutic intervention to simply a change in surveillance.[15] This "instantaneous" value of diagnostics makes them ideal for a PFV payment structure.

Due to the complexity of molecular diagnostic results, the determination of "standard of care" and coverage should to some extent be based on the decision support provided to the physician along with the result. For example, if a physician decides on a course of action different than one that would have been taken without the diagnostic, then the test demonstrates utility and the diagnostic provider should be reimbursed. If the physician takes appropriate action as a result of a diagnostic and its associate decision support, the physician should be considered to have delivered the standard of care and should also be reimbursed.

Intellectual Property: Business Constraints

Pharmaceuticals and other therapies generally enjoy a relatively long period of post-approval patent protection, and consumption patterns that may last for several years. The rate at which molecular diagnostics are evolving means that the useful lifetime of diagnostic patents could be significantly shorter than for therapeutic patents. Further, molecular diagnostics are almost always deployed as a single instance (i.e., one set of biomarkers). Even if a patent remains viable, it is likely that an enhanced version of the diagnostic would become available prior to the protocol endpoint. In other words, because molecular diagnostic technology evolves so rapidly, patents for these diagnostics are much more likely to be obsolete than are patents for medical devices or slower-moving technologies.

PROPOSAL: A MARKET-DRIVEN, SELF-REGULATING APPROACH

The alternative to CED proposed herein leverages advances in technology to exchange information, and the vast amounts of data created by molecular diagnostics, to allow for a more market-driven, self-regulating, PFV approach to health care.

A Self-Regulating System

The driver for the interactions between the payor, diagnostic provider and the physician/patient is reimbursement (in addition to the more altruistic desires to improve outcomes). Reimbursement drives two opposite, but complementary cycles (Figure 3).

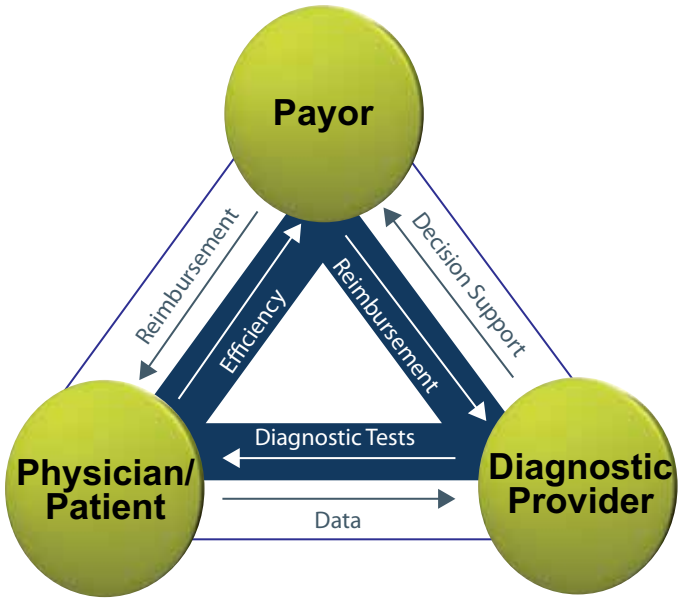

Figure 3: Two cycles actively linking payors, physicians, and providers to efficiently deliver health care.

Counter clockwise cycle:

- Patients and physicians want diagnostic providers to develop tests that improve treatment decisions.
- Payors want patients and physicians to efficiently use nascent diagnostics (i.e., correctly order and interpret results leading to lower overall costs, less waste and improved outcomes).
- Diagnostic providers want payors to provide reimbursement for their innovations (a driver for this cycle).

For the complementary clockwise cycle:

- Diagnostic providers want data supporting the clinical utility of their new tests.
- Payors want decision support systems from diagnostic providers to help physicians correctly 1) order diagnostics, 2) interpret the results, and 3) select the most appropriate treatments.
- Physicians want payors to provide reimbursement for efficiently practicing medicine (a driver for this cycle).

> The need for decision support systems to help physicians improve use and interpretation of tests was highlighted in a recent study of US medical records by the Centre for Health Systems and Safety Research, at the University of New South Wales. The investigators found that doctors in the United States fail to follow up as many as 62% of clinical pathology laboratory tests and up to 35% of radiology reports. This means that they are missing critical diagnoses. In turn, this causes delays in treatments for many conditions, including cancer.[16]

These complementary cycles provide a unique opportunity for a paradigm shift in how molecular diagnostics are developed, approved, reimbursed, and continually studied. Molecular diagnostics are particularly poorly suited to CED and Fee-For-Service (FFS) reimbursement and are particularly well suited to an alternative process and pay-for-performance reimbursement (Figure 4).

	CED and FFS	Alternative Process and PFV
Stages of Development		
Design…likely to continually morph as more data is collected	Fixed set of experiments using a fixed protocol	Let the biomarker set morph and guide physicians in the use of the evolving results
Approval…likely to be required for many very similar variations	Granted or not granted based on the protocol	Remove the concept of approval for molecular diagnostics. The physician makes informed decisions about the appropriateness of a diagnostic given the indicators and available data
Reimbursement…values are likely to be strongly contested—high value results	Reimbursed or not, regardless of appropriateness of the test	Reimbursed on a sliding scale if treatment is altered.
Additional indications … likely to be discovered as more data is collected	Additional studies need to be funded and undertaken	The developer can promote use of the diagnostic, by assuming varying amounts of the risk associated with the cost
Interested parties	**Incentivized to:**	**Incentivized to:**
Developers	Have the diagnostic ordered as much as possible	Have the diagnostic ordered only where it might alter the course of treatment
Payors	Not prescribe the diagnostic because it might not alter the course of treatment	Have the diagnostic ordered whenever the physician believes it will alter treatment
Physicians	Limit access to diagnostics; difficulty in getting coverage for their patients	Prescribe any diagnostic and provided with all available data to make an informed decision

Figure 4: Comparing the status quo (CED and FFS) to an alternative process based on PFV from the perspective of development of a diagnostic and each of the interested parties.

The key elements that allow molecular diagnostics to advance from series of static stages of development to the more fluid market-driven cycle described in Figure 4 are risk sharing and data exchange. The end result should be a model that allows the agile refinement of practice guidelines that efficiently optimize healthcare.

Shared Risk

Risk sharing for medical coverage is a relatively new concept. After Johnson & Johnson received a coverage rejection in 2006 for its multiple myeloma agent, Velcade, from the UK's National Institute of Health & Clinical Excellence (NICE), it proposed the Velcade Response Scheme.[17] This scheme essentially placed the payment burden back on the developer in cases where the therapy was ineffective. About the same time, Genomic Health

launched Onco*type*DX. This molecular diagnostic for the determination of recurrent invasive breast cancer in estrogen receptor positive and lymph node negative women, had significant validation, but lacked clinical utility data. Lee Newcomer at United Healthcare led an effort with Genomic Health to develop a risk sharing model for Onco*type*DX.

An important aspect of risk sharing as it applies to molecular diagnostics involves managing risk through decision support tools (discussed below). Both the ordering of diagnostics (e.g., when to use a molecular diagnostic, which specific analytes should be tested) and the interpretation of results are complex. As part of sharing risk, payors must collaborate with diagnostic providers to ensure they can provide correct guidance for physicians so that the right tests are ordered at the right time and so that the right treatment decisions result.

There are two important notes about risk sharing, a relatively labor-intensive methodology. First, risk sharing is not being proposed as a primary, long-term solution, but rather a model that allows clinical utility data to be accumulated while providing appropriate remuneration in the dynamic molecular diagnostics market. Second, to avoid the complexities of risk sharing but still allow for some non-covered procedures, a pre-authorization process is sometimes used. While pre-authorization does avoid some complexities it is highly inefficient, time-consuming, and can significantly increase costs.[18]

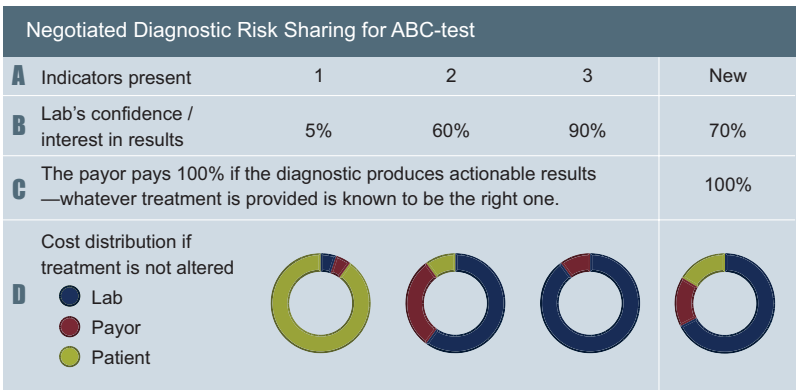

Figure 5: Hypothetical negotiated diagnostic risk sharing. Provider expresses its confidence in its test, guiding coverage and cost distribution.

As an example of how a risk sharing model might work, assume a hypothetical diagnostic, ABC-test (Figure 5). The risk sharing model is based on the idea that the lab should be paid (see the Considerations for Reimbursement section) if the diagnostic produces actionable results. ABC-test has three indicators, each with equal prognostic weight (row A). The lab, using its own data, expresses the risk it is willing to take that the diagnostic will produce actionable results (row B). If the lab is highly confident that the diagnostic will produce actionable results, it

could make this percentage high—effectively saying that if the diagnostic fails to produce actionable results, the lab will absorb the cost. This confidence level can then be used by payors to make a coverage determination (row D).

For ABC-test:

- **For one indication**, the diagnostic provider has very low confidence that the diagnostic will alter treatment. It expresses this by indicating that if the test does not alter the course of treatment, it will only absorb 5% of the cost—a clear signal from the lab to the payor that the test should not be covered in this case.
  - The payor will likely follow the lab's guidance and not provide coverage for the test in this case.
  - The physician and patient can then determine if they feel the test will be beneficial, knowing that the patient will likely be responsible for the bill.
- **For three indications**, the diagnostic provider is confident (90%) that the diagnostic will alter the standard treatment. It expresses this by indicating that if the test does not alter the course of treatment, it will absorb 90% of the cost—a clear signal from the lab to the payor that the test should be covered.
  - The payor will likely follow the lab's guidance and provide coverage; the lab has already placed a large bet on the test altering the course of treatment.
  - The physician and patient have high confidence that the payor and diagnostic provider believe the diagnostic is appropriate and one of them will cover the cost.
- **For a new indication**, one for which the diagnostic provider thinks the test might be useful but lacks clinical utility data; the lab can also place a bet. The extent to which the lab wants the data and believes that its diagnostic can alter treatment is expressed by the risk it is willing to take.
  - The payor will likely follow the lab's guidance. If the lab has high confidence in the diagnostic's ability to alter treatment, the payor will probably cover the diagnostic—either it alters treatment (good for the payor; although it will pay for the diagnostic, it will get a better outcome) or it does not (good for the payor, since the lab will absorb most of the cost).
  - The physician and the patient have a confidence level in the diagnostic informed by the willingness of the lab and payor to cover the cost.

- The lab must only be held accountable for these pricing mechanisms if the physician has followed criteria that have been agreed to between the payor and the lab for appropriate patient selection, timing of use of test along care continuum, and treatment guidelines.

It is through this coverage determination that payors must incentivize providers to design appropriate practice guidelines, and incentivize physicians to use new and emerging technologies appropriately. In order for this balance to work fairly, payors must:

- Compel test providers to develop appropriate protocols that clearly demonstrate where and how these tests should be used in the continuum of diagnosis and care;
- Work with providers to facilitate the educational process and to set policies that encourage appropriate and effective use, and discourage less effective, often older, modalities (e.g., limits on number of IHC stains prior to a molecular alternative being mandated);
- Provide mechanisms to measure the effectiveness of these protocols. As an example, Aetna is involved in a program with eviti Inc., to provide participating Aetna oncologists in two states with access to eviti's evidence-based decision support tool.[19]

Together, payors, physicians, and laboratories hold the key to ensuring optimal ordering of new diagnostics.

DATA EXCHANGE SUPPORTS AN OUTCOMES-DRIVEN REIMBURSEMENT MODEL

Data exchange involves 1) the collection of data, 2) a repository in which the data is federated, and 3) the expert analysis and formulation of the data into decision support tools for physicians guiding the ordering of molecular diagnostics and the interpretation of the results. The current regulatory environment forces diagnostic providers to be passive purveyors of tests, not involved in the discipline of their ordering. This forced separation results in the Office of the Inspector General (OIG) preventing the free flow of data between the needed parties. The CED process does not support, and by failing to create an enabling mechanism effectively prohibits, this data exchange.

Data Collection

The collection of data would need to include outcomes, phenotypes exhibited or indicators observed, and specific biomarkers and methodologies. Outcomes, in reference to diagnostics, are probably better referred to as actionable results. Unlike therapeutics, where outcomes (quality of life, survival rate, etc.) may not be known for years, the "outcomes" of most diagnostics are known within days—the physician reads the report, and either takes the same action s/he would have without the diagnostic, or takes a different action. An incentive system must be put in place, potentially as part of the final laboratory report, where reimbursement is tied to improved stratification or diagnosis, prognosis, monitoring or predicting response.

Data Repository

Currently, physicians struggle to keep abreast of the subtle differences between similar diagnostics and then to ensure they are correctly interpreting and acting on them. Developers attempt to collect data about the set of conditions that led to the diagnostic's prescription and the set of actions taken as a result of the diagnostic. Payors struggle to understand the correct ordering of diagnostics and if the diagnostic impacted the course of treatment. Driven by the need for coverage, diagnostic providers are opting-in to Palmetto's MolDx program (PTI codes), the McKesson Z-Codes, and other registry systems. These systems provide a promising beta test for how such registry systems might work (e.g., they provide the additional specificity that was lacking from code stacks), but they also identified a new challenge by being so specific that they prevent variants of the diagnostic from easily being ordered or reimbursed. If during the course of use, a clinically useful biomarker variant is identified, current registry systems set up the variant as a new diagnostic rather than creating a branch. Additionally, the current systems may suffer from a perceived lack of independence needed to be a universal, impartial "single source of truth." This may result in some diagnostic providers being somewhat reticent to contribute the desired level of data needed to optimize healthcare decisions: 1) indications and decision support leading to diagnostic ordering and 2) results and decision support to guide results interpretation.

The National Institutes of Health (NIH) has created the Genetic Testing Registry (GTR)[20] and ClinVar[21] to aggregate test-related information. GTR provides

detailed information about the purpose of the test and the indications (primarily diagnoses) leading to use. ClinVar aggregates information about sequence variation and its relationship to health. Together, these two data resources can provide the foundation for a collaborative, easy to use and impartial repository, with the caveat that the data in any repository is inherently limited by the honesty of the submitters. A solution to facilitate the free exchange of data may be relatively close.

The GTR accumulates clinical utility statements and citations for individual tests and curates professional practice guidelines, position statements, and recommendations. A results database, maintained by the developer, could utilize the GTR to refer to accessioned tests that explicitly describe the diagnostic.

With versioning, changes in biomarkers or methodologies—or other factors—could be delineated clearly for an evolving test and would enable the reporting of outcomes to continue. The GTR currently allows physicians to see a list of molecular diagnostics; view information about validity, proficiency testing, and utility; understand the appropriate use cases (phenotypes/indications); and access a wide variety of resources (relevant trials/studies, molecular details, drug labeling related to companion diagnostics). Developers of diagnostics could also be required to provide a feedback/reporting mechanism as a condition of coverage. HIT vendors would utilize the public, open source data to provide content for optimizing ordering and reporting through EMRs, CPOEs, PMS, etc. The foundation for the proposed paradigm shift in diagnostic prescription, development, and reimbursement is predicated upon the free exchange of data. Physicians must provide data to developers so developers can provide effective decision support tools that allow payors to know diagnostics are being prescribed and interpreted correctly, and payors, in turn, will provide coverage for the diagnostic the physician wants to prescribe. The payor's role must shift from simply paying the bills, to strategically investing in (covering the cost of) diagnostics.

Decision Support

Diagnostic developers—labs—have the most complete information about when to order their diagnostics and how the results should be interpreted. To

ensure physicians have the best possible information, the burden of creating and providing decision support should be placed with the diagnostic provider. An appropriate risk sharing model can ensure that labs provide unbiased information. Registry information will facilitate the timely refinement of such decision support and the eventual establishment of practice guidelines.

Figure 6 shows a highly simplified example of decision support for ordering the hypothetical molecular diagnostic, ABC-test. The data in the table is a summary of physician-reported utilization and treatment decisions. In this example there are again three established indicators, each with equal prognostic weight, and one new, relatively unutilized indicator. Additionally, treatment in this case is assumed to be binary (altered or unaltered), when in practice, there is likely to be a sliding scale as to the extent treatment has been altered. These data, combined with the payors' current coverage decision, allows the physician, with the patient, to make an informed decision about the appropriateness of the diagnostic.

Indicators Present	# of Prescriptions	Altered Treatment
1	100	25%
2	200	32%
3	390	80%
New	10	90%
Total	700	410

Figure 6: ABC-Test decision support for ordering. Empirical data to guide physicians in prescribing the diagnostic and to set payment ratios.

The second critical aspect to a decision support system for molecular diagnostics is the results decision support. Figure 7 shows a highly simplified example of decision support for interpreting the results from ABC-test. The data in the table is a summary of physician reported results and treatment decisions. In this example there are three sets of biomarkers observed, the number of cases each set was observed and the percentage of those cases where treatment was altered. Again, treatment is assumed to be binary. Importantly, the data also includes a physician retrospective—does the physician feel s/he made the right decision. The higher percentage of physicians that feel they made the

Biomarkers Matched	# of Patients	Altered Treatment	Physician Retrospective Altered	Unaltered
50%	300	33%	(n=99) 50% Yes	(n=201) 50% Yes
70%	250	68%	(n=170) 80% Yes	(n=80) 30% Yes
90%	150	94%	(n=141) 90% Yes	(n=9) 20% Yes
Total	700	410		

Figure 7: ABC-Test results decision support. Empirical data guides physician in selecting a treatment.

right decision based on the results of the diagnostic further validates the decision support tool. This data quickly and easily provides physicians with the latest utilization data.

Ideally, a data exchange system supporting data collection, curation, and decision support could be implemented that would allow coverage decisions for new molecular diagnostics with little or no regulation/oversight.

Take Advantage of the Shift Toward Pay for Value (PFV) Instead of Fee For Service (FFS)

As shown in Figure 8, Fee for Service (FFS), the most prevalent reimbursement model in the US healthcare system, is projected to rapidly give way to Pay for Value[22] (PFV). The change is being driven by the exploding costs of health care and is being enabled by the relative ease of data sharing. An FFS system is simpler than a PFV system; under FFS, a service (checkup, diagnostic, treatment) is provided and payment is rendered, whereas PFV requires a feedback loop to determine payment. This feedback loop is a challenge because it requires all parties to use more data; physicians, diagnostic providers, and payors need to consider it.

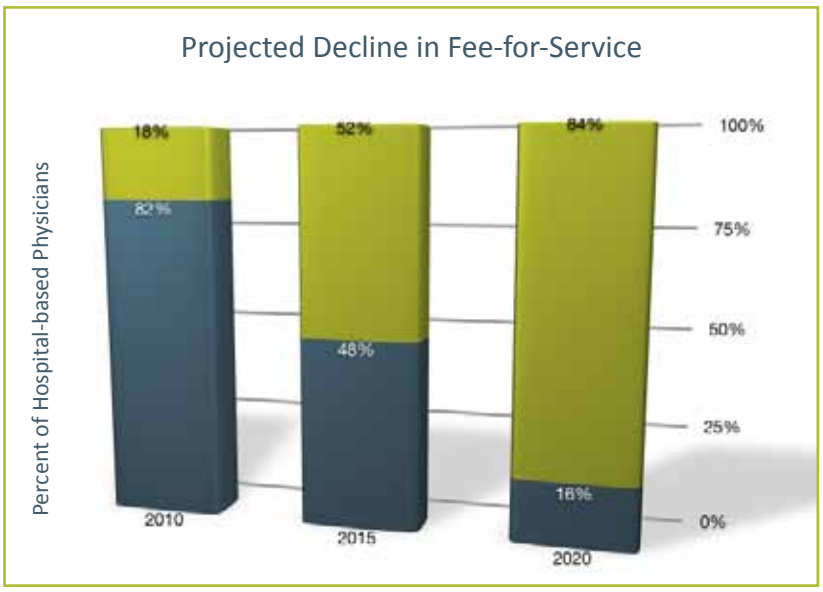

Figure 8: Fee-for-service reimbursement models are expected to be rapidly replaced over the next decade by pay-for-value models.[22]

The processes already in place for molecular diagnostics reimbursement allow for a limited PFV system. As part of the negotiation between developers and payors, conditions for reporting use patterns can be established directly, tying coverage to correct use of the diagnostic. These conditions are almost always part of the CED process while clinical utility is being demonstrated, but do not have to be limited to that process; they can be required after clinical utility has been established. Extending reporting after the demonstration of clinical utility

would allow for the collection of additional data about similar variations on approved use conditions.

CONSIDERATIONS FOR REIMBURSEMENT RATES

In simple terms, there should be a sliding scale for payment responsibility. A test that has little impact on the course of treatment, arguably has little value, and should be reimbursed at a correspondingly low rate. Similarly, a test that significantly alters the course of treatment (compared to without the test) has significant value and should be reimbursed at a correspondingly higher rate (Figure 9). Of course payment for medical services is not this simple and straightforward.

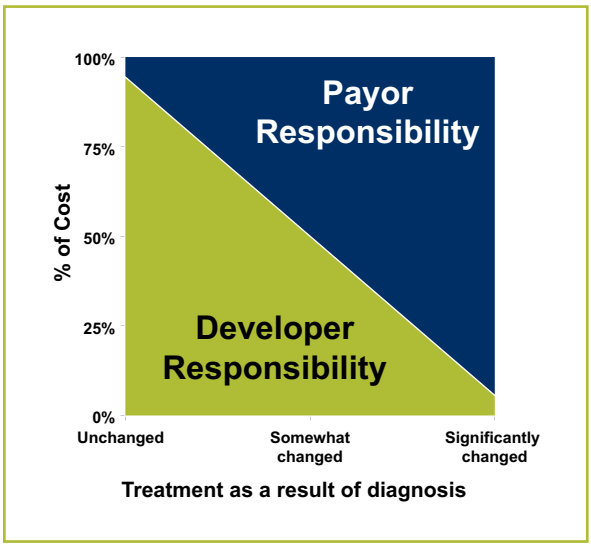

Figure 9: A sliding scale of cost responsibility based on "actionability" of results.

Assuming a philosophy of shared risk/payment for molecular diagnostics based on the degree to which the diagnostic altered the course of treatment, there is still the core question, "What is an appropriate price for a test?" To begin answering this question, look to the analyte being measured (Figure 10).

If the key analytes or sequences being studied by a new diagnostic are new, it is important to understand if there is a similar diagnostic for the same indicated use (different gene, identical condition). If there is a similar diagnostic, with less sensitivity or specificity for the identical condition (traditional PSA vs. ultra-sensitive PSA, CTID vs. IHC), then the new diagnostic should be reimbursed incrementally more than the existing, less sensitive, diagnostic. The reimbursement uptick should be based on the relative superiority of the new diagnostic over its predecessor. If the new analyte is equal to or no better than the existing diagnostic they both should be reimbursed at a discount as they are commodities.

If there is no similar diagnostic for the condition, then the impact on the standard of care must be determined. The new diagnostic should be reimbursed at a rate appropriate for the value it delivers. When the clinical utility is anticipated but not proven, the diagnostic initially should be reimbursed at cost plus, until

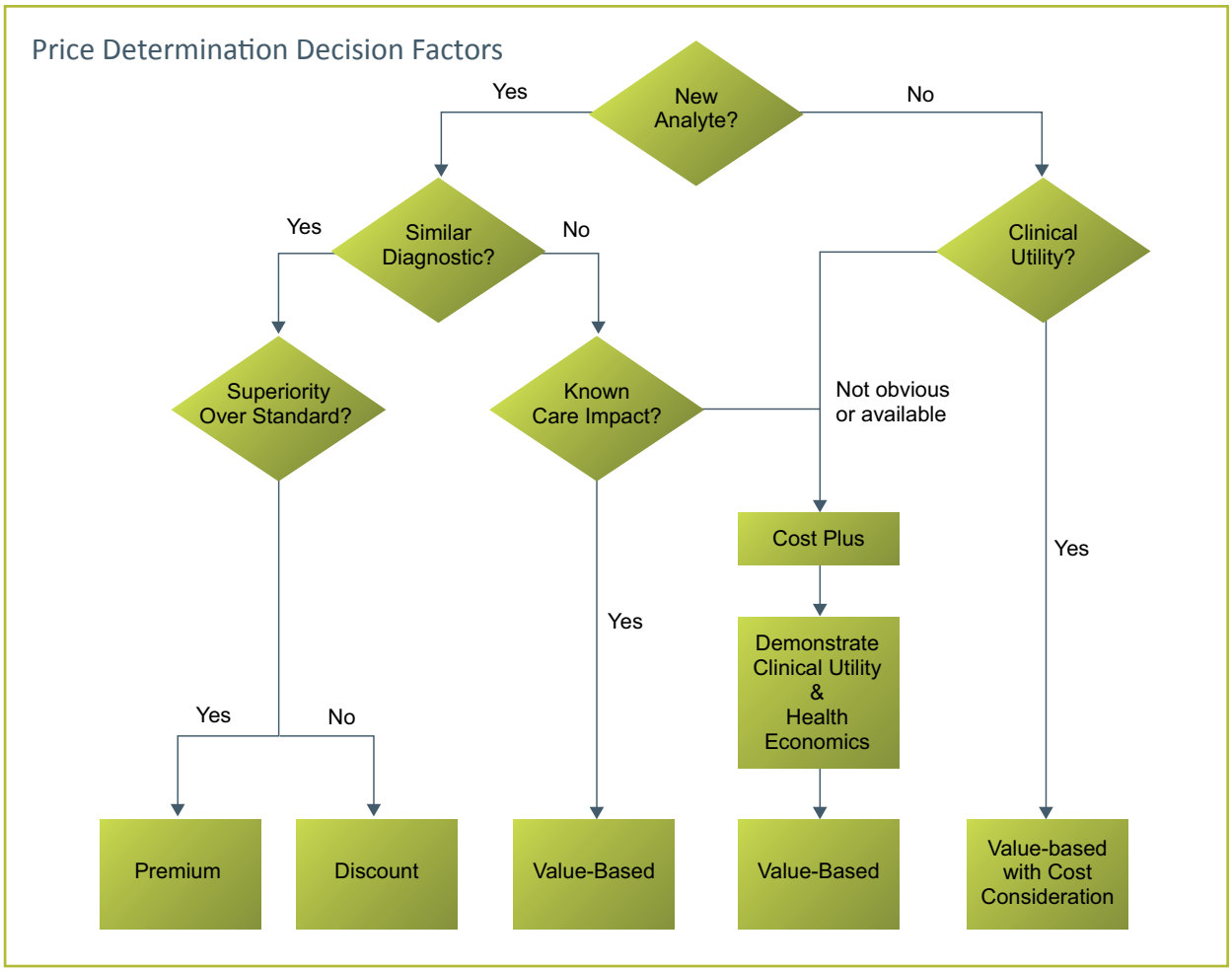

Figure 10: Proposed price determination decision methodology for an analyte.

clinical utility and overall health economic value is determined. At this time the test should be reimbursed based on its value. There are a number of established methods for determining the value of specific diagnostics that should be used.[23, 24]

Finally, if the analyte being studied is not new, or clinical utility of the existing diagnostic is not obvious or available, the reimbursement rate is essentially cost-plus—there is no justification for anything else. If the clinical utility is known, then a value-based price with cost consideration would be appropriate.

CONCLUSION

For gradually evolving science, therapies and medical equipment that can jeopardize the health and well-being of the patient, the more cautious and lengthy process of a CED may provide an excellent scientific validation assuring that payor resources are not wasted on ineffective treatments.[25] However, in the fast-paced world of molecular diagnostics, the very controls that make CED so effective become a hindrance for the development of a diagnostic that can protect against the misapplication of a therapy. The rigid testing protocols, long testing periods, and the de facto use of CED as a means for private payors to avoid coverage, all make the current and formally proposed changes to CED a roadblock to the development of new molecular diagnostics. Just as is the case with software development and analysis of big data, a new, faster, more dynamic process is needed to ensure that CMS remains a leader in outcomes-based medicine and fulfills the meaning of the National Bioeconomy Blueprint.

A more efficient process providing the speed and agility demanded by patients and physicians, the real-world utilization data needed by laboratories, and the cost assuredness demanded by payors is possible for molecular diagnostics by relying on:

- A risk-sharing, market-driven, pricing structure;
- The free exchange of data including collection, an unbiased repository, and decision support; and
- The healthcare-wide push for pay for value business model.

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