

Clinical Utility or Impossibility? Addressing the Molecular Diagnostics Health Technology Assessment and Reimbursement Conundrum

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1. Introduction and Purpose

Payers, providers, and policy makers in the United States currently face the daunting reality of integrating a rising tide of emerging health technologies into a U.S. health system fraught with quality and cost challenges. At the crest of this wave are emerging molecular diagnostics and targeted treatments, which promise increasingly personalized health care, more efficient and cost-effective health delivery approaches, and improved health outcomes. However, the extent to which personalized medicine approaches can offer succor to our health system depends upon our ability to address a variety of clinical translation, education, health system infrastructure, and policy challenges.

Appropriately applied diagnostic information, adherence to evidence-based best practices, efficient health care information management and improved incentive structures arguably hold the greatest potential to enhance health care reform efforts in the U.S. Use of in vitro diagnostic test information has been estimated to inform approximately 60 percent to 70 percent of all health decisions in the U.S. (while representing approximately 3 percent to 5 percent of hospital health expenditures), and is viewed as a foundation element of good clinical decision-making and patient care.¹ Where test results are clear and actionable, diagnostics may also play a key role in rational cost management by improving treatment decisions and health outcomes, and avoiding wastage of finite health resources.

Targeting diagnosis and treatment is especially important given the looming financial realities associated with the U.S. health system. Recently we have experienced double-digit increases in annual insurance premiums and overall health expenditures are anticipated to double in under a decade.^{2,3,4} Expansion of biologics and specialty pharmacy products whose cost can exceed \$10,000 per month and emerging complex diagnostics with price ranges approaching \$4,000 per test, increasingly place pressure on health stakeholder budgets and raise complex questions about patient access and aggregate affordability.^{5,6,7} Such trends in health spending, viewed as largely unsustainable, have increasingly forced payers, providers, employers, and patients to explore less costly means for achieving high-quality care in an affordable and sustainable manner. Greater emphasis on smarter and more tar-

geted personalized health care will prominently factor into health care reform objectives as we rethink health care delivery in the 21st century.

Despite the potential for molecular diagnostics to enable patient care and cost efficiencies, overcoming existing barriers to diagnostics development, use, and payment will be necessary to fully realize the promise of personalized medicine. Key barriers have been well characterized and include the following:^{8,9,10}

- Lack of clarity and agreement on evidentiary requirements that support coverage of new diagnostics
- Reliance upon antiquated and inefficient coding systems that have not kept pace with technology advancement
- Limited evidence supporting the value of diagnostic tests due to existing regulatory requirements and insufficient incentives for evidence development
- Payment levels for diagnostic tests that do not adequately reflect the value and role of diagnostics in health decision making and care management
- Decentralized and “mosaic” payment systems for health technologies and procedures
- Focus on “sickness care” instead of health prevention and wellness
- Payer concerns regarding the impacts and costs of emerging complex molecular tests
- Limited provider and patient education on use of molecular tests to inform care decisions

Of these barriers, lack of consensus regarding appropriate evidence requirements for diagnostics coverage and ability to obtain value-based reimbursement remain key obstacles to realizing the promise of personalized medicine. While payers increasingly demand more extensive evidence of the value of new diagnostics (particularly when premium payment is expected), manufacturers are reluctant to invest in developing this evidence without clearer indications that return on investment (ROI) will support these additional expenditures. Until clearer “rules of the road” for health technology assessment (HTA) and reimbursement of new gene-based diagnostics are appropriately aligned to value and incentives for innovation, molecular diagnostics will remain in a push-pull conundrum that inhibits translation of personalized medicine into practice.

This paper characterizes current U.S. commercial

payer evidence requirements and decision processes related to HTA, coverage, and utilization management of emerging molecular diagnostics and their implications for innovation, treatment access, and progress towards personalized health care. Source data were generated by a limited 2008 Internet-based survey conducted by the Genomics Biotech Institute (GBI) of the National Association of Managed Care Physicians (NAMCP) member medical directors. This survey was conducted with input from the Personalized Healthcare Initiative of the U.S. Department of Health and Human Services (HHS) to inform ongoing efforts to rationally integrate personalized health practices into managed care. Findings and conclusions focus on addressing the HTA and reimbursement conundrum that remains a substantive limiting factor for emerging molecular diagnostics

2. Methods

The GBI was established in 2003 as an institute of the NAMCP. The NAMCP represents more than 5,500 organizational members and 15,000 corporate and individual members, including medical and pharmacy directors, health system administrators and providers, employers, manufacturers, and other health decision makers involved in U.S. managed care medicine. The mission of GBI is to bring these key stakeholders together to consider the implications of genomics, biotechnology, and other emerging health technologies for improving patient outcomes and health care delivery.

The survey was randomly disseminated to 674 NAMCP members and 58 total responses were obtained. Of the total respondents, 26 identified themselves as medical directors at commercial managed care organizations (MCOs) and 32 identified themselves as medical directors of health system and provider organizations (e.g., academic medical centers, hospital and other health systems, large physician practices). The sample also included payer decision makers from leading U.S. MCOs (i.e., Aetna, Cigna, WellPoint, United Healthcare), which collectively represent more than 115 million covered lives in the U.S. To better characterize findings, survey data were augmented with in-person interviews with U.S. managed care medical or pharmacy benefit directors.

Limitations of this analysis may include respondent bias, as it was not possible to determine whether respondents held a particular interest in personalized medicine and/or are early adopters. Based on the limited number of respondents, survey findings may not be fully representative of U.S. medical and pharmacy director perspectives, but do point to trends in payer and provider views on personalized medicine and uptake of the products of this growing field.

3. MCO Processes for Evaluating Molecular Diagnostics

Historically, the vast majority of in vitro diagnostic (IVD) tests (i.e., tests conducted outside of the body using blood, saliva, urine or other samples) have been of little concern to managed care organizations (MCOs). In the aggregate, diagnostics are thought to represent only around 2 percent to 5 percent of aggregate provider health expenditures, and as such have faced less payer scrutiny compared to more costly in vivo imaging tests, biopharmaceuticals, medical devices, and procedures.¹⁰ In fact, many payers are limited in their ability to track diagnostic utilization via claims given the non-specific and somewhat archaic nature of diagnostics U.S. coding systems required for test billing. Because of this, many payers have not yet invested in development of the explicit HTA practices, decision criteria, and utilization metrics for diagnostics that have long been applied to drugs and biologics. As a result, evaluation of diagnostics is currently conducted in a highly variable manner by U.S. commercial MCOs.

In recent years, following sequencing of the human genome and other scientific advancements, complex molecular diagnostics have begun to emerge which break the “conventional mold” of payment for diagnostics (generally ranging in the \$10s to low \$100s), with new test prices in the \$1,000s. This departure from lower cost “commodity-priced” tests is due to several factors, including: our ability to leverage new knowledge of genomics and biomarkers; and the complexity and cost of performing complex gene sequencing tests, expression arrays and multiplex testing.

Challenges of New Diagnostics for MCOs

Despite their promise, the higher pricing of some complex molecular tests has stimulated concern from the U.S. payer community. Emergence of new higher cost tests such as OncoType Dx (Genomic Health), AlloMap (XDx), and ChemoFX (Precision Therapeutics) have helped placed diagnostics “on the radar screen” of many payers.¹¹ This awareness is predominately related to concern that a flood of tests that command similar price points is eminent given the commercial success of some of these tests, despite their potential value for treatment decision making. Depending upon their utilization, our survey indicates that payers anticipate that costly innovator molecular tests are poised to have a greater budgetary impact on health expenditures than simpler predecessor diagnostics (irrespective of the validity of this perspective). As such, complex molecular tests are likely be increasingly subject to more rigorous risk/benefit assessments and coverage constraints.

Further, because existing current procedural ter-

minology (CPT) codes are not associated with payment rates that cover the costs of many emerging tests, a small number of test providers are considering direct-to-payer contracting strategies and novel approaches to demonstrate the clinical and economic value of their molecular tests. Some of these strategies, albeit limited in number, have been reasonably successful and stimulated other test developers to pursue similar approaches. However it is currently unclear whether MCOs will face an expanding barrage of complex costly diagnostics in the coming years. There are early signs that some emerging molecular diagnostics (e.g., tests for warfarin dosing) will not uniformly command the high relative prices of outlier diagnostic tests and prices will lower over time based on “free market economics” and competitive pressures.¹²

Payers are also faced with complicated scenarios where decisions must be made on patient claims for new tests well before HTAs by leading groups such as the Agency for Health Care Research and Quality (AHRQ) and the Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC) are available. In the absence of explicit decision criteria to support diagnostic HTA, decisions regarding diagnostic tests may be inconsistent and result in suboptimal patient access to beneficial tests.

Payers, HTA groups and government efforts such as Evaluation of Genomic Applications in Practice and Prevention (EGAPP) program of the Centers for Disease Control and Prevention (CDC) are beginning the move towards evidence expectations, HTA processes, decision criteria, and management practices that consider the unique attributes of diagnostics and implications for personalized health practice.^{13,14} Recent attention to U.S. evidence expectations for diagnostics by the Centers for Medicare and Medicaid Services in two MedCAC meetings in 2009 are illustrative of the growing interest in characterizing the role of diagnostics in a time of unprecedented U.S. health reform. U.S. commercial public and commercial payers are also beginning to apply management controls to some expensive tests similar to those applied to costly biopharmaceuticals (e.g., prior authorization, step therapy, utilization reviews).¹⁵ These trends effectively “raise the bar” for new test evaluation and reimbursement as payers seek to better characterize the value that beneficiaries will receive relative to the costs of testing to the health plan.

Challenges of Evolving Evidence Requirements for Diagnostic Test Providers

While payers have always sought information on the clinical and economic value of new health technologies, the growing pressure to demonstrate outcomes-oriented value is a relatively new pressure for the diag-

nostics and clinical laboratory industries. In the past, the vast majority of in vitro and in vivo diagnostics clinical studies were geared towards demonstrating the sensitivity, specificity, and predictive value of tests. From this information, stakeholders could indirectly infer the potential for changes in patient management (e.g., treatment selection, differential dosing) and consequent implications for patient health outcomes.

As evidence-based medicine (EBM) concepts have become broadly accepted over the past 10-15 years, payers and their HTA agencies increasingly seek direct evidence of the impact of technology use on health outcomes, as demonstrated by rigorous clinical trials and observational studies. During this time, payers and HTA agencies have developed preferences for evidence from randomized controlled trials (RCTs) versus other study types (e.g., prospective and retrospective observational studies) that are more subject to bias and confounding effects but potentially less externally valid. Additionally, evolution of EBM approaches have more proportionally centered on characterizing the value of treatments, which has inadvertently resulted in what appears to be a “single yardstick” perspective of HTA that often ignores technology type and application, intended use and practical factors related to evidence development and commercialization of some technologies (e.g., alignment of the specific evidence questions that we are trying to answer with expectations for the appropriate study designs to answer those questions).

These trends in EBM and HTA have resulted in expectations by some payer decision makers for “Cadillac evidence” versus focus on evidence that is minimally reasonable and sufficient for sound decision-making. At this juncture it is important for those at the vanguard of evidence based medicine to carefully distinguish “got to have” vs. “nice to know” evidence expectations for diagnostics (or different types of diagnostics) and set standards accordingly. This is not to say that diagnostics should be held to lesser evidence standards than other technologies, only that evidence expectations for diagnostics have not yet been appropriately agreed upon and may not appropriately take into account practical realities of evidence generation specific to this technology type. On the other hand, it is clear that the evidence supporting some available diagnostic tests could be improved to better characterize value to the individual and society. Striking the right balance between ‘minimally burdensome’ and “necessary and sufficient” evidence development approaches will be important to rational assessment and uptake of diagnostics going forward.

As discussed, compared to drugs and biologics, diagnostics-focused EBM approaches are “early stage” and inconsistently applied in practice. A number of practical reasons

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Exhibit 1: Key Factors that Differentiate Diagnostics, Devices and Drugs/Biologics

Evaluation Factor	Diagnostic (IVD)	Device	Drug or Biologic
Operator skill may influence outcomes	H	H	L
Influence of multiple practitioners	H	H	L
Iterative development during clinical studies	L	H	L
Post-approval maintenance costs	L	H	L
Subject to risk-based market classification for regulatory approval	H	H	L
Sample size	L/I	L	H
Feasibility of blinding or placebo controls	Depends	L	H
Length of product life cycles	L	L	H
Realized patent protection	L/I	L	H
Follow-on products have regulatory requirements similar to innovator	L	L	I
Traditional evidence hierarchy approaches "fit"	L	L	I

Source: Faulkner E, Richner R, Goodman C. Evidence hierarchies chapter. Medical devices and diagnostics outcomes research: issues and good research practices. International Society of Pharmacoeconomics and Outcomes Research. Publication in progress.

why generation of RCT-based evidence can be impractical (or in some cases impossible) for diagnostics includes but is not limited to the following:¹⁶ limited return on investment potential versus drugs, limited ability to set value-based prices, limited realized intellectual property protection, and difficulties in implementing controls or blinding applied to drugs. Exhibit 1 indicates some of the key differences between diagnostics, devices, and drugs to further illustrate these challenges.

Further, because diagnostics do not have similarly robust profit margins compared to many treatments, opportunities for innovation must be balanced carefully against the financial realities of developing diagnostics. Due to uncertain evidence expectations and reimbursement potential, diagnostics manufacturers may be reluctant or unable to support the same types of large, costly clinical trials historically funded by the pharmaceutical industry. Additionally, expectations for randomization across all or the most relevant treatment scenarios would result in large and comprehensive studies where trial costs may not balance against the value of obtaining direct evidence of improved health outcomes. This is particularly true in circumstances in scenarios where indirect evidence assessment or data modeling approaches may be sufficient to address payer value questions with reasonable certainty to inform decision-making. However, payer acceptance of indirect evidence and modeling approaches is highly variable at present and universally accepted criteria and methods for diagnostics and personalized medicine have not yet emerged.

Of the drivers required to stimulate greater investment in diagnostics evidence generation, (a) clearer and more consistent evidence requirements, and (b) improved opportunities to capture value-based reimbursement for diagnostics would most markedly improve manufacturer incentives to produce tests, based on findings of this survey and recent diagnostics policy reports.^{17,18,19}

The Current Foundation for Payer Value Assessment and Decision-Making

The current foundation for payer value assessment, coverage, and payment of new diagnostics currently juxtaposes the availability of evidence against the evidence that payers consider ideal. Because much of the diagnostics literature has historically centered on accuracy, predictive value, and (sometimes) change in patient management instead of health outcomes, payers and HTA agencies often find the evaluation of diagnostics challenging. This section explores payer perspectives on availability and use of diagnostics information.

Sources of Information Used to Inform Payer Decision-Making:

The GBI survey asked health plan medical directors to indicate which sources of information payers consider most pertinent to diagnostics health technology assessment. Exhibit 2 indicates the primary sources of evidence that U.S. payer respondents currently rely upon to assess the reimbursement potential of new diagnostic technologies.

Not surprisingly, peer-reviewed journal articles rank highly with 58 percent of respondents looking to

Exhibit 2: Sources of Evidence that US Payers Rely Upon to Assess the Reimbursement Potential of Diagnostics

Resource	Most Important (%)
Hayes, Inc technology Assessments	62
Peer-reviewed journal articles	58
BCBS Technology Evaluation Center technology assessments	54
CMS decisions	47
Other private managed care coverage policies	31
AHRQ technology assessments	23
USPSTF technology assessments	23
Cochrane systematic reviews or other systematic reviews	23
ECRI technology assessments	23
Professional society opinions/positions	12
EGAPP diagnostics assessments	4
NICE recommendations	0

Source: 2008 National Association of Managed Care Physicians Member Survey.
Payer responses: n = 26.

primary data to assess the value of new tests. However, because payers also operate in the “age of information overload,” they also currently seek out synthesized secondary data reviews of existing bodies of evidence (e.g., systematic reviews and meta-analyses) to draw conclusions about the safety, effectiveness (or cost-effectiveness), and value of new health products.

The Agency for Health Care Research and Quality (AHRQ) and the BCBS TEC are the closest thing to national HTA bodies existing in the U.S., as compared to national HTA bodies for single-payer health systems such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. Despite the recognized role and value of these U.S. resources for HTA, these groups were less frequently cited as information sources for diagnostics assessment by payer respondents (23 percent and 54 percent respectively) than one might anticipate. This may have occurred because (a) these groups do not evaluate in vitro diagnostics technologies with the same frequency as other technologies, (b) some payers may be unfamiliar with these sources of information or (c) these groups are not structured/empowered to make direct coverage recommendations in same manner as other global HTA groups.²⁰

In addition, the U.S. Preventive Services Task Force (USPSTF) is well recognized for producing rigorous HTAs of screening diagnostics, but U.S. commercial MCOs often look to Medicare coverage policies to inform their own coverage decisions on screening tests instead of acting upon USPSTF reports as they emerge. Another government-affiliated source of diagnostics

HTA, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) supported by the U.S. Centers for Disease Control and Prevention (CDC), is at present rarely used by payer respondents (<5 percent), primarily because this group is newly established and the number of tests assessed to date is comparatively limited.

Survey results indicated that the most frequently used source of HTAs on diagnostics (62 percent) is Hayes, Inc, a commercial organization that develops assessments for the U.S. payer community. One of the main reasons that respondents cited use of Hayes is that this organization can provide HTAs of reasonably high quality more rapidly than government or government-associated HTA organizations and in a format customized to the needs of payer decision makers. This may indicate that while methodological rigor is important to payers, timeliness and presentation of information in a “top-line,” actionable, and recommendation-oriented format are equally valuable to payer decision-making. As HTA agency processes for diagnostics evaluation continue to evolve, it will be important that evidence evaluation deliverables evolve in tandem to meet public and private payer information needs and support timely decision-making.

U.S. MCOs also rely on the decisions of other payers to inform their own reimbursement recommendations. The most influential of U.S. payer coverage decisions are those determined by the largest U.S. payer, the Centers of Medicare and Medicaid Services (CMS), with almost 50 percent of survey respondents acknowledging use of CMS policies to inform their own decisions. Alternatively, the polic-

Exhibit 3: US Payer Evidence Requirements for Assessing the Reimbursement Potential of Diagnostics

Factor	Important to know (%)	Got to Have (%)
Test Performance (sensitivity, specificity, predictive value)	100	50
Safety	0.4	–
Clinical validity/clinical usefulness	15	70
Δ in patient management/actionable results	58	70
Clinical utility (Δ in patient outcomes)	27	4
Cost/cost offsets	15	–
Comparative Effectiveness	0.4	–
Cost-effectiveness	0.8	–

es of other leading U.S. MCOs (e.g., Aetna, Cigna, Humana, United Healthcare, WellPoint) were cited by just more than 30 percent of respondents (where policies are made publicly available). This leveraging of existing payer coverage policies in decision making for new diagnostics is also a sound reason for increasing clarity or consistency of diagnostics criteria, particularly considering the broad influence of CMS policies on commercial MCO decision-making.

Current Evidentiary Foundation for Decision-Making

While historically evidence of analytical validity (i.e., evidence that the test detects what it is purported to)²¹ has been sufficient to inform diagnostics coverage decisions, payers are increasingly interested in evidence of clinical validity (i.e., accuracy with which a test predicts the presence or absence of a clinical condition or predisposition) and clinical utility (i.e., evidence that use of test information improves health outcomes). Many payers often cite evidence of improvement of health outcomes as a key criterion in rendering diagnostics reimbursement decisions, indicating that evidence of clinical utility is essential to diagnostics coverage, even though this information is not always available in practice.

Given this stated preference for evidence supporting diagnostics, it is important to question how payers currently define clinical utility, a term that is largely specific to diagnostics evidence evaluation. Is this a term that is widely accepted in the payer community or one limited to diagnostics industry and evidence-based medicine experts? When asked to define clinical utility, the majority of payer respondents (62 percent) actually describe clinical validity. This variable payer understanding of terminology used in evidence-based assessments for diagnostics supports the need to educate U.S. health decision makers re-

garding diagnostics and improve the consistent acceptance of language used to characterize the value of diagnostics. Variable acceptance and understanding of the “language of diagnostics” has the potential to inhibit advancement of personalized medicine by setting up misaligned expectations for clinical trial design, investment, and evidence requirements for diagnostics reimbursement.

The GBI survey responses also indicate that most payer decisions today are based on evidence of analytical and clinical validity, but not clinical utility. Exhibit 3 identifies key evidence factors that U.S. payers cited as ‘important to know’ vs. ‘got to have’ when assessing coverage and payment of diagnostics. Of the 26 payer respondents, 70 percent indicated that evidence of clinical usefulness and beneficial changes in patient management are the most critical ‘got to have’ evidence factors. This result runs contrary to stated payer preferences for evidence that technology use improves health outcomes. In fact, only 4 percent of respondents actually cited requirements for direct evidence that use of a test improves health outcomes, although 27 percent of respondents indicated that it would be important to see such evidence.

Reasons for the disparity between ideal versus accepted payer evidence requirements to support reimbursement of diagnostics could be: (a) lack of clarity around diagnostics evidence terminology, (b) the fact that direct evidence of the clinical utility of diagnostics may be unavailable or (c) payer recognition that the evidence-base for diagnostics is proportionally weighted towards studies of accuracy and predictive value. It is uncertain why responses regarding test performance in the “important to know” vs. “got to have” categories differs so significantly, unless payers presume that this evidence is a minimum requirement to characterize the value of diagnostics.

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Survey findings also indicate that evidence of sensitivity, specificity, and predictive value is minimally sufficient to secure coverage. Going forward, test manufacturers will need to demonstrate stronger proof linking test use to beneficial changes in patient management and clinical utility (either directly or indirectly) to improve the odds of securing reimbursement.

A small percentage of payer respondents (15 percent) indicated that they would like to see evidence that use of a test has the potential to reduce downstream costs and health resource utilization. Virtually no payer respondents currently reported requiring evidence of comparative- or cost-effectiveness. Such indicators of product value are not explicitly required by public and private payers in the U.S. at present, although payers have always considered the comparative benefit of new technologies versus the standard of care. Recently, influential groups such as the Medicare Payment and Advisory Commission (MedPAC), the office the Assistant Secretary for Planning and Evaluation (ASPE) and the U.S. Congress have considered the potential integration of comparative- and cost-effectiveness into health care reform efforts. Following upon such policy discussions, the 2009 stimulus package signed by President Obama dedicates \$1.1B towards comparative effectiveness research. However, the extent to which funding would focus on molecular diagnostics and personalized medicine remains unclear.²²

Given the methodological and financial challenges associated with diagnostics development, integration of comparative or economic evidence requirements for diagnostics should be tempered by realization of real world limitations of test development under the current U.S. health system. This especially includes lack of clarity surrounding evidentiary requirements and limited potential to secure value-based reimbursement. Additionally, comparative effectiveness requirements that may emerge for diagnostics should incorporate practical complicating factors including comparator selection challenges (e.g., comparison of IVD vs. imaging tests) and lack of comparators in some testing situations.

Emphasis on New Processes and Metrics for Diagnostics Evaluation

Despite recent payer concerns regarding the expansion of molecular diagnostics, only 7.6 percent of payer respondents have currently developed explicit metrics to evaluate the value of diagnostics. Of the payer organizations that have developed special approaches for diagnostics, the most often cited tools are inclusion of clinical experts and/or additional peer-review when conducting diagnostics HTA and rendering coverage decisions. However, some large U.S. commercial health plans did indicate that explicit diagnostics re-

view processes were being considered, which could have marked implications on market access and reimbursement for diagnostics in the U.S.

While no explicit evidence criteria or diagnostics evaluation methodologies were described by survey respondents, some payer respondents suggested that development of uniformly accepted criteria or metrics for diagnostics evaluation would be beneficial (particularly if originating from an authoritative group like CMS or the Blue Cross Blue Shield Association). Clearer and more broadly accepted criteria and metrics would also better enable test manufacturers to evaluate the risks associated with new test development efforts more accurately and consistently.

Few payer respondents (23 percent) indicated that they currently employ different criteria when evaluating FDA approved “kit tests” versus non-FDA approved laboratory developed tests whose reproducibility is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). However, some payer respondents did note that non-FDA approved tests (i.e., laboratory developed tests) are often subject to heightened payer scrutiny of clinical effectiveness, safety, and value, since these characteristics are not currently covered under CLIA requirements. Payer respondents also noted that this two-fold pathway for U.S. diagnostics regulatory approval (i.e., FDA and CLIA) can result in inconsistent development of evidence to inform reimbursement decisions for new tests and may represent safety risks and suboptimal population-level decision making.

The recent IVD Multivariate Index Array (IVD-MIA) draft guidance issued by FDA has attempted to further crystallize requirements for complex molecular tests, routing many that would have previously followed a CLIA approval pathway into the FDA review process.²³ While this guidance has the potential improve the consistency of regulatory test review for some complex tests, it has faced significant resistance because it would functionally raise evidence hurdles for some laboratory-developed tests.

4. Role of Health Decision Makers in Evaluating Molecular Diagnostics

Recognizing that payment for health services, including molecular diagnostics, is the responsibility of multiple stakeholders in the U.S. health supply chain, HHS also hoped to better characterize role that key decision makers should play in evaluating molecular diagnostics. The survey asked respondents about three of the key stakeholder groups that influence diagnostics coverage and access and what role each group could play in diagnostic test evaluation:

- MCO medical and pharmacy directors that render reimbursement decisions and are responsible for

Exhibit 4: Role of Key Health Decision Makers in Evaluating Molecular Diagnostics

Decision Maker Category	Percentage of Payers Indicating that the Decision Maker Plays a Key Role	Range of Responsibilities
Health plan medical and pharmacy directors	79.4%	<ul style="list-style-type: none"> • Primary role in HTA and evaluating clinical value of new health technology • Serve as clinical advisors to providers and patients within the framework of the plan • Develop and enforce coverage policies and manage beneficiary access • Final decision maker on beneficiary claims
Pharmacy benefit management companies	22.4%	<ul style="list-style-type: none"> • Play an advisory role for technologies covered under the pharmacy benefit • Contribute to HTA in scenarios where drug use is governed by diagnostic test results
Employers and employer coalitions	52.4%	<ul style="list-style-type: none"> • Influence inclusion or exclusion of new health technologies or technology types based upon perceived cost-benefit tradeoffs • Influence the scope and nature of diagnostics coverage policies enacted by the contracting health plan(s) • Challenge medical or pharmacy director's denial of claims involving diagnostics in exceptional situations

Source: 2008 National Association of Managed Care Physicians Member Survey. Payer and provider responses: n = 58

management of public and private health plans

- Pharmacy benefit management (PBM) organizations that provide benefit management services to health plans, and
- Employers or employer coalitions that are ultimately responsible for payment of health services.

Exhibit 4 provides aggregate responses to this question and indicates (a) what percentage of payer respondents perceive that these stakeholders have a role in new test evaluation and (b) what the scope and nature of this role should be.

As might be expected, the majority of respondents (~80 percent) perceive that commercial and public payers play a primary role in evaluating diagnostics and informing decisions regarding test access and reimbursement. Further, because payers serve as key gatekeepers to technology access in the U.S., payer acceptance of new diagnostics is strongly associated with market adoption by providers and patients, particularly in the case of emerging complex molecular diagnostics. This would suggest that development of HTA

methodologies and decision metrics for diagnostics and personalized medicine should have significant focus on meeting on payer information and education needs.

As aggregate cost and utilization management of new specialty pharmacy products becomes increasingly challenging and with many new market entrants are on the horizon, almost 25 percent of respondents believe that PBMs can also play a significant role in diagnostics evaluation. Leading PBMs such as Medco, CVS Caremark, and others are working towards evolving unique capabilities in this area given: (a) their broad access to treatment and cost data and (b) their relationships with smaller MCOs that do not have similar resources to leading commercial health plans (e.g., WellPoint, United Healthcare). In addition, more than 50 percent of payer respondents indicated that large employers and employer coalitions of smaller employers (a) have significant influence over health care purchasing decisions and (b) play a key role in determining access requirements for molecular diagnostics and personalized medicine

technologies based on perceived benefits and funding limitations.

As real world applications of personalized medicine continue to expand and enter mainstream medicine, the role of payers, benefit management companies and employer groups is likely to expand and become increasingly sophisticated in the coming years. Other key decision makers that will play a significant role in uptake of molecular diagnostics and personalized medicine applications include government policy makers, medical and other specialty societies, clinicians, and patients (particularly given recent emphasis on healthcare cost shifting). Strong collaboration and communication among these stakeholders will be necessary to ensure appropriate adoption and balanced risk/benefit tradeoffs for all participants in evolving personalized health practice.¹⁹

6. Conclusions

At a time when health technologies increasingly fall under the microscope of health care reform, it will be important to: (a) move towards a common understanding of the methodological and practical challenges associated with diagnostics evidence development and test evaluation, (b) balance stakeholder information requirements against “real world” development challenges to ensure access to safe and effective personalized medicine products, (c) determine the potential of personalized medicine products to improve quality and cost of care on a case-by-case basis, and (d) characterize the practical and business implications of personalized health practice.

As explicit evidence standards and HTA criteria for molecular diagnostics and personalized medicine continue to evolve, this survey suggests several considerations important to their successful and rational integration into practice. These include the following:

1. Pursue Solutions-Focused Collaborative Engagement

Our increasing ability to refine diagnosis and treatment decisions based upon biomarker information presents U.S. health decision makers with a new host of opportunities and challenges. Although diagnostics and personalized medicine approaches promise more efficient and cost-effective health decision-making, not every technology will yield the same level of benefit and some may in fact be cost additive or unnecessarily limit access to beneficial medications if not integrated properly.

Several influential groups, including the Institute of Medicine (IOM), the President’s Council of Advisors on Science and Technology (PCAST), the Secretary’s Advisory Council on Genetics, Health and Society (SACGHS), and the Lewin Group have recently illuminated key challenges, opportunities and action steps necessary to better address integration of

molecular diagnostics and personalized medicine into the fabric of U.S. health care. However, action on these items has been rather limited in light of broader health reform initiatives in the U.S. While diagnostics and personalized medicine will not ameliorate all of our health system quality and cost challenges, greater emphasis in this area will be important to realizing future paradigms of health care delivery. It is now time to build upon past lessons and pursue a practical architecture of workable solutions for molecular diagnostics and personalized medicine.

Because integration of increasingly personalized health care practices is complex and affects many areas of care delivery, collaborative multi-stakeholder approaches will be necessary for rational integration. Single stakeholder or government-only decision processes that do not account for the practical business realities of moving towards personalized health care are unlikely to result in practical or tenable outcomes for other key stakeholders. Input from payers, providers, patients, and technology manufacturers will help ensure that adopted approaches improve quality and cost of care, are financially viable, and support continued innovation.

2. Create a Roadmap for Diagnostics to Guide Evidence Development

While existing tools of evidence-based medicine (e.g., criteria for evaluating the strength of study design and susceptibility to confounding effects) can be applied to diagnostics evaluation, current employment of these tools does not generally take into account the unique attributes and methodological challenges associated with molecular diagnostics. Development of an ‘evidence roadmap’ for diagnostics which aligns test application (e.g., screening, diagnosis, prognosis, monitoring) and key decision criteria would be a useful step towards improving the clarity and consistency of diagnostics assessment. Clarifying and evolving appropriate evidence standards for diagnostics would also help ensure that manufacturers, payers and policy makers are “working from the same playbook” and have defined “rules of the road” for diagnostics evidence development. While several groups are considering differential EBM practices for diagnostics, no single approach has yet emerged as standard in the U.S. Replicating these efforts may provide little tangible benefit for diagnostics EBM, but critically evaluating similarities and differences among existing approaches and/or HHS-supported efforts to identify consensus approaches would be a useful step forward.

A universally acceptable “evidence roadmap” should extend beyond current attempts and appropriately link the key types of evidence questions associated with diagnostics and the most likely and rational

study designs necessary to answer these questions. A diagnostics evidence roadmap should also focus on development of “sufficient” evidence for rational decision making instead of “ideal” or “best” evidence approaches that may extend beyond reasonable characterization of test value without considering the value or costs of obtaining the information and/or its relevance to “real world” decision making. On the other hand, evidence standards must also be robust enough to satisfy payer decision makers and ensure that introduction of new tests into the treatment continuum does not result in unanticipated adverse effects or unnecessary access barriers.

3. Employ HTA Practices That Reflect the Unique Attributes of Diagnostics

Arriving at universally accepted EBM practices for diagnostics is only one step towards resolving the molecular diagnostics technology assessment and reimbursement conundrum. Improving consistency of HTA practices for diagnostics is also important for rational integration of diagnostics and personalized medicine into practice. At present, HTA approaches for diagnostics are variable, but appear to fall into two broad categories: (a) minor modifications of EBM practices currently applied to drugs and biologics (i.e., adaptations of “RCT only” approaches), and (b) hybrid EBM approaches that account for some study design and methodological issues inherent to diagnostics. Neither of these “approaches” fully incorporate evidence issues specific to technology type and account for “real world” considerations relevant to value assessment and use of diagnostics.

Even when leading U.S. evidence evaluation groups do try to take diagnostics-specific factors into account, there is often significant variability in their approaches. This is primarily because there is presently no standard approach for assessing diagnostics or consensus regarding appropriate evidence expectations. Process heterogeneity can result in variable technology assessment outcomes, patient access to testing and ability to employ the information from diagnostics for patient treatment or management decisions. This is not to say that HTA outcomes associated with other technologies should not vary among evaluators, only that the range of HTA variability appears to be more erratic for molecular diagnostics compared to other health technologies and implications for coverage policy development and access are less consistent.

Improved clarity and consistency of HTA practices for diagnostics and personalized medicine would be an important step towards improving integration of beneficial tests into U.S. personalized health care practice. HTA practices should take into consideration the intended application of the test in practice

and scale expectations for value demonstration accordingly.

Payers and HTA organizations must also consider the potential impact of the test in the context of care. When particularly costly molecular diagnostics in the \$2,000–\$4,000 range entered the market in the early 21st century, many payers were concerned that the majority of future tests would be similarly costly and require greater management oversight than ever before. However, in practice only a small fraction of the hundreds of available clinical diagnostic tests, perhaps less than 1 percent, command such high payment rates and many available molecular tests fall in the range of \$150–\$500. Assuming the value case for a particular test is clear and safety is not a concern, one critical question is how much effort should a health plan medical director managing a multi-billion dollar health plan expend to evaluate and track a \$250 molecular diagnostic? What are the risks of not doing so? These questions are particularly pertinent when test information informs use of a \$20,000–\$50,000 per year drug or similarly costly surgical procedure. While tests in the U.S. are not explicitly assessed based on economic factors, the potential of diagnostic information to influence downstream resource use is not inconsequential.

In cases where use molecular diagnostics is a requirement of treatment selection or use, one must consider the rarity of the biomarker(s) in the target patient population. For such personalized medicine scenarios, the number of patients that must be tested to find one applicable patient and cost of the test must be balanced against the incremental value of targeted treatment use vs. broader or standard of care treatment approaches. In cases where the biomarker is exceedingly rare and/or reflects a small proportion of the treatable patient population, the cost of achieving improved benefits in such populations may exceed overall cost and quality benefits associated with standard of care approaches. One the other hand, if a test informs efficient treatment use in a significant portion of the patient population, as in the case of KRAS testing and use of panitumumab²⁴, other applications of personalized medicine appear to be obvious and cost-effective. Because of such scenarios, it may be reasonable to consider top-line economic implications of personalized medicine along with the clinical factors typically considered in US HTA.

In addition, because of the rapid nature of test entry in the U.S. market, application of horizon scanning and rapid HTA mechanisms for diagnostics may help to identify and focus HTA resources on high impact tests. This would also help address scenarios where patient claims for new diagnostics outstrip the health

plan's ability to evaluate the test and render appropriate coverage decisions. Such a function could be coordinated on a national level by the AHRQ Evidence-based Practice Center (EPC) program or the EGAPP working group of CDC.

4. Evaluate Options to Bring U.S. Diagnostics Reimbursement into the 21st Century

Aside from methodological challenges relevant to diagnostics and personalized medicine technologies, reform of diagnostics reimbursement approaches has been cited as a key action step by many government advisory groups.^{25,26,27} This is an important but long overlooked component of the diagnostics technology assessment conundrum.

As discussed previously, payment for diagnostics in the U.S. is complex, involving an a la carte menu of codes to describe key test elements (e.g., polymerase chain reaction, DNA sequencing, DNA expression analysis, multiplex testing), each with an individual payment amount. Additionally, diagnostics payment has historically been marginal versus other health technologies and the category is frequently treated as a commodity, irrespective of the fundamental importance of diagnostic information to health care decision-making. Compared to the biopharmaceutical industry, the vast majority diagnostics have little pricing latitude, are highly subject to price erosion, have limited realized patent protection and yield a marginal ROI. As such, diagnostics manufacturers have comparatively limited budgets for product development and limited ability to pursue certain evidence development activities or absorb losses in the absence of value-based reimbursement.

Unless reimbursement mechanisms in the U.S. change to better reflect the value of diagnostics, it is unlikely that diagnostics manufacturers will be able to pursue the gambit of evidence development activities that have evolved as standard business practices of their drug industry counterparts. As evidence requirements for diagnostics continue to mature, if evidence development and reimbursement incentives are misaligned, technology uptake and evolution in molecular diagnostics and personalized medicine will remain suboptimal. In scenarios where reimbursement falls well short of increasing payer evidence requirements for securing reimbursement for diagnostics, some test developers may forgo innovation altogether. Policy development efforts must carefully balance evidence requirements and reimbursement realities if advancement of molecular diagnostics and personalized medicine is important to the U.S. health reform agenda.

Future Considerations for HHS

As the U.S. Department of Health and Human Services (HHS) is engaged to address various aspects of

health care reform, more efficient use of molecular diagnostics and personalized medicine approaches can play a role in achieving overall quality improvement and cost containment objectives. Short-term investment in these technologies also paves the way for realization of a longer-term vision of improved health care processes and outcomes via broader application of biomarker inform and increasingly personalized health care delivery. To fully realize this promise, HHS can play a key role in addressing elements of the diagnostics evidence-based medicine and reimbursement conundrum that currently limits uptake and use of potentially transformative technologies. By bringing key stakeholders together in solutions-focused activities to address evaluation, reimbursement, policymaking and rational uptake of molecular diagnostics and personalized medicine, HHS can expedite the translation of these technologies from research into practice. **JMCM**

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