ADVANCED DIAGNOSTICS: Innovation, Reimbursement, And Coverage Challenges

Developers of novel advanced diagnostics face many challenges that dramatically constrain both innovation and the ability to provide new tests to clinicians and patients. Will planned changes in pricing detailed in the Protecting Access to Medicare Act of 2014 and new guidelines on evidence development make a difference?

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- Innovation in diagnostics is poorly protected and innovators cannot be certain they will reap the benefits of their efforts.
- Pricing of in vitro diagnostics in the US has historically been set on a cost rather than value basis, making it difficult for innovators to capture a fair share of the value they create.
- The demand for evidence required prior to providing coverage for many of these advanced tests is often unrealistic or inadequately thought out.
- Planned changes in pricing detailed in the Protecting Access to Medicare Act of 2014, and new guidelines on evidence development may address some of these challenges.

Advances in in vitro diagnostic testing have had a large and positive impact on the provision of health care over the past 15 years. This has been particularly apparent in oncology, starting in 1998 when **Genentech Inc.** launched its blockbuster treatment for HER2 positive breast cancer, *Herceptin* (trastuzumab). The development, approval, and launch of Herceptin occurred in conjunction with a companion test developed by **Abbott Laboratories Inc.**'s **Abbott Diagnostics**, and represented the first of a growing class of oncology drugs with companion diagnostics. Similarly, molecular prognostic tests such as **Myriad Genetic Inc.**'s *BRACAnalysis* test for BRCA1 and BRCA2 mutations can identify women at significantly elevated risk for developing breast or ovarian cancer, enabling at-risk women to consider medical management including more frequent monitoring procedures or risk-reducing surgery, when appropriate. **Genomic Health Inc.**'s *Oncotype DX* test helps guide treatment decisions by predicting the benefit of chemotherapy and the likelihood of recurrence.

Advances in diagnostics such as these are not limited exclusively to oncology. For example, noninvasive prenatal testing now allows at-risk expectant mothers to test for chromosomal abnormalities in the fetus by analyzing fetal DNA in a maternal blood sample. This advance promises over time to greatly reduce the use of more invasive and higher risk amniocentesis.

These selected examples of diagnostics-enabled improvements in health care could be viewed as evidence that innovation in advanced diagnostics – that is, those that use novel technology, biomarkers, or informatics to enhance clinical decision-making and ultimately patient outcomes – is flourishing and proceeding at a healthy pace. Unfortunately, that is far from the truth. Developers of these novel tests face many challenges that dramatically constrain both innovation and the ability to provide new tests to clinicians and patients. Three of these

challenges stand out in particular. First, innovation in diagnostics is poorly protected and innovators cannot be certain they will reap the benefits of their efforts. Second, pricing of in vitro diagnostics in the United States has historically been set on a cost rather than value basis. This makes it difficult, and often impossible, for innovators to capture a fair share of the value they create, and has the perverse effect of favoring more complex – therefore, higher cost – tests over simpler tests. And third, the demand for evidence required prior to providing coverage for many of these advanced tests is often unrealistic or inadequately thought out, particularly in light of the first two challenges.

These three issues are not new – solutions have often been hotly debated. A lack of consensus, as well as conflicting interests, have made it difficult for the industry to rally behind broad-based solutions. Recently, planned changes in pricing detailed in the Protecting Access to Medicare Act of 2014 (signed on April 1, 2014), and new guidelines such as the MolDX Clinical Test Evaluation Process (September 2014) from Centers for Medicare and Medicaid Services (CMS) contractor Palmetto GBA LLC on evidence development have been put forward and in some cases adopted.

Below we discuss the three core issues in more detail, and provide our thoughts on how, and whether, these recent changes will help.

CONSEQUENCES OF UNPROTECTED INNOVATION

Advances in in vitro diagnostics face a very different regulatory environment than do pharmaceuticals. While arguably more flexible than that for pharmaceuticals, including potentially lower investment requirements for approval, this environment affords innovators much less protection from me-too competitors than pharmaceuticals. For incremental improvements to the range of simple, well-understood tests used routinely in medical practice, the existing framework may well be appropriate. However, for advanced diagnostics that require substantial up-front investment in areas such as biomarker identification, test development, demonstration of test validity, and ultimately, proof of clinical utility, this lack of protection is limiting both the flow of investment funds and test development activity.

Intellectual Property

In theory patents can provide some of the desired protection; in practice, however, that is rarely the case. Relatively few patented technologies in this market have offered strong protection to the innovator. Attempts to patent markers such as genes, notably the patents held by Myriad on BRCA1 and BRCA2, have been invalidated by the US Supreme Court (Association for Molecular Pathology et al. v. Myriad Genetics Inc., et al.). The result is an environment where "me-too" tests can and do come to market quite quickly. This market does not operate analogously to the patent protection and market exclusivity model of pharmaceuticals.

Coding

Interestingly, the coding of diagnostic tests impedes the innovator's ability to protect its work. Historically, obtaining a CPT code for a new test has been a time-intensive process, often taking years. In the interim, assuming a test provider is able to obtain coverage for its test, generic codes generally are used that describe process steps (e.g., sample preparation, PCR amplification). The result is a code "stack" that provides little if any visibility into what test is being conducted, let alone the supplier of that test, should there be alternatives. Once a CPT code is obtained, it is generally not specific to a particular kit manufacturer or laboratory – any manufacturer or lab with a valid test is free to use that code. For payors and providers it is therefore difficult to discern who is providing a given test or whether material differences worth considering exist across providers. In effect, an innovator that gains coverage for a test with a new CPT code paves the way for competitors to rapidly follow.

Commercialization

The existence of multiple regulatory paths to market for diagnostic tests further complicates the situation. For example, an innovator, whether a manufacturer of an FDA-cleared test through a pre-market approval process (PMA) or a CLIA lab developing a novel laboratory developed test (LDT), can face competition from other CLIA-certified labs developing their own "home-brews" or LDTs. Because these tests bill with the same code, these laboratories can in effect free-ride on the development efforts of the original innovator. Thus, regardless of which regulatory path the original innovator selects, competitors have accessible, relatively straightforward paths to follow.

An example of this dynamic occurs with the companion diagnostic tests used to qualify patients to receive specific drugs, notably cancer therapeutics. These tests, which must go through a PMA approval process, have been subject to replication by individual CLIA-approved laboratories, reducing the market available to the diagnostic innovators. Innovators suggest that a substantial share of the market for certain cancer companion diagnostics has been taken by LDTs. The FDA notified Congress in July of its intent to publish an oversight framework for LDTs. The proposed framework is expected to include some form of pre-market approval for higher-risk tests such as those that compete with approved companion diagnostics. The exact timing of this guidance is unclear, but when it is put in place it will likely impact competition in companion diagnostics.

It is worth noting that we do not view the existence of multiple regulatory pathways as a problem in and of itself. Although the topic has been hotly debated, there are strong arguments in favor of maintaining both forms of regulatory clearance. What is at issue is the ability to sufficiently protect innovations, regardless of the regulatory pathway, such that these innovations are pursued and brought to market.

The Protecting Access to Medicare Act of 2014 suggests additional changes are coming to the coding process. By 2016, CMS will be required to adopt temporary HCPCS codes to identify new advanced diagnostic tests. These HCPCS codes will be unique to a specific manufacturer or laboratory. In theory, this should put an end to the practice of code stacking for new tests and provide greater clarity to payors. In the case of companion diagnostics, this requirement should enable payors to discriminate between the FDA-approved tests as they appear on drug labels, and alternative LDTs (or other FDA-approved tests). While this will not ensure market share for the innovator or provide for a period of exclusivity, it will likely require specific evidence of test performance from competing tests.

This particular change to coding requirements is a partial solution at best. If these coding changes are carefully and appropri-

ately implemented by CMS and adopted by payors, both of which are substantial open questions, they can have the effect of encouraging innovation in diagnostics.

CHANGING FROM COST-BASED TO MARKET-BASED REIMBURSEMENT

In vitro diagnostics have long faced a challenging reimbursement environment in the US. This is particularly true with regard to new tests requiring investment in novel science. Specifically, in vitro diagnostics of all types have been subject to a cost-based reimbursement system implemented by CMS. This system has historically provided the basis by which all reimbursement is set, with private payors keying their payments to the CMS schedule, plus or minus a percentage. As discussed above, this system has the perverse effect of correlating reimbursement amounts with the complexity of a test rather than its value. Prices for new tests are typically "cross-walked" from other tests that are deemed to have similar complexity. An alternative process, "gap-fill," is rarely used but still closely tied to costs rather than value.

For older, more commoditized diagnostic tests, this reimbursement regime can cause CMS to overpay, as there is no clear mechanism in the process to allow for increased competition in test provision. More importantly, for new, advanced in vitro diagnostics, obtaining a "fair" reimbursement is challenging. Notwithstanding the case with a handful of highly reimbursed tests such as Genomic Health's Oncotype DX or Myriad's BRACAnalysis, most developers struggle to obtain what they perceive to be adequate reimbursement, resulting in the unintended consequence of further reducing the incentive for innovation.

Perhaps in recognition of these issues, the Protecting Access to Medicare Act of 2014 puts forward an alternative payment structure for advanced diagnostics. The new law requires policies to be implemented that will introduce a market-based mechanism for setting CMS reimbursement levels. Specifically, beginning on January 1, 2017 CMS will base reimbursement levels for new tests on an average of the prices realized from private payors. A similar mechanism has been in place for several years for infused and other non-retail drugs reimbursed under Medicare Part B. The consequences are significant not simply because a major customer (CMS) is shifting its reimbursement strategy but also because a publicly available cost-based benchmark is being removed from the market. All stakeholders will now have to consider appropriate reimbursement levels without having the CMS rate to rely upon. The effectiveness of this change will depend greatly on how CMS implements the new requirements, but it seems clear that for manufacturers and laboratories with the resources to demonstrate the value of their tests to private payors, the change will increase the incentive to develop value-creating innovations.

An interesting consequence of these changes is the impact on private payors and smaller laboratories. Payors will need to build the capability and capacity to evaluate the evidence for new advanced diagnostics and make decisions on appropriate reimbursement levels. Similarly, smaller labs providing LDTs with unique HCPCS codes (as described above) may need to make their individualized cases to payors in order to obtain coverage. Historically, such activities were primarily conducted by a smaller group of larger labs and innovators. It is also likely that test providers will see more variability in reimbursement levels and different payors evaluating evidence differently, as well as more price volatility as more evidence of a given test's value accumulates.

Looking forward, the new CMS rules will contribute to an environment in which more value-based innovation can be expected. While this may foster the development of more innovative and commercially successful diagnostics, it also raises the bar for all diagnostic developers, and smaller companies may find the future competitive environment more challenging as a result.

ONE TEST'S ODYSSEY: CANCER OF UNKNOWN ORIGIN

In recent years two companies have attempted to commercialize molecular diagnostic assays designed to provide clinicians improved information about cancers of unknown primary (CUP). The prognosis for CUP patients is particularly poor. Treatment options are limited as, by definition, patients present with metastatic disease, and because very little is known about the origin of the cancer. Both Pathwork Diagnostics Inc. and **Rosetta Genomics Ltd.** developed tests that use the molecular makeup of the cancer cells to provide insight on the cancer's origin.

Pathwork Diagnostics' test was cleared by the FDA in 2008 (for frozen samples) and again in 2010 (for formalin-fixed, paraffin-embedded samples). The company received a positive coverage determination from Medicare in 2011, but struggled to capture significant coverage in the private insurance market. It also struggled in most cases to achieve anything more than minimal reimbursement when the test was used. Pathwork Diagnostics had conducted a number of retrospective studies to demonstrate the economic value of its product, but in the end payors were not convinced of the test's clinical utility. The firm declared bankruptcy in April of 2013 and its assets were subsequently acquired by **Response Genetics Inc.** Rosetta Genomics appears to have experienced more success than Pathwork. It markets a similar product, and while its sales are relatively modest (approximately $550,000 in the first half of 2014), it is growing. Rosetta Genomics has Medicare and expanding commercial coverage.

We can't predict the ultimate success of Rosetta Genomics' test or Pathworks' test under new ownership. However, it seems reasonable that information on the origin of CUP patients' disease is of value to clinicians and patients. Perhaps greater clarity around clinical utility evidence requirements could accelerate adoption of such tests. Or perhaps more aggressive coverage with evidence development approaches should or could be employed. In any case, it is clear that the hurdles that new diagnostic tests need to scale after they are approved are quite high and opportunities to assess their ultimate value for patients and health care systems are consequently limited.

PROBLEMS CAUSED BY UNCLEAR EVIDENCE REQUIREMENTS

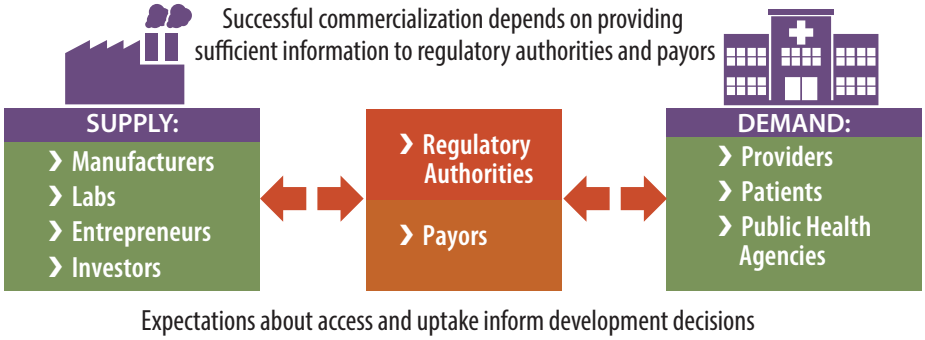
Providers of advanced in vitro diagnostics also face critical challenges with respect to obtaining coverage for their tests. Specifically, the demand for evidence of the clinical utility of these tests has been increasing. When available, the value of real-world data (e.g., retrospective analysis of the impact of a test based on usage in real-world clinical settings) is largely discounted in favor of prospective trials. Even small prospective studies, especially randomized controlled trials, are expensive. The issues discussed above make these expenditures difficult to justify.

For example, Palmetto GBA's *MolDX* program provides guidance on clinical utility evidence for molecular diagnostic tests. MolDX provides for six levels of evidence in its guidelines. However, any evidence package without at least one study at MolDX's level 2A or above is rejected without full clinical review. All study designs of level 2A or higher are prospective studies, making prospective trials a de facto requirement under these guidelines.

Moreover, there is poor guidance on and considerable confusion over how to design appropriate prospective studies for diagnostic tests. Too often, evidence and study requests from payors are framed from a pharmaceutical perspective, which fails to take into account that although all diagnostics provide additional information to a clinician that can impact treatment decisions, a diagnostic is not a medical intervention in and of itself and cannot be evaluated as such. This is not to suggest that the impact of advanced diagnostics cannot be substantial – the evidence to the contrary is clear. Nor are we suggesting that evidence of clinical utility is unimportant. Rather, evidence requirements must take into account the differences between diagnostics and interventional treatments. As noted by Ralph Riley, global leader for health economics and pricing at **Johnson & Johnson**'s **Janssen Diagnostics**, "The cost of establishing clinical utility may be the single most expensive part of test development. Applying therapeutic standards to the diagnostic space will preclude acceptable ROI for new diagnostics in the current payment environment."

Exhibit 1

Innovators Must Understand Gatekeeper's Needs



SOURCE: Analysis Group

The most obvious way to address the differences between diagnostics and interventions is to try to understand how treatment decisions change in the face of newly available diagnostic information. Such "treatment pattern" studies are enormously informative, but not necessarily easy to design. Often it is difficult to anticipate the many ways in which thoughtful clinicians can and will take advantage of new information. Studies therefore need to collect fairly broad treatment pattern data to ensure that unforeseen impacts are captured. Outcome-related endpoints such as survival or relapse rates are of course the outcomes of ultimate interest to both clinicians and payors. However, the cost of providing such data given the current economics of the diagnostics industry will be difficult or impossible to justify in many cases.

In addition to clinical utility studies, payors will continue to require evidence on the economic impact of these tests. Often, though not always, estimates of economic impact can be obtained from the clinical utility studies if they are appropriately designed.

Given the cost and risk associated with efforts to demonstrate clinical utility (*see sidebar, "One Test's Odyssey: Cancer Of Unknown Origin"*), diagnostic companies should communicate with key stakeholders including regulators, payors, and key opinion leaders early and often. Developing an early understanding of the likely evidence requirements for a developer's specific test is necessary to determine whether further investment is justified and to ensure that investment is not wasted on evidence that won't meet payors' needs. (*See Exhibit 1.*)

THE WAY FORWARD

Providing more individualized therapy to patients through the use of advanced diagnostics holds great promise for the future of medicine. The evolving environment for advanced diagnostics should ultimately facilitate greater innovation than the current regime. Rewarding innovation, providing pricing that appropriately reflects value, and creating standards for evidence requirements are all part of the solution. Though there are some indications of positive movement, other developments are less encouraging. Industry and policy makers will need to continue to work together to strike the right balance and ensure that the tremendous potential of advances in diagnostics are realized. IV

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