



A Molecular Diagnostic Perfect Storm: The Convergence of Regulatory & Reimbursement Forces that Threaten Patient Access to Innovations in Genomic Medicine

Selection of members of the 2014 Clinical Practice, Economic Affairs, and Professional Relations Committees of the Association for Molecular Pathology:

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Executive Summary & Recommendations:

The Human Genome Project was an international, collaborative research program whose goal was the complete mapping and understanding of all the human genes, which are collectively referred to as the "genome." The pioneering effort of the Human Genome Project and other genomic research generated extensive data about human DNA enabling scientists and clinicians to develop more powerful tools to study complex diseases. These diseases, such as cancer, diabetes, and cardiovascular disease constitute the majority of health problems in the United States. In his testimony before the U.S. House Subcommittee on Health, Committee on Energy and Commerce in May 2003, Francis Collins celebrated the successful conclusion of the Human Genome Project as "the true dawning of the genomic era," emphasizing that there "is an ongoing vital role for the federal government in enabling the future of genomics, and especially in applying it to benefit human health."¹

More than a decade later, researchers and medical professionals in universities, cancer centers, clinical laboratories, and pharmaceutical/manufacturing companies across the country have honored the public trust in the Human Genome Project by developing hundreds of innovative diagnostic tests and therapies that are advancing modern medicine in ways that would have been impossible without this breakthrough. Cancers treated like chronic illnesses, the causes of mysterious inherited conditions now identified, and rapid detection of emerging infectious diseases like Ebola and pandemic flu are just a few of the advances stemming from this investment. A recent example in the *New England Journal of Medicine* details the remarkable story of a cancer survivor whose life was prolonged beyond expectation solely based on the result of a laboratory developed procedure (LDP), and its therapeutic implications.² The case is a 57-year-old woman who was diagnosed with a highly aggressive and near-universally fatal type of metastatic thyroid cancer. Her doctors ordered an LDP called whole-exome sequencing, a technique similar to that used to complete the Human Genome Project. The DNA fingerprint revealed a mutation that rendered the tumor sensitive to a specific chemotherapy agent. After treatment, the patient was almost fully cancer free for 18 months, which is extraordinary in light of the typical prognosis of this type of tumor – a mere 5 months median survival. By using a procedure developed in a

molecular diagnostics laboratory based on the pioneering work of the Human Genome Project, this patient was able to live *disease free* for more than a year longer than expected.

However, the breakthroughs made possible by mapping the human genome are being endangered by government regulations which are threatening patient access to these truly revolutionary treatments. Unbeknownst to most patients, a storm is brewing in Washington that could significantly threaten development and coverage of these new tests. A long list of efforts by the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), the two federal agencies that claim oversight over laboratory developed procedures (LDPs), are at the heart of this brewing storm. On the one hand, the FDA recently announced that it intends to regulate LDPs requiring that laboratories submit applications for enormously expensive premarket review for thousands of LDPs if they wish to continue offering them to patients. Laboratories and the LDPs that they provide are already regulated by the Clinical Laboratory Improvement Amendments (CLIA) program at CMS, state health agencies, and third party federally recognized organizations. The FDA's new policies will effectively reformulate existing medical device regulations and consider healthcare providers as manufacturers, which will impose substantially new and duplicative requirements on clinical laboratories and hospitals. Of even greater concern, the FDA proposed policy could potentially stifle innovation by not allowing professionals the flexibility to improve and adapt already approved tests, essentially freezing outdated tests in time. Additionally, the FDA has recently issued a final guidance for "companion diagnostics," which are tests that are paired with a drug therapy. This guidance document restricts the development of these tests, in most circumstances, to a one test-one therapy model, and furthermore, requires that they are approved or cleared contemporaneously potentially limiting patient access to testing not developed in concert with a therapy.

Meanwhile, CMS who runs Medicare, the nation's largest insurer and whose actions are frequently mimicked in the private sector, has taken a heavy handed approach in denying coverage or reducing payment for many medically necessary molecular pathology tests. This has created a challenging environment for innovators to translate new genomic discoveries into clinical applications. For example, Medicare refused to pay for many molecular pathology tests during the first half of 2013. For certain commonly-utilized tests, such as cytogenomic arrays and Fragile X testing, which are important diagnostic tests for children with developmental delay, Medicare continues to deny coverage mistakenly believing that these tests are never appropriate for the Medicare beneficiary population.³ For example, adult males with previously undiagnosed Fragile X syndrome who develop tremor ataxia later in life, may be on Social Security disability, and therefore are Medicare beneficiaries. They are denied access to Fragile X testing to guide appropriate care management. Additionally, at least one of the Medicare Administrative Contractors (MACs), the companies that establish local coverage policies and process claims for Medicare, requires that laboratories that develop these innovative tests meet complex and costly mandates to secure reimbursement even for well-established diagnostics. These policies are jeopardizing the ability of even the largest laboratories to continue to provide innovative testing. Compounding these issues are a number of questions around overlapping requirements between the two agencies. Caught squarely in the middle are health care providers – those developing and delivering innovative treatments – and patients, who are the beneficiaries of this innovation.

While CMS and FDA officials have not publicly announced consolidation of laboratory testing as a goal, it does appear to be an inevitable outcome of the agencies' initiatives through their policy decisions. Significant reductions in the number of clinical laboratories offering molecular tests will have far-reaching negative effects for the healthcare system, including creating barriers to innovation, declining opportunities for specialized training regarding these complex tests, restricting direct interaction between molecular professionals and clinicians, and most importantly limiting patient access to medically necessary testing. Even more concerning, further encumbrances are around the corner as the reforms to payment under the Clinical Laboratory Fee Schedule (CLFS) newly enacted under the Protecting Access to Medicare Act (PAMA) are implemented in the next one to two years.

The Association for Molecular Pathology (AMP) is an international nonprofit medical society that has as its mission to advance the clinical practice, science, and excellence of molecular and genomic laboratory medicine through education, innovation, and advocacy to enable highest quality health care. Its members are board-certified pathologists, doctoral scientists and other laboratory medicine professionals who practice in the majority of clinical molecular diagnostics laboratories in the United States. They both develop and provide a professional interpretation for the novel, high quality molecular tests that are utilized daily in medical decision-making in all medical areas including cancer, infectious diseases, heritable disorders, and histocompatibility testing. Molecular pathology professionals are responsible for the design, validation, performance, and interpretation of the results associated with testing services provided by their laboratories. By closely monitoring every aspect of these important medical services, they have additional opportunities to promote patient safety, and therefore, are unlike any boxed and shipped medical devices including scalpels, artificial joints, or diagnostic kits, which are intended to be used by customers who are independent from the company that manufactured them.

In numerous papers, comment letters, and position statements, AMP has addressed the consequences of this gathering *perfect storm* of regulatory and reimbursement forces directed against molecular diagnostic testing with numerous recommendations designed to preserve patient access to appropriate testing and mitigate burgeoning negative impact on healthcare.

Recommendations:

1. Oversight for most laboratory developed procedures should remain at CMS under CLIA regulations, which should be modernized.
2. The FDA should eliminate the one test – one drug pair, approved or cleared in concert in the current companion diagnostics paradigm, which is unsustainable over time, and facilitate the utilization of additional diagnostics including multi-gene sequencing assays.
3. The FDA should use notice and comment rulemaking for substantive policy changes regarding LDPs, or at least conduct an economic impact study. In addition, draft guidance documents that fail to be finalized after a defined time limit should be withdrawn.
4. Regulator and payer policies should also reflect the contribution of molecular diagnostic laboratories to medical training and the necessary interaction between laboratory professionals and clinicians to support proper ordering and utilization of tests.

5. CMS should authorize payment for all claims previously filed using Tier 1 and Tier 2 molecular pathology CPT codes, retroactive to January 1, 2013, without requiring submission of an appeal for every claim unless a MAC has issued a Local Coverage Determination (LCD) for non-coverage that complies with existing regulatory requirements, including code-specific notice and comment.
6. When any new molecular pathology CPT codes are implemented, including those for multi-gene sequencing assays, the new CPT codes should share the same disposition of any other new Medicare service and should presumptively be covered. MACs should continue to have the authority and discretion to create exceptions, *i.e.*, non-coverage or limitation on coverage determinations, through the existing LCD process.
7. CMS should not establish a single MAC to make recommendations or administer pricing, coverage, and payment decisions as this will undermine the LCD process and render all such determinations National Coverage Determinations (NCD), thus skirting the NCD process.
8. CMS should abandon the use of unique identifiers that discriminate among tests within a CPT code based on any criteria.
9. CMS should provide state Medicaid departments with information that will assist their coverage and pricing determinations so that our most vulnerable patients do not suffer lack of access to care due to bureaucratic constraints.
10. Congress should pass legislation to significantly reduce or eliminate the reporting penalties included in “Improving Medicare Policies for Clinical Diagnostic Laboratories” provision (Section 216) of PAMA. The reporting requirements and penalties will be burdensome for laboratories of any size, and could be impossible for smaller laboratories, which provide essential care to their local community.

The Storm’s Cumulus Stage: Shifting FDA Regulatory Requirements

FDA’s Draft Guidance for Oversight of Laboratory-developed Tests

On October 3, 2014, the U.S. Food and Drug Administration (FDA) released a draft guidance that sets forth a proposed framework to regulate laboratory developed procedures (LDPs).⁴ In order to exert authority over LDPs, the FDA has defined LDPs to be a class of *in vitro* diagnostics (IVDs), and thus subject to the medical device regulations as indicated in the Federal Food Drug & Cosmetic Act (FD&C Act). Historically, FDA requirements have applied only to medical device manufacturers that develop, box, and distribute test kits to laboratories. The new guidance on LDPs, if finalized, would impose new regulations in an attempt to force all innovative molecular testing services into the FDA’s outdated medical device framework, which was established in the 1970s to oversee the safety and effectiveness of medical devices, such as implants, hearing aids, and surgical tools. The FDA Commissioner and other federal agency leaders have explained that because of the advances in test complexity, particularly genomic sequencing, they believe it is necessary to establish a risk-based regulatory framework for the FDA to ensure that LDPs are properly validated.

In reality, LDPs are unlike any medical device because they are designed, developed, validated, performed, and the results interpreted all within the same laboratory by appropriately trained professionals. Unlike conventional, distributed, manufactured IVD test kits, LDPs are a medical service throughout the entire process. Molecular pathology professionals consult with ordering physicians in determining the appropriate services to perform, given an individual patient's clinical presentation. Importantly, they interpret the results of the test service in the context of other medical information. The procedures they develop, perform, continuously monitor, and continually improve distinguish LDPs from other medical devices, which are distributed to a wide range of users in the U.S. and around the world. As a result of the involvement of the appropriately qualified professional in every aspect of the service, the process of an LDP mitigates risks and promotes safety to the patient.

Yet, FDA intends to regulate LDPs as medical devices using the framework outlined in the draft guidance document. Guidance documents represent the FDA's current thinking on any given topic and does not bind the FDA to any proposed regulations. Considering that this new policy will be a dramatic change from the status quo, it is particularly troubling that the FDA plans to use guidance to establish these new policies for LDPs rather than using notice and comment rulemaking, which provides legal certainty to stakeholders and requires that the FDA better evaluate the economic impact of imposing new regulations. Numerous professional organizations, including AMP, representing hospitals, clinical laboratories, physicians, other health care providers, and patients in a joint letter have requested that the FDA withdraw the draft guidance on LDPs and instead pursue notice and comment rulemaking.⁵

Among the FDA's stated goals in the draft guidance are assuring analytical and clinical validity. However, analytical validity is already addressed by Clinical Laboratory Improvement Amendments (CLIA) regulations under CMS, which subjects laboratories that offer molecular and genetic LDPs to the most stringent regulations and requires regular proficiency testing. Assuring clinical validity is not directly evaluated by CLIA⁷; however, CLIA regulations require that the laboratory director and technical supervisor ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this regulation is the responsibility of the laboratory director to use medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies could not be said to be "required for patient care."⁶ Thus, the effective clinical purpose or clinical validity is typically documented by the laboratory in review of medical literature. In the draft guidance, the FDA states that laboratories may be able to use documented medical literature to establish clinical validity for the premarket review of select LDPs; however, the type of information required for which LDPs is unclear. Demonstrating clinical validity in the same way as a manufactured product is usually beyond the capability of even large laboratories in isolation, as this requires extensive prospective or retrospective clinical studies. The challenge of demonstrating clinical validity varies widely depending on the category of testing, which can include testing for rare inherited diseases, cancer diagnosis and prognosis, pharmacogenetics, and infectious diseases.

Should FDA continue to push for their oversight of LDPs, critical operational questions will need to be addressed. These questions include conflicts between CLIA and FDA regulations. For example, the FDA restricts off-label promotion of IVDs, though CLIA has clinical consultation requirements in practice of laboratory medicine. Will FDA regulations restrict the ability of pathologists and other medical

professionals to discuss the medical usefulness of a particular LDP? Will clinical laboratories, which already have malpractice insurance, now also need product liability insurance? One of the primary distinctions between an LDP and a manufactured test, or test system, is the fact that a manufactured test is packaged and shipped, with package inserts (*i.e.* labeling) to be heeded by individuals in customer laboratories. The Quality System (QS) Regulation/Medical Device Good Manufacturing Practices⁷ include requirements for the design, development, production processes, installation, and other design controls to mitigate the risk associated with the test. Compliance with Quality System Regulations⁷ requires the implementation of extensive policies and procedures, which will be completely new requirements to most clinical laboratories. How does the application of the FDA's quality system regulations apply to laboratory services when there is no definable "device," no packaged product? Likewise, where there is no product to "label," what is meaningful labeling and to whom is the labeling directed? The FDA intends to require Medical Device Reporting (MDR) for LDPs as well, which requires manufacturers to track and report adverse events that caused or may cause death or serious injury⁷, even though similar requirements are already in place as mandated by CLIA. However, the risk of the vast majority of LDTs causing or contributing to a death or serious injury is exceedingly low. Nevertheless, compliance with the MDR would necessitate that laboratories develop policies and procedures for reporting adverse events as well as an infrastructure to analyze potential adverse events, including maintenance of records of investigations and analyses. Although the costs of these activities is high, the overwhelmingly likelihood is that the extensive surveillance laboratories would need to pursue would not yield any reportable events. As a result of the various additional regulatory burdens, laboratories may need to hire experts in regulatory compliance to ensure compliance with both CLIA and FDA. While many, if not most, large reference laboratories already have such infrastructure in place, medical center based and smaller laboratories may not have mechanisms to absorb the costs imposed on "manufacturers" by the FDA.

Of utmost concern is that the proposed regulations create nearly insurmountable barriers to adapting and improving LDPs in favor of risks that have yet to be clearly documented. Many of the modifications that are made to an LDP are made in consultation with other physicians in an effort to deliver the best care to patients and thus, fall within the scope of their medical practice. Requiring a new application in order to incorporate new scientific findings disincentives laboratories from improving tests, and essentially freezes the LDP in time regardless of the advances in science. The overall success of precision medicine in patient care is dependent on the ability to quickly modify a test using the best and most relevant scientifically-verified information available.

FDA's Companion Diagnostics

In 2014, the FDA released a final guidance on IVD companion diagnostic products.⁸ The current companion diagnostic regulatory model is the situation in which a pharmaceutical company partners with a test manufacturer to achieve FDA approval. With the current paucity of FDA-cleared/approved companion diagnostics, this model usually results in one laboratory test per instrumentation platform, placing constraints upon an already overcrowded laboratory infrastructure. The FDA's primary focus should be on the companion biomarker, rather than the brand of associated diagnostic tests. From a medical and physiologic standpoint, the relevant parameter is the biological relationship between the

biomarker at issue and its associated therapeutic product, not the individual test or tests by which the biomarker is detected. Often clinical laboratories, especially smaller laboratories, implement use of a platform that can be utilized for many different clinical tests. One platform for multiple tests is more efficient for equipment maintenance costs, for capital equipment costs, for training of technical personnel and maintaining their competency, for limited laboratory space, etc. There is no regulatory requirement for pharmaceutical and test manufacturers to develop multiple cleared analytes on one instrument. To date, very few companion diagnostics have been approved on a shared instrument.⁹

Furthermore, the FDA's draft guidance on LDP regulation states that FDA intends to assign all companion diagnostic tests to a high-risk category. As a result, laboratories will potentially be required to submit their companion LDPs using a Pre-Market Application (PMA), the most expensive pre-market review process because often it requires clinical trials. Aside from the absence of established risk criteria applied to each individual test's methodology as a basis for their placement in the high-risk category, the FDA appears to be casting aside the risk mitigation that occurs with a board-certified professional's (both ordering and laboratory) oversight and expertise in running the test and subsequently managing the patient. There are many existing examples of LDPs for biomarkers that have been applied in connection with therapeutic products to great effect without using FDA pre-market review. Such tests include KRAS mutation testing in association with anti-EGFR therapy in metastatic colon cancer, EGFR mutation testing in non-small cell lung cancer, BCR-ABL testing in chronic myelogenous leukemia, PML-RARA testing in acute promyelocytic leukemia, and flow cytometry testing in association with monoclonal antibody therapies in hematopoietic malignancies.

Clinical Laboratory Services Oversight

LDPs are already highly regulated under a multi-part framework including CLIA, state laws, and accreditation by deemed authorities, such as the College of American Pathologists. That framework requires extensive validation of the quality of diagnostic services, yet also allows laboratories the flexibility to develop and validate laboratory tests quickly, and, thus, adopt new scientific knowledge and rapidly respond to unmet public health needs, such as pandemic outbreaks of viral disease (e.g., influenza A H1N1, SARS, MERS). CLIA regulations allow molecular pathology professionals to continually improve LDPs and establish analytical validity while providing the flexibility and nimbleness to mount a rapid response in order to place needed diagnostic tests into routine clinical practice. The manufacturing regulations under the proposed FDA framework would not.

Additionally, most IVDs in clinical laboratories undergo some sort of modification, which converts them to LDPs. Under Clinical Laboratory Improvement Amendment (CLIA) regulations¹⁰, the laboratory must validate any modification, including simply changing the type of specimen being tested. For example, whole blood is the only approved specimen type for the cystic fibrosis (CF) IVDs. This excludes fetal testing, which requires testing of amniocytes or chorionic villus samples. A laboratory that performs fetal diagnosis of CF is required to validate these specimen types, and such modifications change the IVD to an LDP. Under the proposed FDA oversight framework⁴, medical professionals in laboratories would now be considered "re-manufacturers" rather than utilizing approved products off-label and required to

submit these modifications to the FDA as a full Pre-Market Approval (PMA) or 510(k). Such testing as fetal diagnosis of CF may no longer be available, if the FDA draft guidelines are finalized.

Further challenging the scalability and appropriateness of FDA regulation is the adoption of exome and to some extent whole-genome sequencing, which have rapidly become standard of care intended to end diagnostic odysseys in cases of rare diseases. In the early days, clinical exome sequencing made headlines due to a number of initial success stories, where sequencing not only identified the molecular cause of a disorder that had stumped patients' doctors for years, but also pointed toward treatments that made remarkable impacts on the patients' lives — for example, in the case of the patient Nic Volker, exome sequencing by the Medical College of Wisconsin led to a life-saving cord blood transplant.¹¹ If the FDA requires clinical validity for every marker in the exome, one can imagine the daunting and practically unachievable process it would take to achieve clearance for a test that provides information on hundreds, if not thousands, of markers.

Unlike distributed laboratory tests, LDPs involve board-certified professionals at every stage and as such have an opportunity at every stage to promote patient safety. With a distributed test kit or system, a manufacturer under FDA oversight ensures that the product was manufactured correctly for its intended use. The device is then distributed through interstate commerce across the U.S. However, with LDPs, a healthcare professional (e.g., molecular pathologist) is involved in designing and validating the test, purchasing manufactured products/instruments, determining appropriateness given the clinical presentation, and interpreting the results in the context of other medical information.

Several alternative methods for regulating LDPs outside of the FDA are currently available and represent model systems with many aspects that could be emulated on a national level. For example, the New York State Department of Health (NYSDOH)'s Clinical Laboratory Evaluation Program (CLEP) currently issues permits to approximately 1,000 laboratories, and approximately 900 patient service centers in New York State on an annual basis. In addition, CLEP certifies, on a biennial basis, approximately 3,100 certificates of qualification to individuals to serve as directors/assistant directors of these clinical laboratories and blood banks. Many larger laboratories already have NYSDOH accreditation. NYSDOH's CLEP has been acknowledged by CMS through their granting of exempt status from CLIA for laboratories located in and holding New York clinical laboratory permits.¹² In New York, all technical procedures employed in a laboratory shall be of proven reliability and generally accepted by leading authorities in the specialties of laboratory medicine and/or approved by the Department.¹³ A laboratory can perform only those assays for which the performance characteristics have been established and validated, or if already established (typically by a manufacturer) verified at the site where the assay will be performed. For NYSDOH, laboratories performing any non-FDA approved or in-house developed assays must submit materials to have these assays reviewed and approved for use in New York State (or for New York State residents).¹⁴ There have been a number of significant delays in bringing a number of new and improved testing services to New York residents (VMP, personal experience). Due to the backlog, this approval process was taking greater than two years for approval in most cases. How these delays impacted New York patients is unknown. Responding to concerns expressed by various organizations, NYSDOH improved the process by which they are granting conditional approvals to tests in New York State

licensed laboratories, resulting in advances in molecular diagnostic testing to be put into practice for providing high quality health care to New York residents.

Use of such alternative regulatory pathways outside of the FDA, rather than requiring all molecular and genomic diagnostic tests to undergo FDA review and approval as proposed by some¹⁵, are more beneficial for the delivery of high quality health care. AMP and a number of other organizations support Clinical Laboratory Improvement Amendments (CLIA) modernization to enhance the oversight of laboratories where molecular pathology professionals' services are offered. The CLIA model of oversight has served as the engine of innovation in this space and rapid application of validated clinical discovery to patient care; therefore, any change of oversight of LDPs should involve enhancements to CLIA. Regulations designed for distributed tests and implantable devices are not appropriate for LDPs, which are medical services. Although the CLIA regulations do not explicitly require laboratories to verify clinical validity of LDPs, the regulations can be interpreted to mandate this assessment. Additionally, CLIA regulations can be updated to more clearly require laboratories to provide information on clinical validity. Because LDPs are developed or validated in CLIA-certified facilities, providers of LDPs are knowledgeable about the CLIA regulations, and therefore, changes to the regulations can be implemented with minimal burden to clinical laboratories. In addition, accreditors currently operate on behalf of CLIA and modernized regulations can be adopted in the required periodic inspections. A great deal of the requirements outlined by the FDA in the draft guidance are already required or could be easily implemented by CLIA including reporting of characteristics deemed to be necessary for proper test performance, the establishment of quality systems that address the total test process to ensure accurate, reliable, and timely results, and the establishment of systems to address adverse events.

Advancing to the Storm's Mature Stage: Uncertain or Poor Coverage and Payment

The U.S. government, through programs like CMS, pays for approximately half of the country's health care. While diagnostic testing comprises less than 5% of hospital costs and about 1.6% of all Medicare costs, their findings influence as much as 60-70% of health care decision-making.¹⁶

New CPT Codes

In the Medicare Physician Fee Schedule (MPFS) Proposed Rule issued in July 2012, CMS articulated its concern with improving the accuracy of coding and payment for molecular pathology services. Prior to 2013, laboratories billed for molecular pathology services using unique combinations of CPT "stacking" codes that describe each step of the procedure required to perform the test. Because of concerns that payers could not determine the specific tests performed when billed under the stacking codes, the American Medical Association's CPT® Editorial Panel adopted an entire new subsection of the Pathology Section of CPT to describe molecular pathology procedures. With the introduction of these new codes, the stacking codes were retired effective January 1, 2013, and laboratories were required to report molecular pathology tests using the new codes.

For purposes of implementation of the new codes, CMS requested public comments as to whether the new CPT codes appropriately report clinical diagnostic laboratory tests (and thus should be reimbursed

under the CLFS) or are better classified as physicians' services (leading to reimbursement under the Physician Fee Schedule, PFS). In the MPFS Final Rule CMS concluded that molecular pathology tests should be paid under the CLFS. CMS stated its position that not all molecular diagnostic tests require interpretation by a physician (e.g., MDs), and explained that these tests oftentimes can be reviewed by other specialists (e.g., PhD geneticists). However, placement of CPT codes on CLFS identifies all molecular pathology tests as technical rather than professional services. This erroneously implies reduced need over time for professional interpretation. For those tests that require physician interpretation, CMS created a new G code (G0452) for physician interpretation and report, with reimbursement for this new code based on claims data from the CPT stacking code for physician interpretation and report [total relative value units (RVUs) set at 0.55].

The publication of the Final Payment Determination under the CLFS is particularly important because it finalizes the process for rate-setting for the new codes. Consistent with its Preliminary Payment Determination, CMS determined that the rates for each of the molecular pathology codes were to be set using the gap-fill methodology. In comparison to cross-walking—which would have assigned payment rates by reference to the rate established for comparable procedure(s)—the gap-fill methodology requires the Medicare Administrative Contractors (MACs) to set payment rates considering a number of factors, such as what laboratories charge (including discounts), resources, what other payers pay for the same test and what the contractor pays for similar tests.¹⁷

With the implementation of the new molecular pathology (MolPath) CPT codes, the government and private payers were not prepared to reimburse claims for the 114 new CPT codes. Nearly all clinical laboratories and pathology group practices were not paid for over 6 months by MACs and many private health insurers. This created severe hardships (*i.e.*, difficulties covering employee salaries, reagents/supplies) for laboratories that had a largely molecular test menu.

Decreased Reimbursement or Lack of Coverage for Clinical Testing Services

Non- or delayed payment is not the only issue; laboratories face two other problems. First, some of the Medicare contractors have decided that a portion of the 114 newly-introduced molecular pathology CPT codes are not medically necessary. This non-coverage determination means those contractors will not pay for certain tests ordered by physicians for their patients. This in part may be due to the fact that Medicare covers individuals 65 years of age and older and that particular tests are not typically relevant to that population, such as testing to diagnose cystic fibrosis or fragile X syndrome. Often when Medicare makes a coverage decision other payers (e.g., Medicaid, private insurers) follow the same policy without considering the reasoning supporting the decision. Consequently, tests that physicians believe to be medically necessary and had been using for years are now being denied coverage. Second, the contractors set rates that are at least 40% and as much as 60% lower than they paid previously under the code-stacking arrangement. In some cases, the level of reimbursement does not cover even the cost of the IVD test kits. Deciding that some molecular diagnostic assays and genetic tests are not medically necessary is particularly disconcerting to the medical field because such decisions place a *dark cloud* over the advances in genomic medicine. It results in patients not getting tests that physicians believe are in their best interests. One such example is TRICARE's policy of non-coverage for molecular

diagnostic tests provided to beneficiaries seeking care through the community provider network. In July 2014, TRICARE announced a demonstration project permitting access to selected LDPs.¹⁸

In the 2014 Physician Fee Schedule Final Rule, the CMS announced plans to reset rates on the Clinical Laboratory Fee Schedule based upon technological changes. Many in the industry note that DNA sequencing costs have decreased. While this is true with respect to reagent costs (*i.e.*, with respect to the original cost to sequence the human genome), it does not account for the significant investment needed for equipment, IT infrastructure, and personnel to analyze and interpret the results. Also, most of FDA-cleared assays, especially molecularly-based, have not decreased in price. In fact, many prices have increased annually. Secondly, many in the industry fear that rates on the CLFS could be reduced by at least 30% or more for older established tests. The rule provided a great deal of latitude to CMS with no guardrails to prevent drastic cuts, and it was not clear if stakeholders would have the opportunity to request reconsideration.

Protecting Access to Medicare Act of 2014

On April 1, 2014, President Obama signed into law H.R. 4302, Protecting Access to Medicare Act of 2014 (PAMA). This Bill prevented CMS from revaluing the CLFS based upon technological changes. In addition, PAMA has a provision that The Secretary of the Department of Health and Human Services (HHS) now has the authority to designate up to four MACs to establish coverage policies and/or process claims for payment for laboratory tests for the entire Medicare program. It is possible that this could result in either the national expansion of Palmetto's MoDx program or the implementation of a system similar to the Durable Medical Equipment (DME) where the jurisdiction of all clinical laboratory tests would come under the jurisdiction of one or only a handful of MACs. Another requirement, starting January 1, 2016, laboratories must report the market data that CMS will to use to determine CLFS prices. Failure to properly report this data can result in a penalty to the clinical laboratory of as much as \$10,000 per day per test. This will place another heavy burden on clinical laboratories since few can implement IT infrastructure, staff, and other mechanisms in place to report, such information. Another section constrains Medicare officials from dropping the price for any single clinical laboratory test by more than these amounts for each year (e.g., \$100 test in 2016):

- 10% in 2017 (\$90.00)
- 10% in 2018 (\$81.00)
- 10% in 2019 (\$72.90)
- 15% in 2020 (\$61.97)
- 15% in 2021 (\$52.67)
- 15% in 2022 (\$44.77)

Were CMS to implement price reductions of this amount on a single test in each of the six years, it could cut the price of a laboratory test by 55%, compared to the base year. It is known that CMS wants to reset prices for the 20 highest-volume tests (note, none of the top 20 tests are molecular-based)¹⁹ that represent more than half of what is spent annually on Medicare Part B CLFS.

In CMS's final rules for the 2014 Hospital Outpatient Prospective Payment System (OPPS), CMS finalized its proposal to bundle all laboratory testing, except molecular diagnostic tests, into a hospital outpatient visit fee rather than reimbursing for the CLFS tests separately when they are provided in relation to the primary procedure. This policy has the potential to promote increased utilization of large reference laboratories for billing and reimbursement.

Palmetto GBA's Pilot Program

At least one MAC (*i.e.*, Palmetto GBA) implemented differential pricing between IVDs and LDPs for the new molecular pathology CPT codes. Currently, most MACs use CPT codes that are analyte-specific and method agnostic and do not differentiate between IVDs and LDPs. Prior to their implementation, CMS contracted with Palmetto GBA for a trial coverage and payment program for the new CPT codes. Palmetto designed MolDX, which includes McKesson-owned Z-Code Identifiers. A Z-code is a unique 5-character alpha-numeric identifier code associated with a specific advanced diagnostic test and is assigned based on the uniqueness of each laboratory's test or manufacturer's product being registered. For example, a test for the same analyte but performed by a different laboratory methodology would be considered unique and thus would merit a unique Z-Code Identifier. This system is designed to complement the current CPT codes. IVDs can be distinguished from LDPs and differential pricing implemented. Each laboratory in Palmetto's jurisdiction that would like to obtain coverage for a molecular test must meet the requirements of the MolDX program. The laboratory must obtain a Z-code and if the test is an LDP, the laboratory must also submit a detailed technical assessment of published test data so that Palmetto GBA assesses the quality of the validation (analytical validity) to determine clinical utility, and thus Medicare coverage and pricing. A multi-society coalition, which includes AMP, has protested to CMS that regulation of the quality of LDPs is not within the purview of payers, but overseen by CLIA.

The Perfect Storm's Damage: The Consequences of Consolidation

Consolidation of molecular diagnostic testing has obvious benefits in terms of economies of scale, allowing the purchase of more expensive equipment, greater opportunities for automation, large batch sizes, all potentially leading to lower costs per test; however, focusing only on the cost per test neglects a number of issues that are inevitable consequences of laboratory consolidation. Academic medical centers such as major cancer centers are often at the forefront of translating research discoveries to patient care, but they lack the resources necessary to address all the changing regulatory requirements and thus could shutter their molecular laboratories or significantly reduce services.

Because of rapid advancements in genomics, clinicians often have an incomplete understanding of the uses and limitations of molecular diagnostic testing. For example, oncologists may frequently order molecular diagnostic testing for the detection of minimal residual disease without knowing whether the patient's neoplasm even contains the targeted molecular marker. Clinical laboratory professionals can help clinicians order appropriate tests so that health care resources are not wasted on unnecessary testing and so that patients with a low pretest probability are not subjected to the risk of a false positive

test leading to unnecessary anxiety and unneeded therapy. For this reason, a number of institutions, clinical laboratory professionals and laboratory-based genetic counselors²⁰ have been collaborating with their medical colleagues to take over responsibility for choosing molecular diagnostic tests. At Vanderbilt University Medical Center, this type of collaboration has resulted in considerable financial savings while at the same time improving patient care.²¹

Much of the published work on the development of new clinical tests comes from university medical center and hospital-based laboratories. This may be in large part because the incentives in the academic world (*i.e.*, “publish or perish”) are different than in reference laboratories. This is not to neglect the impact of innovative testing developed in commercial reference laboratories, as well as the considerable impact of commercial development of new testing platforms. Reference laboratories play a particularly important role in the development and performance of tests for genetic disorders, where consolidated testing provides a greater opportunity to validate a test using a threshold minimum number of specimens and interpret rare genetic variants. In addition, some reference and university-based laboratories specialize in certain areas, often referred to as “boutique laboratories” and promotes a center of excellence in that particular area as not one or a few laboratories can do everything. More laboratories create more opportunities for innovation in the design of new tests and testing strategies.

Consolidation of molecular testing to a few large reference laboratories would hinder the ability of diagnostic product manufacturers to invest in the invention of new technologies, software, reagents and comprehensive test systems. Manufacturers often achieve their best profit margins from hospitals and smaller laboratories. These profits not only reward investors, they are re-invested in continued innovation, and innovation introduces risk. Manufacturers must offer deep volume discounts, including placing instruments at no cost (*i.e.*, reagent rental) to compete effectively in the larger reference laboratory market. If the number of hospital customers were to decline significantly, or disappear altogether, it is unlikely that manufacturers would be able to progress sufficiently in the high risk business environment that provides only a few large customers.

The molecular pathology laboratory both locally and at large referral laboratories plays an important role in training residents and fellows. The purpose of training in a molecular pathology laboratory is to familiarize the trainee with the use of molecular testing to aid in the diagnosis and management of disease. As described in the new Molecular Genetic Pathology Milestones from the Accreditation Council for Graduate Medical Education (ACGME), at Level 4 (ready for practice) the resident “Is proficient in consultation regarding test utilization and treatment decisions based on advanced precision diagnostics and personalized medicine.”²² Thus, the ACGME expects a high level of knowledge on the part of the resident regarding molecular genetic pathology testing. This type of understanding is usually achieved by having an on-site molecular pathology laboratory, so that the resident can learn about all aspects of molecular testing including how and when to use molecular testing, the methods used by the laboratory to answer clinical questions, most importantly considering the limitations of each technology, and the integration of the molecular test result into the diagnosis and treatment of the patient. If academic medical centers shut their doors, the large reference laboratories, who also participate in training programs, will not have enough resources to accommodate training all future molecular pathology professionals in precision diagnostics.

The rapid pace of development in molecular diagnosis reveals that this field is nowhere near maturity. This is due to new discoveries in basic science revealing new information about the influence of genotype on inherited disease and disease risk, new and evolving viruses, new targets for the development of drugs, and new technologies for the development of tests. All of this innovation results in improved patient care. Ultimately, this innovation will very likely result in less expensive testing as laboratories take cost into consideration, and devote development efforts toward lowering costs in a competitive environment. Consolidation of testing into a small number of laboratories may eventually slow aspects that contribute to cost control, development of innovative methods and strategies, and competition. We do not see these anti-competitive effects now because there are many molecular diagnosis laboratories both commercial and hospital-based.

Conclusion and Call to Action

The completion of the human genome sequence and availability of next-generation sequencing is leading to the next major advancements in molecular medicine. However, even as laboratories continue to make great strides in diagnostic abilities, a number of *clouds* are developing in the health care delivery system that threatens progress. Regulatory requirements have been proposed that would be costly, inefficient, and impose “square peg in a round hole” requirements on laboratories and medical professionals. Decreased reimbursement and non-coverage compounds the problem, leading to fewer resources for developing new testing technology. Highly innovative clinical laboratories, even those in major cancer centers, are at risk of discontinuing innovative testing services due to these pressures, which will lead to testing being concentrated in a few large referral laboratories. This in turn could lead to fewer opportunities for test development, unnecessary costs to the healthcare system, limited availability to train the next generation of physicians and laboratory healthcare professionals, and slowed innovation in molecular medicine. Due to the rapidly changing nature of molecular pathology, we call for regulatory agencies and insurance companies to cooperate to support a health care system environment that can continue to rapidly innovate as new discoveries in science are made, with the goal of improving human health. It is often quoted that 70% of medical decisions are based on laboratory tests.²³ Sustaining the various environments where excellent laboratory testing services, medical education, business interests and academic innovation can thrive will be critical to the best interests of all patients. To fully realize the *bright light* of genomic medicine, we must calm the *perfect storm* of regulatory and reimbursement challenges.

Glossary

Clinical Laboratory Fee Schedule (CLFS): the rates established under Medicare that determine what and how much laboratory services are paid.

Current Procedural Terminology (CPT): universal coding system to describe medical procedures and services to entities such as physicians, health insurance companies and accreditation organizations and is used for reimbursement.

Cytogenomic array: a type of DNA test that is designed to detect chromosome aberrations.

Department of Health and Human Services (HHS): is the part of the federal government that's responsible for administering programs that deal with health and welfare.

Fragile X syndrome: A genetic form of mental retardation that occurs more often in males, but also occurs in females though the symptoms are usually milder.

In vitro diagnostic (IVD): are used in the analysis of human samples, such as blood or tissue, to provide information in making health care decisions.

Laboratory-developed procedure (LDP): a service that is developed and performed completely within a single laboratory.

Medicare Administrative Contractors (MACs): private health care insurers that process medical claims for Medicare beneficiaries.

Physician Fee Schedule (PFS): the rates established under Medicare that determine what and how much physician services are paid.

Relative value units (RVUs): measure of value used in the United States Medicare reimbursement formula for physician services.

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- ² Wagle N, et al. NEJM 2014;371:1426-1433.
- ³ https://www.cgsmedicare.com/ohb/coverage/mopath/mopath_reimbursement.html, accessed 4June2014
- ⁴ Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), issued 03 Oct 2014. 2014. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf>
- ⁵ Letter to FDA Commissioner Margaret Hamburg, 18 Nov 2014, http://www.amp.org/publications_resources/documents/Sign%20On%20Letter%20FDA%20Rulemaking.pdf
- ⁶ U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services, Report of the Secretary's Advisory Committee on Genetics, Health, and Society, April 2008
- ⁷ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=820>, accessed 4 November 2014
- ⁸ In Vitro Companion Diagnostic Devices; Guidance for Industry and Food and Drug Administration Staff, issued 06 Aug 2014. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>
- ⁹ <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>, accessed 21May2014
- ¹⁰ CFR § 493.1253(b)(2)
- ¹¹ <http://www.jsonline.com/news/health/111224104.html>, accessed 21May2014
- ¹² http://www.wadsworth.org/labcert/clep/ProgramGuide/CLRS_Program_Guide_Update_03_05_09.pdf, accessed 07Jan2015
- ¹³ § 58-1.10(g) of Part 58 of Title 10 (Health) of the Official Compilation of Codes, Rules and Regulations of the State of New York
- ¹⁴ <http://www.wadsworth.org/labcert/clep/Administrative/ChangeForms.htm>, accessed 21May2014
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- ¹⁶ The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care. Lewin report, 2005
- ¹⁷ 42 C.F.R. § 414.508
- ¹⁸ <http://www.tricare.mil/ldt>
- ¹⁹ Office of the Inspector General Report. Comparing Lab Test Payment Rates: Medicare Could Achieve Substantial Savings (OEI-07-11-00010), 2013.
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- ²² <http://www.acgme.org/acgmeweb/tabid/142/ProgramandInstitutionalAccreditation/Hospital-BasedSpecialties/Pathology.aspx/MolecularGeneticPathologyMilestones.pdf>, accessed 7October2014
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