MOLECULAR DIAGNOSTICS

Regulatory and Reimbursement Innovation

Rachel A. Lindor,1,2 Scott J. Allocco,3 Lee Cheatham,4 Denis A. Cortese,5 Ralph F. Hall,6 William J. Mangold Jr.,7 Vincent Pizziconi,8 George Poste,9 Bruce Quinn,10 Mollie Roth,11 Michael J. Saks,12 E. Robert Wassman,12 Raymond L. Woosley,13 Gary E. Marchant1*

Coverage with evidence development and parallel review for molecular diagnostics aid regulation and reimbursement.

Molecular diagnostic tests play an increasingly critical role in the delivery of more effective, efficient, and personalized health care. It has been widely anticipated that these tests will improve health outcomes by enabling providers to optimize treatment selection for individual patients. Despite their capacity to improve health care, these tests face regulatory and reimbursement challenges that hinder their development and impede their integration into routine health-care delivery.

Two innovative programs with the potential to help overcome some of these hurdles are coverage with evidence development (CED) and parallel review (Fig. 1). The U.S. Food and Drug Administration (FDA) and Centers for Medicare & Medicaid Services (CMS) are currently evaluating these programs for more widespread application, with molecular diagnostics being a major potential target for both. Here, we assess the potential applicability of CED and parallel review for improving the molecular-diagnostics commercialization pathway and offer recommendations for strengthening these innovative programs.

DIAGNOSIS: NEW METHODS NEEDED

Molecular diagnostics include tests that inform the prediction, diagnosis, prognosis, and treatment of disease through the detection or measurement of a variety of molecular entities, such as DNA, RNA, and proteins. The FDA and CMS both play key roles in the development and commercialization of these tests. The FDA requires diagnostic tests that qualify as medical devices to provide a “reasonable assurance of safety and effectiveness” before they can be marketed, whereas CMS is tasked with determining whether products are “reasonable and necessary” before they can be covered by Medicare. Although these statutory mandates appear to overlap, they are clearly distinct under the law and have been implemented very differently in practice.

Recent policy changes by FDA and CMS have created uncertainty about the clinical evidence needed to meet the requirements of both agencies. For example, FDA is considering potential new regulatory oversight of laboratory-developed tests (LDTs)—diagnostic tests developed and performed within a single laboratory. FDA is also revising its policies on the oversight of co-developed therapeutic products and companion diagnostics and is in the midst of making major changes to the commonly used 510(k) clearance process (in which medical devices can be cleared for marketing by comparison with existing devices). Meanwhile, although CMS still relies on the same (and undefined) “reasonable and necessary” threshold for coverage, its implementation of these criteria seems to be shifting toward requiring stronger and more clinically relevant data on effectiveness and patient outcomes than they have in the past (1).

These shifting evidentiary expectations create an environment that requires increasingly costly generation of clinical evidence to meet different regulatory criteria yet does not provide the predictability, clarity, or financial incentives for product developers to invest in the larger studies needed to meet the new evidentiary standards. Moreover, the delays and costs incurred between FDA approval and a CMS coverage decision may be major impediments to the clinical use of and future investment in these medical technologies.

The ultimate solutions to the regulatory and reimbursement dilemmas confronting molecular diagnostics may require sweeping statutory or regulatory changes that are unlikely to occur in the current political and economic climate. In the meantime, incremental but valuable progress may be possible within the existing statutory and regulatory frameworks. In particular, two innovative policy initiatives—CED and parallel review—hold promise for reducing key bottlenecks in the evaluation of innovative medical products by FDA and CMS. CED enables CMS to provide interim reimbursement coverage for new items and services on the condition that the products’ sponsors collect additional clinical evidence to inform CMS’s ultimate coverage decision. Parallel review enables sponsors to meet with both CMS and FDA early in a product’s review process to clarify and synchronize the agencies’ respective evidentiary expectations, reducing inefficiencies and inconsistent data requirements.

There is currently a window of opportunity to expand and strengthen both CED and parallel review, especially with regard to high-value molecular diagnostics. The Obama administration’s Presidential National Bioeconomy Blueprint recently proposed expanded use of both policies to enhance biomedical innovation (2). A recent Institute of Medicine workshop also highlighted CED and parallel review and their relevance for molecular diagnostics (3).

COVERAGE WITH EVIDENCE DEVELOPMENT

By statute, the U.S. Medicare program provides coverage for products that are “reasonable and necessary” for the diagnosis and treatment of Medicare beneficiaries. CMS has distinguished diagnostic services, which are performed on individuals with signs or symptoms of a disease, and preventive and screening services, which are performed on individuals without any manifestations of disease. Medicare has historically covered many diagnostic services while limiting coverage of screening and preventive services to the few that are specifically mentioned in statute. The U.S. Affordable Care Act (www.healthcare.gov/law/full/index.html) amended the statute to allow CMS to cover any preventive services it deter-
mines are “reasonable and necessary for the prevention or early detection of an illness or disability” and that have been endorsed by the U.S. Preventive Services Task Force (www.uspreventiveservicestaskforce.org), but it remains unclear how these provisions will affect Medicare coverage practices in the future.

The responsibility for determining whether specific products meet the “reasonable and necessary” threshold is shared between CMS and regional Medicare administrative contractors. CMS makes roughly 10 to 20 national coverage determinations (NCDs) each year through a statutorily prescribed 6- to 9-month process that requires systematic evidence evaluation, publication of a proposed decision, response to public comments, and issuance of a final decision. NCDs apply nationwide and supersede any conflicting decisions made by contractors. Regional contractors make the vast majority of coverage decisions each year through a similar but less rigorous process. These local coverage determinations (LCDs) apply only to the items and services provided in the geographic regions overseen by the contractors. However, in the case of some molecular diagnostics, all testing nationwide is conducted in a single laboratory and is therefore evaluated and reimbursed by a single local contractor, which means that any LCDs made for these tests are de facto NCDs.

NCDs made by CMS may dictate coverage decisions in a number of ways. Occasionally, they provide coverage for an item or service in all cases or deny coverage in all cases. In some cases, they defer decision-making to the regional contractor. Most commonly, the NCD provides coverage only in the specific circumstances supported by the available evidence. In 2006, CMS formally outlined the additional option of using CED as a separate form of conditional coverage (4).

CED allows CMS to provide temporary reimbursement for promising new technologies while additional clinical data are generated to better inform the agency’s longer-term coverage decision. To receive reimbursement for their use of the product, providers may be required to participate in a clinical trial or registry in order to generate the clinical evidence required by CMS.

Fig. 1. Pruning the path. Shown are schematics of FDA regulatory approval and CMS reimbursement pathways for hypothetical diagnostic products. Parallel review and CED can expedite movement to market.
Clinical research performed in the context of CED is covered by CMS rather than by the product sponsors. This mechanism can help sponsors of new products overcome the cost of generating the high-quality clinical evidence required by CMS while also enabling CMS to make more evidence-based long-term coverage decisions and to provide patients earlier access to promising new technologies.

CMS has used a CED-style policy 18 times, beginning in 1995. The first one evaluated the effect of lung volume reduction surgery in the treatment of emphysema and illustrates the mechanism’s potential for improving CMS’s coverage process (5). In response to the growing popularity of the surgery but inadequate data on its effectiveness, CMS limited its coverage of the procedure to participants in a multicenter clinical trial. The study revealed that the procedure benefitted only a small subset of patients while actually increasing mortality for others. Using these data, CMS restricted coverage of the procedure to the patient subset for which clinical benefit was identified. This approach, which required a one-time $35 million outlay for research costs, saves CMS an estimated $150 million annually by eliminating reimbursement for ineffective interventions (6).

The early successes of CED demonstrated its potential to promote more evidence-based coverage decisions by CMS. However, only two applications of the policy have resulted in revised NCDs, whereas the other studies have not yet started or are ongoing. Recognizing the unmet potential of CED, CMS announced its intention to revise the policy in 2011 and solicited public comments through January 2012 (7). In November 2012, CMS issued a new draft guidance for CEDs and sought additional public comment through early 2013. According to the Bioeconomy Blueprint, “CMS believes that the lessons learned during the initial implementation of CED can inform its more frequent use and create predictable incentives for innovation while providing greater assurance that new technologies fulfill their initial claims of benefit” (2).

Molecular diagnostics provide a promising class of products for the application of CED. CMS and other payers often require different clinical data to pay for new molecular diagnostics than FDA requires for approval of those tests. CED offers a useful pathway to obtain additional data on the value of a diagnostic test without blocking the deployment of promising and innovative tests. For example, CMS recently applied CED to tests that enable genotype-guided dosing of warfarin (8).

To expand the use of CED for molecular diagnostic tests, CMS should address the following bottlenecks:

(i) Clarify the ability of CED to complement postmarketing requirements of FDA approvals. In determining that a molecular diagnostic product is safe and effective, FDA sometimes requires the sponsor to collect additional data in a postapproval study. The requested data may overlap with data CMS needs for coverage decisions. CED-based coverage for postapproval studies would help ensure that the studies are actually conducted. Before this option can be pursued, the mechanism and authority for linking an FDA postapproval study with a CED study must be clarified.

(ii) Clarify procedures and safeguards for local contractors to use CED. The majority of Medicare-coverage decisions are made by local contractors, yet CED has only been defined for NCDs. The ability of local contractors to make CED decisions has raised concerns about more costly, inefficient, and inconsistent coverage patterns, especially if local contractors study the same products using different methodologies and end points. However, some molecular diagnostic tests are conducted only in a single laboratory nationwide and thus are evaluated and reimbursed by just one local contractor. The application of CED to such tests could serve as pilot cases to determine local contractors’ capacity to apply CED. The appropriate safeguards for regional contractors’ use of CED must be devised before broad expansion to local contractors can occur.

(iii) Use CED within an abbreviated NCD process. The normal time period for an NCD is 9 months, which is viewed as a problematic delay by product sponsors who would like CMS payment to promptly follow FDA approval. It should be possible to issue a CED decision within 3 months of FDA approval while still maintaining the required 30-day period for public comment. This abbreviated mechanism would likely make the CED route more attractive to new product sponsors without sacrificing the quality of data collected for CMS.

PARALLEL REVIEW
In October 2011, FDA and CMS launched a parallel review pilot program under which the agencies concurrently evaluate medical devices for approval and coverage, respectively (9). The pilot program is scheduled to run for 2 years, although the time frame can be revised by the agencies as the program is tested in practice. The program allows CMS to begin its coverage determination process for new devices while they are being evaluated by FDA. This voluntary program leaves the review standards of each agency intact while seeking to reduce inefficiencies that arise when the agencies’ data requirements are applied in seriatim rather than in unison.

As the Bioeconomy Blueprint noted, “By engaging CMS earlier in the process, the parallel review program is expected to limit the duplication of effort on the part of product sponsors and agency reviewers and reduce the time it takes new products to enter the market and receive payments from Medicare and other providers” (2). Although companies have always been able to informally consult with CMS during product development, the parallel review pilot project offers an opportunity to expand and formalize how FDA and CMS coordinate their product reviews (10).

The parallel review pilot program is restricted to medical devices and, specifically, products that meet one of the following criteria: (i) new technologies for which the sponsor or requester has a preinvestigation-device exemption (IDE) or an approved IDE application designation (initial steps in seeking FDA approval to commence clinical testing); (ii) new technologies that require an original or supplemental application for premarket approval (PMA) (the most rigorous FDA approval process for medical devices) or a petition for de novo review; or (iii) new technologies that fall within the scope of a Part A or Part B Medicare benefit category and are not subject to an NCD (10). Many molecular diagnostics will fall within one of these categories and would be eligible to participate in the program. The data requirements applied by both FDA and CMS are generally more uncertain for molecular diagnostics than other medical devices, making them particularly well positioned to benefit from the coordinated review and data requirements offered by parallel review.

To date, only one molecular diagnostic product (ColoGuard; Exact Sciences) has participated in the parallel review pathway (http://investor.exactsciences.com/2010AR/fda/index.html). The lack of wider participation may be due to the novelty of parallel review, which could be perceived as simply substituting one kind
of uncertainty for another. Moreover, product developers are also concerned about obtaining coverage from numerous private payers and may be reluctant to focus their data-gathering too narrowly on CMS’s requirements, especially if their products are designed for patient populations that do not fit neatly into Medicare’s coverage categories. In such cases, the product developer may anticipate a more favorable outcome by focusing on negotiations with individual local contractors and private payers. Most importantly, an early negative NCD decision could destroy any prospects for a product’s commercial success. Companies may be unwilling to subject their products to this “all or nothing” gamble.

Minor revisions to the parallel review pilot project may make the program more attractive to molecular diagnostic test developers and provide faster access and better evidence for payers, providers, and patients. These changes include:

(i) Reconsider eligibility of molecular diagnostics cleared under 510(k). The current pilot program excludes devices subject to a 510(k) clearance because many 510(k) applications do not include substantial clinical data. Moreover, because the 501(k) pathway is generally already more expedited than PMA approval, there may be less need for parallel review for most medical devices. However, molecular diagnostic products submitted to FDA through the 510(k) pathway are much more likely to include clinical data and take longer to receive clearance than other products, making the 510(k) exclusion less justifiable for these tests. Venture capitalists invest preferentially in 510(k)–eligible diagnostics as opposed to those required to go through a full PMA, suggesting that removal of the current 510(k) exclusion could increase interest in the program by venture-backed companies. Similarly, the program should be flexible enough to accommodate future new regulatory pathways for diagnostic products, such as those being discussed for LDTs, and future pathways developed for new technologies such as whole-genome sequencing.

(ii) Remove NCD requirement from initial stages of parallel review. The pilot project was designed specifically to reduce the time between FDA approval and CMS national coverage determinations. Although there is a mechanism for participants subsequently to opt out of an NCD, the fact that an NCD is the presumed outcome of the program may deter developers who fear a negative decision from entering the parallel review track. If CMS remains neutral as to whether it will issue an NCD or allow local contractors to issue their own LCDs, which are less risky for developers, more diagnostic developers may participate in the parallel review program. Although product sponsors already have the option to consult with CMS during product development, many sponsors of new products currently spend substantial time and resources pursuing local coverage; thus, tying parallel review to LCDs could reduce this burden.

(iii) Provide incentives for use of parallel review. The perception that parallel review could increase the risk of receiving a negative NCD can create a disincentive for product developers to participate. The FDA and CMS could provide incentives that balance this concern, such as by granting priority review for participating products to further speed their market entry or by linking the review with CED to defray the cost of data collection. Because the agencies have discretion about which products to accept into the parallel review program, they could choose to direct these incentives at products that appear particularly promising for patients.

Although the parallel review pilot project is limited to three to five devices per year, it can facilitate a more efficient regulatory and reimbursement process for participating products and provide additional clarity about the evidentiary needs of both agencies for related products.

**Promise for Patients**

Molecular diagnostics is the fastest growing segment of the in vitro diagnostics market. CED and parallel review provide innovative regulatory and payment pathways that can expedite, coordinate, and facilitate data generation and clinical adoption of these products. The ongoing reevaluation of these programs by CMS and FDA opens a window of opportunity to expand their productive application to this segment of biomedical innovation.

**References and Notes**


**Competing interests:** S. J. A. is a cofounder and member of the Board of Directors of BioMarker Strategies. G.P. serves on the Board of Directors of Monsanto and Exelixis and the Scientific Advisory Board of Synthetic Genomics. E.R.W. serves as Chief Medical Officer at Rosetta Genomics, Generation Health, and Helicos Biosciences; as PT Medical Director at BioCell Center; is the sole proprietor and a consultant at Life Designs Ventures; and is a cofounder of and Chief Medical Officer at Good Start Genetics.

Regulatory and Reimbursement Innovation
Rachel A. Lindor, Scott J. Allocco, Lee Cheatham, Denis A. Cortese, Ralph F. Hall, William J. Mangold, Jr., Vincent Pizziconi, George Poste, Bruce Quinn, Mollie Roth, Michael J. Saks, E. Robert Wassman, Raymond L. Woosley and Gary E. Marchant

Sci Transl Med 5, 176cm3
DOI: 10.1126/scitranslmed.3005437