

**Potential Solutions to Regulatory and Reimbursement Barriers for Molecular Diagnostics:  
Parallel Review and Coverage with Evidence Development**

**Workshop Discussion Paper**

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Both the FDA and CMS play key roles in the development and commercialization of new medical technologies. In the case of medical devices, the FDA ensures that new devices provide a “reasonable assurance of safety and effectiveness,” while CMS determines whether those products are “reasonable and necessary” for the care of Medicare beneficiaries. Though these statutory mandates appear to overlap, they have been interpreted much differently in practice, with the FDA focusing predominantly on safety and effectiveness in the context of controlled clinical trials and CMS focusing primarily on patient outcomes in the real-world settings of clinical care.

As a result of these discrepancies, the information requirements of FDA and CMS have traditionally represented separate hurdles for the sponsors of new products. Because products must be cleared or approved by the FDA before they are covered by CMS, many product sponsors seek to satisfy the evidentiary needs of the FDA before even considering the needs of CMS. This process often results in a significant delay between FDA approval and CMS coverage while product sponsors are generating the additional data needed by CMS. The frequent reliance of third party payers on CMS coverage decisions means this delay can significantly affect the rate of adoption and overall success of new technologies.

The regulatory and reimbursement hurdles posed by FDA and CMS have recently faced much criticism, especially in the context of medical device oversight. New technologies are increasingly denied approval and coverage due to a lack of data, largely because companies sponsoring the technologies face challenges generating the high quality data needed by the agencies. Foremost among these challenges is dealing with the substantial uncertainty regarding the agencies’ respective data requirements for their regulatory and reimbursement decisions. Perhaps no subset of medical devices faces greater difficulty in meeting the requirements of these agencies than the emerging generation of molecular diagnostic tests, a critical technology for the implementation of personalized medicine.

Molecular diagnostics face unique challenges for at least three major reasons. First, payment for most of these tests is based on a fee schedule that is widely perceived to under-reimburse for the costs and value of the test. Second, the tests are often grouped into codes that do not have the granularity to distinguish between different testing platforms and methods, making it difficult to study the performance of individual tests. Third, policy changes by the FDA and CMS have created much uncertainty about the type and strength of clinical evidence needed to meet the agencies' expectations for approval and reimbursement. For example, the FDA recently indicated its intention to begin regulating laboratory developed tests, continues to revise its policies regarding the oversight of co-developed products, and is apparently reconsidering its routine use of the 510(k) clearance, the most common path to market for all types of devices. Meanwhile, CMS still relies on the same "reasonable and necessary" threshold for coverage that it always has, though the agency's interpretation of this phrase seems to be moving towards one that requires stronger and more relevant clinical data than it did in the past.

Together, the reimbursement shortfalls and shifting evidentiary expectations combine to create a system that relies on expensive and inefficiently-generated evidence but does not provide the matching clarity or financial incentives for product developers to generate that evidence. The delays and costs incurred between securing FDA approval and CMS coverage are often significant and serve as major holdups for the widespread use of new technologies and deterrents for investment in these technologies. If these problems are not addressed, they will continue to thwart investments in molecular diagnostic technologies and broader progress in personalized medicine.

This workshop will focus on two ongoing policy initiatives—parallel review and coverage with evidence development (CED), both of which are designed specifically to reduce key bottlenecks in FDA and CMS' review of innovative medical products. In brief, parallel review enables product developers to meet with both CMS and FDA early in a product's review process, with the goal of clarifying the agencies' evidentiary expectations and reducing the inefficiencies that often result from addressing the agencies' data needs separately. Coverage with evidence development enables CMS to temporarily cover new products that are not yet supported by sufficient evidence to meet CMS' "reasonable and necessary" coverage threshold while additional data are generated to inform CMS' long-term coverage decision.

While the optimal solutions to the regulatory dilemmas facing molecular diagnostics may involve sweeping statutory or regulatory changes, these are less likely to be successful in the current political and economic climate – and certainly not in the short term. In contrast, both parallel review and CED are currently open to agency review and modification at this time, creating a window of opportunity to propose changes that have the potential to strengthen the utility of these policies and promote the development and use of high value molecular diagnostic technologies.

The following brief analysis provides an overview of the history and substance of parallel review and CED, their current status, and a set of discussion questions that may be relevant to improving the value of these policies.

## Parallel Review

### **Description:**

Initiated by FDA and CMS in the fall of 2011, the parallel review pilot program provides a mechanism for the two agencies to concurrently evaluate certain medical devices for approval and coverage, respectively. Specifically, the program allows CMS to begin its national coverage determination (NCD) process earlier, while the product is still being evaluated by FDA. This voluntary program does not change the review standards of either agency but rather seeks to reduce the inefficiencies that often arise when product sponsors address and fulfill the FDA's evidentiary needs without simultaneously considering whether the same data collection process could be used to address CMS's needs as well. By bringing both agencies to the table with the product sponsor earlier in a product's development, the parallel review process is designed to highlight the similarities and differences between the agencies' data needs and help sponsors avoid performing duplicative and inefficient studies, thereby reducing the time and costs of bringing new products to patients.

### **Previous use:**

While a handful of products have been accepted for the parallel review pilot program and are currently under review, no products have gone through the entire parallel review process. One product currently taking part in the pilot is Exact Science's Cologuard, a molecular diagnostic assay for stool markers of colorectal cancer.

### **Current status:**

FDA and CMS initiated the pilot program in November 2011, nearly a year after a notice requesting public comments on parallel review generated 36 public comments. In response to those comments, the agencies amended the parallel review process in a number of ways intended to make it more flexible and attractive to product developers:

- In response to concerns that parallel review would commit products to a national coverage determination, the agencies added a provision allowing participants to opt out of the process:

*"A sponsor/requester may withdraw from, and FDA and CMS may terminate, parallel review up until the time of CMS's public posting of an NCD tracking sheet."*

- In response to comments expressing concern over the confidentiality of data shared during the parallel review process, the agencies emphasized that it would maintain the confidentiality standards set forth in their memorandum of understanding:

*"FDA and CMS recognize that the following types of information transmitted between them in any medium and from any source must be protected from unauthorized disclosure: (1) trade secret and other confidential commercial information that would be protected from public disclosure pursuant to Exemption 4 of the Freedom of Information Act (FOIA); (2)*

*personal privacy information, such as the information that would be protected from public disclosure pursuant to Exemption 6 or 7(c) of the FOIA; or (3) information that is otherwise protected from public disclosure by Federal statutes and their implementing regulations (e.g., the Trade Secrets Act (18 U.S.C. § 1905), the Privacy Act (5 U.S.C. § 552a), the Freedom of Information Act (5 U.S.C. § 552), the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and the Health Insurance Portability and Accountability Act (HIPAA), Pub. L. 104-191).”*

- Many comments asked for clarification regarding the timelines of the parallel review process. In response, the agencies agreed to review applications for the program within 30 days of submission, after which time products would follow the normal FDA review process and timeframes:

*“ (FDA/CMS consideration) The Agencies intend to meet to consider a nomination within 30 days of receiving a complete nomination containing the information described previously. The Agencies may contact the sponsor/requester to request supplemental information.*

*(Sponsor/requester Notification) Upon completion of the consideration meeting, the Agencies will notify the sponsor/requester whether the product is an appropriate candidate for the parallel review pilot program.*

*(Acceptance Meeting) If deemed an appropriate candidate, the Agencies will meet with the product sponsor/requester, either in person or by phone.*

*(FDA Review) Parallel review candidates will be reviewed according the normal FDA review process. Participation in parallel review will not affect user fees, review timeframes or procedures, or the FDA standard of approval, which is reasonable assurance of safety and effectiveness.*

*(CMS NCD Review and Timing) CMS will begin its informal review process sometime after submission of the PMA or de novo petition. For PMAs, this will typically begin after the PMA-specific Panel meeting of the FDA Medical Devices Advisory Committee.”*

The parallel review pilot program is currently 6 months into its planned 2-year pilot, though the timeframe can be shortened or lengthened as desired by the agencies depending on the response.

### **Parallel Review Discussion Questions:**

- 1) What are the key benefits and concerns with the parallel review concept? What are the best ways to address the concerns?
- 2) Are molecular diagnostic products good candidates for utilizing parallel review?
- 3) Why aren't companies using the parallel review pilot program? Are there concrete additional steps the government could take to encourage greater interest in parallel review?
- 4) Does the opt-out provision provide enough assurance to product sponsors that they will be able to keep their product from being the subject of an NCD? Can parallel review provide useful guidance on coverage decisions even if that decision is ultimately made by a local contractor rather than as a NCD?
- 5) Do the confidentiality provisions in the MOU provide sufficient assurance to sponsors that their data will be just as secure in the parallel review process as in the usual sequential process of FDA and CMS evaluation?
- 6) Does the explanation of the timeframes provide enough assurance to sponsors that the review of their products will not be unduly slowed due to their participation in parallel review?

## Coverage with Evidence Development (CED)

### **Description:**

A coverage determination refers to a decision about whether Medicare will pay providers for certain items or services. By statute, the program is prohibited from paying for items and services that do not fall within at least one statutorily defined benefit category and those that are not “reasonable and necessary” for the diagnosis and treatment of Medicare beneficiaries. Though the phrase “reasonable and necessary” has never been explicitly defined, it has been interpreted to require a showing that an item or service improves health outcomes in Medicare beneficiaries. The responsibility of determining whether items and services fit this definition is shared between local Medicare administrative contractors and CMS. If an NCD has been made by CMS, it supersedes any relevant local coverage determinations (LCDs).

CMS makes just 15-20 NCDs each year through a statutorily prescribed 6-9 month process requiring systematic evidence evaluation, publication of a proposed decision, response to public comments, and issuance of a final decision. Rarely, the agency decides to either cover the item or service in all cases, to deny coverage in all cases, or to formally leave coverage at the discretion of local contractors. More commonly, CMS issues a national coverage determination that provides coverage only in limited circumstances, as supported by the available evidence. As of 2005, CMS has the additional option of using coverage with evidence development (CED) as a form of conditional coverage.

CED allows CMS to provide temporary payment for promising new technologies while clinical data are generated to better inform the agency’s longer-term coverage decision. For example, this policy would allow CMS to reimburse for the cost of a new product on the condition that clinical data are being collected to demonstrate the product’s effectiveness among Medicare beneficiaries. In order to receive reimbursement for their use of the product, providers would be required to participate in a clinical trial or input specific clinical data into a registry, creating a body of clinical evidence that CMS will eventually use when making its long-term coverage decision. Research performed in the context of CED differs from research performed for most new products in that the cost of the product being evaluated (but not the administrative cost) is paid for by CMS, rather than by the product sponsors or private researchers. This cost-sharing mechanism not only helps product sponsors but also provides patients with faster access to promising products while reducing the chances that CMS will end up paying for ineffective products.

### **Previous uses:**

CMS used a CED-style policy for the first time in 1995 and has since used it in 12 additional decisions (see Table 1 below). To date, data from CED have only been used to revise two national coverage determinations, while the other applications have not yet started or are ongoing, including one CED study currently evaluating the efficacy genotype-guided dosing of warfarin.

CMS first used a CED-like mechanism to study the effect of lung volume reduction surgery in the treatment of emphysema. In response to the growing popularity of the reduction surgery and limited data on its effectiveness, CMS collaborated with the National Heart, Lung, and Blood Institute and the Agency for Healthcare Research and Quality to run a multi-center randomized controlled trial. CMS limited coverage to patients treated at one of 17 clinical sites following the clinical trial protocol established by the National Institutes of Health. The results of the study, published in 2003, revealed that the procedure benefitted only a small subset of patients and actually increased the mortality rate for others. Using these data, CMS issued a national coverage determination restricting coverage only to the patient subset identified by the study. It has been estimated that this trial, which required a one-time \$35 million outlay for research costs, saves CMS \$150 million annually by preventing it from paying for ineffective treatments.

CMS also used data collected through CED to inform its coverage of PET scans in the management of various cancers. Prior to the 2005 decision to use CED, CMS had a non-coverage policy for the use of PET in managing most forms of cancer but received a number of requests for reconsideration in the context of specific cancers. In response to these requests, CMS commissioned AHRQ to perform a formal technology assessment. The inconclusive results of the technology assessment highlighted the need for additional information and led CMS to propose the use of CED, carried out through a registry. By 2009, enough data had been collected to conclude that PET scans did improve at least the initial treatment strategy for certain cancers, though the data remained inconclusive for the later stages of management. Using these data, CMS revised its policies to provide broad coverage for the initial treatment stages of the cancers being evaluated, while maintaining the CED policy for later stages.

Private payers have also capitalized on the utility of CED-style coverage policies. Blue Cross Blue Shield (BCBS) demonstrated the value of this type of conditional coverage in its evaluation of treatment methods for women undergoing high dose chemotherapy for breast cancer. At the time, many patients were choosing to undergo autologous bone marrow transplant. However, an internal evaluation by BCBS suggested more data were needed to evaluate the risks and benefits of this procedure. In response, BCBS decided only to pay patients who were enrolled in one of the ongoing clinical trials for this therapy. Despite initial public opposition to this decision, enough patients eventually enrolled in these trials to confirm that the bone marrow treatment actually increased rather than decreased the risk of death. Armed with these results, BCBS and many other insurers stopped covering the procedure, averting an estimated 200 ineffective procedures, 60 unnecessary deaths, and \$200 million in wasted spending each year.

The success these efforts demonstrated the potential of CED to promote more rational spending within CMS and spurred interest in its continued use. However, more recent applications have failed to lead to coverage changes and highlight the need for CMS to reconsider its implementation of CED, as it is currently doing.

**Current status:**

Recognizing the unmet potential of CED, CMS removed the guidance document governing the application of CED in the fall of 2011, announced its intention to revise the policy, and solicited public comments through Jan 2012. Comments were specifically requested regarding: a) the use of CED outside of the national coverage determination process, b) the impact of CED on the Medicare program, and c) suggestion for ways to apply CED to maximize its benefit to Medicare beneficiaries. CMS also plans to convene the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) in May 2012 to discuss the characteristics of evidence appropriate to trigger CED. The overall goal of this revision is to enable CMS to make better informed coverage decisions, in a way that improves the health of Medicare beneficiaries while also reducing barriers to foster innovation in health care.

**CED Discussion Questions:**

- 1) What are the major benefits and concerns about CED? How can those concerns be addressed?
- 2) Are molecular diagnostic products good candidates for CED?
- 3) Does CED create new opportunities for CMS and FDA collaboration?
- 4) The pilot program for parallel review suggests that CED could be used to help generate additional data when those provided by product sponsors prove to be insufficient for CMS' coverage decisions. How could the use of these policies together improve the efficiency of molecular diagnostic oversight?
- 5) Are there any other avenues, outside the individual NCD process, that could make CED more responsive or efficient?
- 6) Is CED a useful mechanism for private payers? What additional benefits or concerns are raised in those contexts? How can (or should) private insurers be encouraged to use CED more?

Table 1: CED Applications<sup>1</sup>

Subject	Year	Type of Study	Results	Funding Source	Limitations
Lung volume reduction surgery	1995	Trial (pre-CED)	Study completed in 2003. Revised NCD to cover a subset of patients	Public (NHLBI & AHRQ)	Took 7 years for completion of study and NCD due to slow enrollment.
FDG-PET imaging for diagnosis of early dementia	2004	Registry (pre-CED)	Trial ongoing. No changes to NCD.	Private	Unable to obtain funding for trial. Facilities asked to cover their own costs, so most withdrew. Only 1 site currently recruiting patients.
FDG-PET imaging for cancers (other than the 9 types already covered)	2005	Registry (CAD)	Registry ongoing. NCD revised to cover initial dx. CED still in place for PET in treatment stage.	Private	Questions about quality of data submitted to registry (due to lack of training on how to use registry and few incentives for providers to check data).
Implantable cardioverter defibrillators to prevent MI	2005	Registry (CAD)	Registry ongoing.	Originally private. New study is partly public (NIH)	Original registry did not collect long-term endpoints needed by Medicare. New effort started in 2010 to capture long-term data.
Off-label use of certain colorectal cancer drugs	2005	Trial (CAD)	Some trials completed, some ongoing. No change to NCD.	Public (NCI)	Delays in patient enrollment led to the closing or suspension of 7 of the 9 trial sites. Also, existing trials were used that did not assess relevant outcomes.
Cochlear implantation	2005	Trial (CAD)	No study started.	None	No private or public funding available.
Long-term oxygen treatment	2006	Trial (CAD)	Trial ongoing. No changes to NCD.	Public (NHLBI)	Studies delayed by patient enrollment. Study opened in 2007, expected to finish in 2013, despite only using 4-month outcomes data.
Artificial heart	2008	Trial (CSP)	Trials and registry ongoing. No changes to NCD.	Private (trials) & public (registry, NHLBI)	CED trials active at only 9 hospitals nationwide.
Trial of CPAP as a diagnostic tool for sleep apnea	2008	Trial (CSP)	No study started.		
Genotype-guided dosing of warfarin	2009	Trial (CSP)	Publicly funded trial in progress. No NCD change.	Public (NHLBI)	
PET scanning for bone metastases	2010	Trial (CSP)	Study under development.		
Stem cell transplants for myelodysplastic syndrome	2011	Trial (CSP)	No study started.		
MRI in patients with pacemakers or ICDs	2011	Trial (CSP)	No study started.		

<sup>1</sup> Table contents adapted from: Medicare Payment Advisory Commission, Report to the Congress: Aligning Incentives in Medicare, June 2010; Mohr, et al., Comparative Effectiveness Research Landscape in the United States and Its Relevance to the Medicare Program, 2010.