

To: Centers for Medicare and Medicaid Services
Re: Potential National Coverage Determinations
Date: September 26, 2008

Submitted electronically

The Personalized Medicine Coalition is writing to comment on the list of Potential National Coverage Determinations (NCDs) released by the Centers for Medicare and Medicaid Services (CMS) on July 30, 2008. This letter focuses on gene expression profiling tests and pharmacogenomic testing, as both of these technologies are elements of personalized medicine.

Representing a broad spectrum of academic, industrial, patient, provider and payer communities, the Personalized Medicine Coalition seeks to advance the understanding and adoption of personalized medicine concepts and products for the benefit of patients.

We are pleased that CMS is engaging the healthcare community in conversation about its activities and urge CMS to maintain and expand this dialog. Steps to promote transparency and predictability in CMS' national coverage process are important for the companies engaged in the field of personalized medicine, many of which are small start-ups. For some, it is unclear how CMS makes NCDs for personalized medicine products. The request for public comment on potential NCDs is an excellent demonstration of that process and should serve as a means for improving the dialog between CMS and the stakeholder groups in personalized medicine. It also indicates the willingness of CMS to take a leadership role in personalized medicine.

Gene expression profiling tests and pharmacogenomic testing offer great promise for changing clinical decision making, improving health outcomes and increasing the quality of patient care. However, as this is an emerging industry, a negative NCD could have the unintended consequence of stifling further adoption and development of these important tools and restrict patient access to new diagnostic options. That can be avoided if a transparent, measured approach is taken.

To improve transparency and predictability, CMS should specify how it will decide whether to initiate national coverage analyses for items on the potential NCD list, and should make clear that it will update the list on a regular basis. Maintaining a current list, and providing an explanation for the decision to initiate a NCD or remove an item from the list, are important for product innovators; merely being placed on the potential NCD list could have the unintended consequence of creating a negative impression about a particular product in the clinical, policy or investment communities.

Should CMS proceed with NCDs for pharmacogenomic testing or gene expression profiling tests, we suggest it conduct a Coverage with Evidence Development (CED) of the Coverage with Study Participation (CSP) subtype as outlined in the *Innovators' Guide to Navigating CMS*. We recommend that CMS work with stakeholders to create a process that is sufficient to develop evidence, does not stifle patient access or innovation, and is not overly burdensome. Our reasoning is outlined below.

For some new medical technologies related to personalized medicine [such as new medicines subject to review by the Food and Drug Administration (FDA) and approval based on data from randomized controlled trials] CMS coverage determinations are straightforward, as evidence developed in support of FDA approval provides a sufficient basis for Medicare coverage. For other personalized medicine technologies, however, the different approaches taken by the FDA and CMS in their evaluation of the evidence to cover the cost of the test for patients pose significant challenges to bringing products to market. For personalized medicine to advance and improve the quality of patient care and for innovative companies to continue to assume risks necessary to develop personalized medicine products, decision-making procedures and evidence standards must be clear at each stop along the regulatory/reimbursement continuum, including that required by CMS. **To improve clarity about the evidence CMS will require for coverage of gene expression profiling testing and pharmacogenomic tests, we request that the agency meet with members of the PMC to define appropriate evidence requirements and reasonable pathways for developing the evidence.**

The recent NCD for warfarin pharmacogenomics provides a useful perspective for this discussion. Review of public comments indicates that there is no consensus of opinion regarding the value of pharmacogenomic testing for initial warfarin dosing. Some respondents believe that the additional information provided by pharmacogenomic testing is valuable, improves the quality of patient care, and may save the system costs incurred by avoiding serious adverse events and reducing the time and repeated testing necessary to reach a stable dose. They cite research to support their arguments. Others argue that the evidence does not show improved patient outcomes and suggest that CMS await the findings of randomized clinical trials (RCTs) before making an NCD on warfarin testing.

However, RCTs may not be the appropriate study design for pharmacogenomics and gene expression profile testing. Evidence of clinical utility requires understanding how new technologies affect health outcomes; research participants are followed for some time, and long-term follow-up may be required. This poses a challenge for molecular diagnostic companies because the understanding of molecular genetics is developing rapidly. Scientific progress in this field is such that, by the time the results of an RCT are available, the diagnostic in question may have gone through several generations of improvements. For example, by adding an additional genetic biomarker, the newer

version of a test may account for significantly more of an outcome's variance. That is not to say that any assessment of the clinical utility or medical necessity of a test is rendered invalid by subsequent technological advancements, but to point out that delays in the issuance of coverage decisions can keep valuable state-of-the-art clinical tools out of the hands of clinicians longer than may be necessary. Once a coverage determination is made, it is important to update the NCD quickly to keep pace with emerging data.

High quality clinical evidence for new diagnostic tests is frequently available through other study methodologies in addition to RCTs. **The PMC would like to work with CMS on alternatives to RCTs for evidence development.** Such alternative approaches could include patient registries, observation studies, and adaptive clinical trials. **Furthermore, PMC would like to work with CMS on developing a system for rating the quality of evidence when making coverage determinations for molecular diagnostics.**

Regardless of what type of system for evidence development is designed, it is clear that the regulatory system for product approval and the regulatory system for CMS payment are not designed to be aligned. However, clarification of evidence requirements could help facilitate the development and adoption of personalized medicine. For example, FDA examined the evidence that genotyping for VKORC1 and CYP2C9 provides additional information that is helpful for initial warfarin dosing, and recommends testing for these metabolism and sensitivity genotypes, although information on how to use test results to modify treatment is not provided. Following the re-labeling of warfarin, a number of companies asked for and were granted FDA clearance for tests that quickly measure relevant biomarkers. In the recent CMS posting of the NCD regarding this testing, CMS indicated that it was "concerned by the paucity of evidence available to determine what effect on overall health outcomes, if any, can be confidently attributed to treatment strategies that include pharmacogenomic testing in the determination of dosing."

PMC would like to hold a joint forum with CMS to further explore the issues outlined in this letter. We propose convening a workshop that would:

- examine systems for evidence evaluation for coverage determinations by both public and private payers; and
- discuss the appropriateness of the various evidence evaluation systems for personalized medicine.

Such a dialog would allow CMS to develop a system for coverage decisions that would keep pace with the development of personalized medicine products. Stakeholders could give their perspectives and work with CMS on possible solutions to the evidence barrier surrounding coverage decisions for pharmacogenomics and gene expression

profiling tests. Such a forum may reveal more appropriate evidence models for personalized medicine products and could be used to develop a rating system to determine the quality of evidence regarding them. Such a discussion should include a plan for developing evidence that is not overly burdensome for any one stakeholder.

We offer these comments as a starting point for a dialog between CMS and PMC, an organization that represents key stakeholders in personalized medicine. A favorable NCD on pharmacogenomics or gene expression profiling will support timely adoption of evidence-based personalized medicine technologies, while a negative decision may restrict patient access and stifle innovation in personalized medicine. **As there is no established path for personalized medicine products at CMS, we urge CMS to work with PMC to develop one.** By working with stakeholders, CMS will be able to develop a uniform system that fairly evaluates personalized medicine products.

Personalized medicine promises to improve the quality of patient care, yet it does not fit within the traditional health care system and currently faces significant barriers to adoption. This letter has addressed only one such barrier. PMC member organizations are committed to addressing barriers and finding solutions to them. We look forward to working with CMS and can be contacted at 202-589-1770 or amiller@personalizedmedicinecoalition.org.

Sincerely,

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