American
Clinical Laboratory
Association

January 18, 2012

Louis Jacques, MD
Director, Coverage and Analysis Group
Office of Clinical Standards & Quality
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore, Maryland 21244

RE: Coverage with Evidence Development (CED) Public Comment & Solicitation

Dear Dr. Jacques,

The American Clinical Laboratory Association ("ACLA") is pleased to have this opportunity to submit comments to the Centers for Medicare and Medicaid Services ("CMS") in response to its November 7, 2011, request for stakeholder comments on their experiences with the Coverage with Evidence Development ("CED") policy. ACLA is an association representing independent clinical laboratories throughout the country, including local, regional and national laboratories.

ACLA previously commented on the 2005 Draft Guidance implementing the CED policy. The primary issue of concern to ACLA members in 2005 – the potential for CED to delay development and clinical use of new and innovative clinical laboratory tests – persists today. Indeed, recent actions by CMS and local contractors on coverage for molecular diagnostic testing have amplified those concerns.

To date, CED has been used to restrict coverage of innovative drugs and genetic tests at the cutting edge of medical research (e.g. genetic tests for warfarin, off-label use of cancer drugs.) CDC released a recent study showing that warfarin was implicated in *one third of the emergency hospitalizations* among adults over the age of 65; many of those emergency visits could have been averted by using the genetic test for warfarin response. Medicare's decision to cover the test only under CED was based on the argument that the test had not yet been shown to improve long term outcomes in clinical practice.

While Medicare's CED research may collect valuable new evidence in the long run, the decision to restrict coverage for beneficiaries outside of the CED trials is short-sighted. Additionally, Medicare's policy has led to private payers' deciding not to cover the genetic test until the Medicare trials are complete. The combined effect of those decisions has resulted in a situation where private insurers are not collecting any data on the use of the test in the commercial (under-

65) marketplace, and the Medicare program is missing opportunities to lower healthcare costs by averting warfarin related hospitalizations.

ACLA recommends that CMS examine ways to improve the CED process to alleviate these issues, which are described in more detail below. We appreciate the opportunity to submit these comments, and would be pleased to provide additional information as needed.

Laboratory Tests are Diverse in Their Makeup and Application. We urge CMS to recognize the diversity of tests and their applications and to appropriately prioritize the use of CED on those tests where the knowledge gained will justify the substantial time and expense involved.

The range and diversity of genetic tests is enormous. According to the National Institutes of Health GeneTests online web site (http://www.genetests.org/), there are over 1,600 different diseases for which genetic tests are available. Performing CED studies on this quantity of tests would be an overwhelming task; thus, CMS' prioritizing the use of CED in evaluating clinical laboratory tests is essential.

Likewise, these tests have multiple applications. Diagnostic tests can be used to:

- Detect diseases before symptoms appear – enabling earlier and improved treatments and cures, while averting disease progression and disability;
- Improve patient outcomes and reduce the cost of care by determining which patients do or do not require more costly, aggressive interventions, and evaluating which physicians are practicing in accordance with evidence-based best practices;
- Manage patient care in hospitals where clinical lab tests are used to determine whether a patient should be admitted, what treatment options should be used, and when a patient should be discharged;
- Measure or assess quality of care provided to patients with specific conditions;
- Predict the benefits or harms of taking specific medications, moving drug treatment away from a "one-size-fits-all" approach to a "right drug for the right patient" or "right dose for the right patient" approach; and
- Provide patients and physicians increased control over chronic conditions through personalized "real-time" treatment and disease management regimens – yielding rapid results tailored to a patient's unique circumstances.

Given the broad range of applications for clinical laboratory tests in the Medicare program, CMS' assessments of the evidence should also take into account these varied applications in deciding what level of evidence is appropriate for any given test. For example, where a test is being used to confirm a diagnosis, less rigorous evidence may be sufficient to demonstrate the utility of the test. Where significant therapeutic decisions may be made based on the test results, a higher level of evidence may be required.

Likewise, in contrast to the typically direct relationship between a therapy and health outcomes, the relationship between a laboratory test and health outcomes is usually indirect. It is essential to recognize this difference when planning and conducting CER, including in setting priorities and selection of study design, outcome measures, and other aspects.

Existing Standards are Sufficient for Evaluating Evidence. Well accepted standards exist for judging most clinical diagnostic testing. For the most part, these standards focus on two necessary and complementary requirements (1) the analytical validity of the test - does it consistently and accurately measure the analyte for which it is testing - and (2) the clinical validity - does it consistently identify the clinical condition associated with the analyte in the patient population for whom the test is intended.

Beyond analytical and clinical validity, an assessment of the utility of a diagnostic test should be informed by evidence of the extent to which the results of the test can influence patient management. Because this is dependent upon treatment and other diagnostic options, evidence requirements should be tailored to the condition for which the test is designed.
By nature, diagnostic tests have an indirect impact on health outcomes when compared with therapeutics. Therefore, the evidence of diagnostics' impact on health outcomes may be less direct than the evidence of therapeutics' effects on health outcomes. The perceived benefits gained from lengthy, comprehensive evidentiary methodologies must be balanced against the significant opportunity costs such methodologies often can impose, including disincentives to medical innovation and delayed or denied access to diagnostics that could have avoided negative health outcomes and their associated costs.

It is rare for a laboratory to conduct prospective randomized clinical trials to show that a molecular diagnostic test has clinical utility; this information usually is deduced from other available evidence. Coverage of new molecular diagnostic tests could be delayed by years if CMS and its contractors accept only published studies from peer-reviewed journals of prospective randomized clinical trials, or, in the absence of such studies, refuse to accept other evidence of clinical utility.

Evidence to Support Medicare Coverage Should Expand Beyond Clinical Trials.
Randomized controlled trials (RCTs) should not be the default study design for establishing Medicare coverage of laboratory tests. The need for an RCT is diminished when the therapeutic decision based on accurate test information is well established and when there is strong evidence pertaining to the impact of the therapy on patient outcomes or on a validated surrogate outcome. For example, to determine whether a given test can predict recurrence of a condition, the only way to perform a RCT would be to track patients prospectively over a long period of time to determine whether the condition returned prior to some set endpoint. It could be many years before the results of such a study would be known, thus delaying unnecessarily the availability of an important diagnostic tool and important information for patients.

There is a broad spectrum of evidence that could be considered in evaluating diagnostic tests. While RCTs may be the "gold" standard for some procedures and therapies, they may have significant limitations when applied to many diagnostic situations. Studies of the evidence for laboratory testing should draw on the full portfolio of evolving methods for comparative effectiveness research.

- For example, certain observational studies can provide useful evidence for clinical validity and clinical utility of laboratory tests, including variations in traditional clinical

trial designs; "data mining" of claims data, patient registries, and EHRs; retrospective studies of specimen remnants; and analyses of linked data sets of laboratory data and patient outcomes.

- Genetic testing is often performed and validated using archived specimens that have been stored and catalogued. It is often possible to use such samples, consistent with principles of informed consent and appropriate treatment of patients and patient specimens, to determine whether an individual with a given genetic profile ultimately had a recurrence, or responded to a particular drug or therapy. Such retrospective reviews of archived specimens, in lieu of prospective clinical trials, can result in more rapid determination of the utility of a diagnostic procedure, without adversely affecting incentives to develop beneficial new tests.

Thank you for reviewing our comments. We look forward to working with CMS as it continues to refine the CED policy. If you have any further questions or comments, do not hesitate to contact us.

Regards,

Jen Bowman

Vice President, Policy and Regulatory Affairs

American Clinical Laboratory Association