



**Association for Molecular Pathology**  
*Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology*

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Public Comment from the Association for Molecular Pathology (AMP)

***In vitro Diagnostic Multivariate Index Assays (IVDMIA)***

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Greeting:

AMP is an international not-for-profit educational society representing over fourteen hundred physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing. For the last several years AMP has provided national leadership to advance safe and effective practice and education for molecular diagnostic testing in the health care industry. AMP is “dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics.” Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

AMP supports the development of tests and test systems for *in vitro* diagnostic use and encourages industry to pursue FDA clearance and approval where current regulations require. We would like to comment on the recently issued draft guidance In Vitro Diagnostic Multivariate Index Assays or IVDMIA’s.

The FDA defines IVDMIA’s as “test systems that employ data, derived in part from one or more *in vitro* assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease.” In this guidance, FDA asserts that IVDMIA’s are not within the ordinary “expertise and ability of laboratories” and therefore “raise safety and effectiveness concerns”. The FDA then advises that these test systems meet pre- and post- market review requirements for class II and III devices. AMP questions the agency’s interest in regulating medical algorithms, particularly those that are disclosed by the manufacturer and are transparent to both the laboratory and clinician. The use of an interpretive algorithm is routine in medical practice and should not in and of itself raise specific concerns with the FDA. Algorithms using patient information such

as tumor size, extent of malignancy, and node involvement have long been used to determine recurrence risk and to classify certain cancers. Many laboratory tests cannot be properly interpreted unless patient data is collected. One example is interpreting a glucose reading without knowing when the patient last ate. Many algorithms are published with peer review and are available for professional scrutiny.

As our members routinely design and perform many molecular tests in oncology, hematology, human genetics and infectious disease, we are particularly concerned about the broad language in the document. We feel it could severely reduce the availability of certain laboratory developed testing services, and compromise the quality of molecular test development by laboratories under CLIA, many of which have become the diagnostic or prognostic standard of care. Reduced availability of testing services would limit a healthcare provider's ability to manage patient care, and ultimately limit patient access to new or improved molecular tests. For example, broad interpretation could classify maternal serum screening or Bayesian analysis for cystic fibrosis carrier screening, both of which use well-defined risk calculations, as IVDMIA's. Laboratories offering these tests would not likely be in a position to meet the FDA requirements as manufacturers.

The FDA identifies IVDMIAs not as laboratory-developed tests but as test "systems" that combine data derived from the laboratory assay with an algorithm or calculation to reach a patient-specific result. This definition is not found in the Federal Food, Drug, and Cosmetic Act nor in any regulation from the FDA and was not developed through notice and comment rulemaking. Within this proposed definition, the laboratory is the manufacturer of a test system that is subject to FDA regulation as a medical device. We are unaware of such a definition in any FDA regulation. This area of laboratory operation currently is regulated by the Centers for Medicare & Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988.

AMP respectfully requests that:

- **FDA provide the scientific rationale for their new concerns over the safety and effectiveness of laboratory-developed tests, as well as a justification for their jurisdiction over medical testing algorithms.**
- **FDA convene a classification panel (e.g., as was done in the reclassification of immunohistochemistry tests) so that criteria for determining which tests will be subject to FDA regulation will be transparent to laboratories developing such tests.**
- **FDA clearly and specifically define the scope of IVDMIAs that it intends to regulate.**
- **FDA ensure that any new guidance does not insert FDA into the purview of CMS' regulation of laboratories under CLIA.**
- **FDA apply restrictions requiring PMA or 510(k) clearance of an IVDMIA only when the interpretive algorithm remains undisclosed by the manufacturer.**

- **FDA clarify the scope of its regulations that renders laboratories responsible for meeting criteria as medical device manufacturers, i.e., pre-market review only or all general controls (registration and listing, quality systems, labeling, medical device reporting).**

Thank you for the opportunity to comment on this important document. AMP will provide a formal written comment to the docket, and remains available to work with FDA to develop clear, reasonable guidelines consistent with FDA's mission to "promote and protect" public health in the development of molecular pathology tests, balancing safety concerns with access and availability of exciting new medical breakthroughs.