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Andrew C. von Eschenbach, MD
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5630 Fishers Lane
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**RE: Draft Guidance for Industry, Clinical Laboratories, and FDA
Staff on in Vitro Diagnostic Multivariate Assays (IVDMIA)
(Docket # 2006D-0347)**

The American College of Medical Genetics (ACMG) welcomes the opportunity to comment on the draft guidance on in Vitro Diagnostic Multivariate Assays (IVDMIA) that was recently made available. The ACMG is a medical specialty association whose members include clinical geneticists and clinical genetics laboratory directors in the United States who are board-certified in the specialty of medical genetics. Included in the mission of ACMG are: to advance the art and science of medical genetics by maintaining high standards in education, practice and research; to increase access to medical genetic services and improve public health; and to promote effective and fair health policies and provide technical assistance to government agencies, professional organizations and other medical specialties.

Initially, it is unclear to the ACMG and its members precisely what problems these new guidance documents have been developed to address. There has been considerable commentary about the need to improve the quality of genetic testing on the presumption that such quality problems do, in fact, exist. These claims have typically been unsubstantiated or overly generalized to such an extent that it is unclear whether such problems are specific to genetic testing or merely common to laboratory medicine. For instance, hearings this summer of the House Committee on Aging identified problems related to *nutrigenomic* testing. To the extent that laboratories selling these tests are unable to substantiate their claims based on classical measures of clinical and laboratory test performance characteristics, they are inappropriately advertising and

marketing tests to the public. Clearly, these and other areas of so-called “laboratory medicine” should be addressed by the FDA, the Federal Trade Commission and States Attorneys General, as appropriate. However, such direct-to-consumer and other questionable laboratory test offers should not be confused with long-standing and successful methods developed and utilized by CLIA-regulated clinical genetics laboratories. Moreover, we feel that the potential abuses of such activities are best dealt with (aside from the Federal Trade Commission) by stringent enforcement of existing CLIA/CAP regulations and guidelines for proper test validation, including special attention to issues of clinical validation and utility.

The IVDMIA guidance document addresses the use of tests with underlying computer algorithms that integrate a number of analytical results in order to calculate risks to patients. Although we recognize that there are some tests for which enhanced oversight would be important to the protection of the public and patients, the general language used in this guidance could bring other tests under this rule for which inclusion seems less appropriate and that could impact access to important tests. We are dividing our comments into a section on scientific and clinical issues specific to the IVDMIA guidance document and another addressing issues related to FDA oversight of clinical laboratories.

IVDMIA Guidance Proposal

The ACMG favors transparency in the presentation of the methods used in testing and the information used in the interpretation of the results. Towards that end, it is our view that there are a subset of tests that are potentially captured under this guidance (e.g., some expression arrays) for which oversight of the clinical validity of the markers that are integrated into the underlying algorithms for risk calculation should be assured in order to ensure that the public accesses genetic tests that are safe and effective. Further, we assume that multiplexed genomic arrays do not fall under this rule because multivariate analysis is not required to interpret test results.

Our comments also are directed at the possibility that other important tests, such as prenatal screening for open neural tube defects and Down syndrome, tandem mass spectrometry for biochemical genetic conditions when operated using multiple reaction monitoring (MRM), and DNA microarrays for detection of cytogenetic copy number aberrations may be covered by the FDA’s in vitro diagnostic multivariate index assays (IVDMIA) document proposing additional oversight (www.fda.gov/cdrh/oivd/guidance/1610.pdf). We believe that these clinical assays should not be covered under this proposed guidance document. For example, maternal serum screening does not meet the definition of an IVDMIA and should be excluded from these regulations.

Specifically, they do not meet characteristic 2 of the definition (page 3) which states:

“Employ the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a classification, score, or index). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test.”

Maternal serum screening certainly meets the criteria stated in the first paragraph. Combinations of three, or more, markers are commonplace and an algorithm combines these results with maternal age to compute a patient-specific risk for Down syndrome. The second sentence indicates that to be considered an MIA, other entities cannot independently derive the same results without access to proprietary information. This is not the case for maternal serum screening. It is not only possible to independently derive another laboratory's risk estimate; this is routinely done as part of external proficiency testing. Since 1990, the FP-survey offered by College of American Pathologists (CAP) has routinely 'checked' the computation of Down syndrome risk for participating laboratories. This is done by having the laboratory list the source of its data (parameters) used to compute the Down syndrome risk (these parameters are nearly always published in peer-reviewed journals). The laboratory's responses for maternal age and the serum markers' results are combined with their parameters to independently derive a Down syndrome risk (calculations performed under the auspices of CAP). That risk is then compared to the one reported by the laboratory. Currently, CAP carries out this exercise successfully for more than 90% of participating laboratories (five challenges, three times per year). Most of the remaining laboratories are outside of the United States, or use parameter sets that CAP has not yet implemented because they are relatively rare. Whether, and how, risks have been validated is part of routine CAP inspections that many laboratories undergo and is contained on the chemistry checklist (www.cap.org/apps/docs/laboratory_accreditation/checklists/chemistry_and_toxicology_april2006.pdf, question CHM.32200). Given that an external body has for years, independently derived and validated Down syndrome risks, it would also be possible for another laboratory to do so. A similar proficiency testing program is now being instituted for first trimester (and integrated) Down syndrome screening that will validate those risks.

Because Down syndrome risks are being routinely derived independently and checked for nearly all laboratories offering screening in the United States, such testing does not qualify as an IVDMIA and should be specifically exempted.

With regard to the CGH arrays for copy number variants that are beginning to replace classical cytogenetics and targeted fluorescence in situ hybridization (FISH) assays, it is important that these tests be considered against the traditional risk assessments done by FDA, a concept that is not acknowledged in the current IVDMA draft guidance. It is important to recognize that unlike many molecular tests used in genetic testing laboratories, CGH arrays have prior gold standard technologies (cytogenetics and FISH) against which they are compared. Over 8,000 of these tests have been done at the current time and their use is expanding rapidly. The great majority of tests provided are to improve the limited resolution of cytogenetic testing and to improve the cost of such testing through a higher resolution assay used in individuals with indications for testing that are no different than have been used in cytogenetics for decades. However, tests are interpreted in the same way that classical cytogenetic results are interpreted. Further, it is important to appreciate the differences in the mathematical algorithms used in these tests. They don't integrate tests results with other patient demographic information except for the clinical indications for the testing. They merely provide a high resolution method by which gains or losses of portions of the genome are graphically displayed. Similar to the prenatal screening tests discussed above, results of CGH arrays can be independently derived and confirmed by other laboratories with targeted assays. Further, they do not meet definition 1 of the IVDMA in that they do not "integrate any clinical data to empirically identify variables..." nor do they "employ the algorithm to integrate these variables in order to calculate a patient specific result". Rather, these tests identify genomic regions of gain and/or loss that can be confirmed by another laboratory with a more targeted test.

FDA Oversight of Clinical Laboratories

More generally, the ACMG and its members have significant concerns about the apparent intention of FDA to oversee laboratory-developed tests. There seems to be a total lack of recognition of the considerable differences between laboratory tests developed by manufacturers vs. those developed in individual clinical genetics laboratories. The manufacturing community has shown limited interest in developing kits and tests for the great majority of genetic tests, particularly those for rare and orphan diseases. Their reticence results from the lack of financial incentives to develop products whose costs of development would not be recouped because of limited sales. It was only after promulgation of the ASR rule that a few manufacturers were willing to develop some of the critical reagents used in laboratory-developed tests with FDA oversight. Financial issues are, of course, greatly exacerbated for individual clinical genetics laboratories. If FDA now was to require individual clinical genetics laboratories to submit to oversight and comply with, among other things, the FDA Quality Systems Regulations, the costs of testing conducted by clinical laboratories would become prohibitive, thereby negatively impacting access. Some laboratories

would be forced to remove many tests from their menus. For others, the costs involved in test development combined with the costs of FDA oversight and the associated paper trails would greatly increase the price of genetic tests. This, together with the current low levels of reimbursement for genetic testing, would significantly limit access to only those patients and families who can independently pay for the testing, and many laboratories would simply drop these tests from their menu.

Further, the clinical genetics laboratory community is having great difficulty understanding precisely how FDA could oversee their work in a reasonable manner. Many aspects of the rules that currently apply to manufacturers are inappropriate and unworkable as applied to individual clinical laboratories, and there appears to have been little, if any, consideration of how those rules could be modified to work in the individual laboratory setting. Although it appears that FDA currently is pursuing testing that it considers “high risk”, the mere fact that it leaves open the possibility of further expanding this oversight puts clinical laboratories in the precarious position of having to decide if the combined costs of test development and increasing regulatory oversight prohibit their developing a particular test. These financial issues are further exacerbated by the fact that many of these tests still would be considered investigational (and, thus, not reimbursed or only nominally reimbursed). This scenario would seriously jeopardize future development of many orphan disease tests, many of which already are beset by the difficulties in attaining the statistical power needed to meet historic norms for FDA approval. Moreover, the laboratories that would be most severely affected by this rule change would be those in academic settings – the laboratories that drive advancement and innovation in genetic testing through relatively low volume service delivery. These laboratories commonly develop their genetic tests through a slow iterative process that allows for the tests to evolve in pace with the development of new knowledge. The mere anticipation of such action would have a chilling effect on future test development and advancement of the field, as these laboratories would consider it more prudent not to venture in those directions and instead stick to routine high volume testing.

Finally, for many years, clinical laboratories have operated under the assumption that their practices are regulated through the CLIA process. Congress assigned this responsibility to the Centers for Medicare and Medicaid Services (CMS) and the Department of Health and Human Services has affirmed this through its development of the CLIA rules. Although we acknowledge that CLIA currently sets a relatively low bar for genetic testing laboratories, we strongly believe that the appropriate remedy for this deficiency would be the development of more stringent CLIA requirements, rather than new regulatory requirements from FDA. We are very concerned that the as-yet-unstated plans for FDA to become more directly involved in the oversight of laboratory-developed tests has,

itself, interfered with the development of improvements to CLIA oversight of genetic testing. The fact that recent FDA guidance documents have emerged simultaneously with the surprise decision by HHS to *not* pursue recommendations from the Clinical Laboratory Improvement Advisory Committee (CLIAC) to develop a genetics specialty under CLIA is quite troubling to the clinical genetics community. It is important that a clear plan for how FDA might regulate clinical laboratories be offered. In fact, the proposed unprecedented shift to the regulation of individual laboratories is so significant that actions such as these should be subject to the rule making process under the Administrative Procedures Act. Through our contractual relationships with the College of American Pathologists (CAP) to deliver proficiency testing (PT) to genetics testing laboratories, we have been making steady improvements to both PT and the on-site inspection checklists to expand the requirements on laboratories for documenting analytical and clinical validity of the tests they offer. Further, performance on PT in molecular diagnostics among laboratories participating in the most comprehensive and stringent program available (CAP) has been good.

In summary, while we appreciate FDA's desire to ensure safe and effective testing for the public, we are greatly concerned that application of the proposed guidance would have precisely the opposite result. Towards that end, the ACMG encourages FDA to:

- ◆ refrain from making changes to the way in which laboratory practices are overseen and, thereby, fundamentally and significantly alter the way laboratories currently operate, without a rule making process as required under the Administrative Procedures Act;
- ◆ be considerably more explicit about how they would regulate individual laboratories differently than they do manufacturers in order that the community can reasonably assess the impact of the guidance changes;
- ◆ be more explicit as to the tests and technologies considered to be subject to FDA oversight to avoid slowing innovation of clinical laboratories and manufacturers;

It is important that FDA seek mechanisms through which dialog with laboratory medicine practitioners and industry can be engaged. The ACMG would be glad to work with FDA and CLIA to find more appropriate mechanisms to both ensure the safety and effectiveness of genetic tests and ensure that tests for rare and orphan diseases remain accessible to the public.

Sincerely,

A handwritten signature in black ink, reading "Marilyn C. Jones, MD". The signature is written in a cursive style with a large, prominent initial "M".

Marilyn C. Jones, MD
FACMG
President

A handwritten signature in black ink, reading "Michael S. Watson, PhD". The signature is written in a cursive style with a large, prominent initial "M".

Michael S. Watson, PhD,
Executive Director