

Selected Annotated List of Comments to FDA's September 2006 Draft IVDMIA Guidance Document

Compiled by the Genetics & Public Policy Center

<i>Commenter</i>	<i>Summary of Comments</i>
20/20 GeneSystems, Inc.	FDA's proposal will deter investment in diagnostics, which will discourage innovation, delay the launch of life-saving tests, and discourage product development for personalized medicine and rare diseases. Instead of the draft guidance, FDA should request that Congress provide incentives to accelerate development of new tests and FDA establish a publicly accessible database where labs would provide information about tests.
Advanced Medical Technology Association (AdvaMed)	Supports goals identified in draft guidance. Most members of AdvaMed believe FDA has jurisdiction over IVDMIAs but a few believe IVDMIAs should be subject to CLIA only. Requests further stakeholder input. Requests that FDA clarify which products are subject to regulation before new rules implemented. Requests transition period for labs to comply with new requirements. FDA's IVD approval process needs streamlining to reduce burdens and increase speed. A guidance document may not be most appropriate way to proceed.
American Association for Clinical Chemistry	Supports goals identified in draft guidance but thinks FDA should collaborate with CMS to address its concerns through enhancement of CLIA. Fears that the proposed regulations will be a threat to innovation. Requests that FDA clarify certain ambiguities, particularly in IVDMIA definition and the scope of the IVDMIA requirements and their interaction with CLIA requirements. Believes low-risk tests should be exempt from regulation. FDA should also consider impact on test availability.
American Clinical Laboratory Association	Supports FDA's goals of dispelling regulatory confusion but not its approach to regulating IVDMIAs. FDA should withdraw the draft guidance and proceed through formal notice and comment rulemaking. FDA should narrow and clarify the scope of the IVDMIA draft guidance. FDA should work with CMS to enhance CLIA, which may eliminate need for separate FDA oversight. Also fears that the draft guidance will stifle innovation.
American College of Medical Genetics	Unclear as to what problems the new guidance documents have been developed to address. Strongly believes that enhancements to CLIA are the appropriate way to address deficiencies in laboratory oversight rather than regulatory requirements from FDA. Fears that the proposed regulations will be a threat to innovation, drive up cost and reduce access. Requests that FDA clarify which tests are considered to be subject to FDA oversight.
American Society for Clinical Laboratory Science (ASCLS)	Supports goals identified in draft guidance. Requests that FDA clarify the definitions of IVDMIAs and Class I vs. Class II devices, as well as the differences between the 510(k) and PMA processes. Requests further communication between the FDA and stakeholders, possibly through rulemaking.
American Society for Microbiology	Strongly supports oversight for high-risk laboratory tests, but finds draft guidance difficult to understand and apply. Requests clarification about how the guidance will apply to infectious disease diagnostics, what tests are subject to

	regulation, and what requirements will be. Also asks how the FDA's resources will be augmented in order to complete the IVDMA review process in a timely manner.
American Society of Clinical Oncology	Endorses FDA oversight of IVDMIAs but believes that notice and comment rulemaking and public participation are required. Raises concerns about breadth of IVDMA definition, inadequacy of information regarding regulatory pathways, negative impact on access to tests labeled investigational, conflicting jurisdiction between FDA and CMS, and negative impact on investment in test development. Requests transition period for labs to comply with new requirements.
Association of American Medical Colleges	Supports goals identified in draft guidance and believes FDA is capable of providing the oversight. States that FDA should regulate IVDMIAs in the most expeditious and efficient manner possible. FDA should clarify that the guidance does not apply to research-only tests. FDA might consider "preliminary" or "conditional" approval followed by post-market surveillance.
Association of American Physicians and Surgeons	Opposes FDA's regulation of IVDMIAs. States that such regulation interferes with the practice of medicine and that FDA does not have jurisdiction over laboratory-developed tests. FDA regulation could deter innovation and impede physicians' ability to respond to new health threats. Draft guidance will imperil patient safety.
Association for Molecular Pathology	Questions FDA's interest in regulating medical algorithms. Fears draft guidance could severely reduce availability of tests. Notes that FDA identifies IVDMIAs not as laboratory-developed tests but as test "systems", a definition that is not found in the Federal Food, Drug, and Cosmetic Act. FDA should provide scientific rationale for its concerns and justify its jurisdiction to regulate medical testing algorithms.. FDA should convene a classification panel to develop clear criteria for determining which tests subject to FDA regulation and clarify requirements that laboratories must meet. FDA should apply premarket review requirements to IVDMIAs only when interpretive algorithm is not disclosed by manufacturer and should not regulate areas regulated by CLIA.
AviaraDx Molecular Medicine	Questions classification of IVDMIAs as medical devices and FDA's jurisdiction to regulate them. Asks why the FDA proposes to regulate IVDMIAs but not other laboratory-developed tests. States that if there is going to be a change in regulation, a substantial transition period is necessary. Raises concern that proposal will deter innovation for tests for unmet clinical needs. Proposes that FDA and CLIA regulate new tests based on risk rather than complexity of technology.
Mary Barry, health professional	Believes that CLIA does require clinical validation of tests. If it does not, believes all testing would be made safer if CLIA regulations were modified to specify requirement for clinical validation of tests.
Baylor University Medical Center	Raises many questions about the intent and impact of the guidance. Asks whether the guidance intends to regulate a laboratory technical component, the statistical analysis of testing result, or the clinical application of the test. Asks whether FDA will guide the criteria of the IVDMA testing specificity and sensitivity in diagnosis and prediction of diseases, the minimum number of patient specimens used in testing validation, and the statistical methods employed to generate the algorithm. Will the cost of premarket and postmarket requirements for IVDMA tests be a concern in the future development of new clinical tests after the implementation of the guidance?

BioSignia	Supports FDA oversight of new IVDMIAs but suggests reconsideration of policy on older multivariate models that predict chronic disease risk, since older models can be interpreted by a physician. Notes also that some of the older tests are confined to long-term diseases with low-risk prevention plans such as weight loss. Proposes a change in the definition of IVDMIA to emphasize the necessary tight linkage between the assays and the algorithms.
BlueCross BlueShield Association	Supports FDA's regulation of IVDMIAs. Suggests that IVDMIA definition be clarified. Notes that pre-market approval is particularly important when the test leads to treatment recommendation, but that tests solely predicting risk should also be evaluated for harms that might necessitate pre-market approval. Recommends extending regulation to all "home-brew" testing.
CardioDx	Regulation of IVDMIAs by two federal agencies seems unnecessary; if more oversight is needed, CLIA should be strengthened. Proposal will impede test development because of additional cost and time, particularly for smaller companies that develop tests for rare diseases. Requests clarification on FDA's data expectations and on which tests will be covered and why. Regulation should depend on risk associated with the test rather than complexity. Guidance should accommodate tests for which development is already underway. FDA should collect information on specific tests to determine whether there are specific problems and should proceed via rulemaking.
Cepheid	Refrains from comment on whether laboratory testing services warrant FDA review. Requests that FDA convene a classification panel, followed by formal rulemaking, to determine which laboratory services should be subject to FDA regulation. Classification should be determined based on risk rather than technology. Requests clarification regarding the conditions under which software and/or medical algorithms would be considered medical devices and the rationale for FDA's concerns. Requests clarification regarding what FDA laboratory requirements will be, as well as whether LDTs receiving 510(k) clearance may serve as predicate devices for future LDTs or IVDs. Expresses particular concern about market disruption for products for rare or emerging diseases.
Ciphergen Biosystems	Concerned that the guidance introduces an unnecessary regulatory burden into an area already regulated by CMS; believes strengthening CLIA is a better alternative. Proposed guidance will stifle innovation and drive up costs of tests, and represents an intrusion into the practice of medicine. Guidance is imprecise and may result in non-standardized interpretation and enforcement. Unclear what data will be required to support 510(k) or PMA. If FDA regulates IVDMIA, there should be a transition period.
Claire Altman Heine Foundation	Expresses concerns about draft guidance in its current form. Guidance would prohibit or delay vast majority of LDTs, causing unacceptable delays to patients. FDA should delicately balance safety and accuracy of tests with well-being of patients.
Clariant, Inc.	Expresses several concerns with draft guidance and suggests strengthening CLIA regulations as alternative. Fears additional regulation will stifle innovation; only tests with large market potential will be developed. The definition of an IVDMIA and the regulatory path are unclear, particularly with respect to modifications of LDTs. Requiring review of every change will hinder improvements. Restrictions on labeling and promotion conflict with CLIA requirements. Suggests establishment of test registry as knowledge base for future regulations, exemption of tests that are low risk or that serve small patient populations, establishment of transition period, and clear delineation of authority between FDA and CMS. Guidance could intrude into practice of medicine. Suggests rule-making as appropriate

	procedure.
Clinical Laboratory Management Association	Believes FDA regulation will stifle innovation by increasing costs and time. Recommends that continued regulation of IVDMIAs remain under CLIA. Argues that clinical laboratory tests are services, not commodities. FDA should clarify definitions of IVDMIA and ASR and provide examples. FDA should use the Agendia MammaPrint Test (first cleared IVDMIA test that has claims for genetic profiling for breast cancer) as a “field-tested” template for guidance. Needs to be a transition period during which clinical professionals provide input.
Coalition for 21 st Century Medicine	Proposes that notice and comment rule-making be used and a public workshop be convened. Suggests enhancing CLIA and creating an IVDMIA registry and genetic specialty under CLIA. FDA’s regulation of LDTs should be risk-based rather than technology-based and should be grounded in intended use (e.g. whether claims are intended to make a definitive diagnosis, or to make a yes/no treatment decision). There should be exemption for tests that deal with rare disorders. IVDMIAs supported by data from studies following methods that are accepted by experts in relevant fields should be approved even if uncertainty remains about the clinical utility of the tests, which can be addressed through transparency and disclosure in labeling. FDA should identify the algorithm as the medical device subject to regulation and should allow a reasonable transition period.
College of American Pathologists	Supports FDA’s goals, but believes they would be best achieved through enhancement of CLIA, given the established relationships between labs and CMS. However, if FDA proceeds on this path, recommends that FDA 1) clarify definition of IVDMA, 2) exempt tests that can be independently verified by broader medical community through published methodologies and clinical studies, and 3) limit additional regulations to when tests cannot be independently verified or when there is reason to believe the public’s health is at risk.
Consumer Task Force on Genetic Testing, established by the Genetic Alliance	Asserts that FDA should regulate by rulemaking and should take a broader, more patient-centered perspective. Unclear who and what are covered and unclear whether the guidance reclassifies laboratory services as devices, and if so whether reclassification is appropriate. Should be risk rather than technology-based. Concerned with FDA’s ability to share interest in keeping pace with discovery and commercialization. Concerned that guidance may impede patient access to tests. Guidance interferes with the practice of medicine, changing practice of laboratory physician reporting to ordering physician. Suggests creation of genetics specialty under CLIA as way to address concerns. Also suggests transition time.
Eli Lilly	Supports FDA’s efforts to clarify the regulations and develop policies to address various issues regarding IVDMIAs States that the requirements outlined in the draft appear to be reasonable with the least burdensome approach to manufacturers.
Exagen Diagnostics, Inc.	Overall, pleased with the document. Agrees that IVDMIAs are medical devices to be regulated by FDA. Notes that intended uses of new IVDMIA products greatly vary and may warrant a variety of regulatory approaches. Requests clarification of definition and regulatory status of IVDMIAs; notes that it is clear that IVDMIA applies to laboratories, but not whether it applies to manufacturers.
Expression Analysis	Fears guidance could significantly affect the ability and incentives for labs to develop innovative new tests. Concerned that it introduces unnecessary regulatory burden and believes that modifications to CLIA would be the better approach or, as alternative, the creation of an LDT registry. Should FDA move forward, recommends

	substantial modification to the guidelines. Seeks clear delineation of responsibility and authority between FDA and CMS, identification of standards used to classify IVDMIA. Recommends that tests serving small patient populations be exempt from regulation, and that PMA be required only for tests that are high risk and that result in binary therapy recommendations based solely on test outcome. Would further request a transition period and notice and comment rulemaking.
Genentech, Inc.	Supports FDA's rationale for the draft guidance and risk-based approach to regulating IVDMIA, and particularly supports oversight of IVMDIAs that are used as predictive diagnostics. Believes that oversight could avoid at least three unacceptable scenarios: 1) a patient being deprived of a potentially life-saving or life-extending medicine because of a negative test result to an assay that does not appropriately correspond with all responders of medicine, 2) a patient unnecessarily being administered a medicine, and 3) the substitution of an FDA-sanctioned assay with an assay that has not undergone appropriate clinical validation.
Genetics and Public Policy Center	Supports FDA's involvement in IVDMIA oversight but identifies several concerns. First, FDA should consider genetic tests holistically rather than piecemeal, adopting a risk-based approach to all LDTs rather than separating IVDMIA from all others. FDA should engage all stakeholders before making binding changes and should clarify at the outset its overarching goals in developing the new regulations. Finally, FDA should provide more clarity regarding the definition of IVDMIA and how its regulations will interact with CLIA requirements.
Genomic Health, Inc.	Calls for notice and comment rulemaking and for FDA to convene public workshop before publication of proposed rule. Does not concede that FDA has authority to regulate laboratory services as medical devices, but if FDA proceeds to regulate them as such, proposes that FDA more clearly define IVDMIA, identify the algorithm as the medical device subject to regulation, and allow a transition period. Further suggests that regulation of tests be risk-based and allow for clearance/approval under least-burdensome means, and that FDA ensure that the regulations do not conflict with and are not redundant with respect to CLIA.
Genzyme Genetics	Requests workshop for FDA and interested stakeholders to discuss draft guidance. Concerned about impact on innovation and patient/physician access to new technology. Notes that for conditions affecting small numbers of patients, the only access to valuable testing is through LDTs. Fears that the proposed guidance will be cost-prohibitive for labs, and that diagnostic testing, and therefore personalized medicine, would suffer enormously.
Genzyme Corporation	Requests participatory dialogue process involving other relevant federal agencies and stakeholders, particularly about impact on future innovation. Suggests that definition of IVDMIA be clarified and narrowed so as to exclude well-established tests that FDA may have unintentionally covered in its definition. Urges FDA to address potential conflicts or redundancy with CLIA. Requests transition period.
Hoffman-La Roche	Agrees that FDA has authority to regulate these tests as medical devices and that labs developing in-house tests are acting as manufacturers subject to FDA jurisdiction. Supports the approach outlined in the draft for regulating LDTs in a "least burdensome" way. Urges FDA to clarify the meaning of the term "IVDMIA." Proposes risk-based approach to LDT regulation.
Insilicos Life Science Software	Endorses the guidance document. Notes that physicians rely on accurate information from IVDMIA and believes that risks to patients must be mitigated.

InterGenetics Incorporated	Strongly opposes implementation of draft guidance. Describes impact of FDA's change in approach on its own product development, which caused many investors to pull out. Questions whether FDA's actions were consistent with rulemaking requirements. Proposes augmenting CLIA rather than adding FDA regulations. If FDA does choose to regulate, recommends that FDA develop further guidance for compliance, further define IVDMIA, clearly outline responsibilities to FDA and CLIA and how the interaction will be handled, create an ombudsman to respond to problems when FDA is not responsive, request funds from Congress for managing the anticipated workload, and provide a transition period.
Incontinentia Pigmenti International Foundation	Believes the draft guidance will stifle innovation and reduce the number of genetic tests for diseases like Incontinentia Pigmenti, negatively impacting public health. Recommends that FDA not implement the guidance.
Invitrogen Corporation	Believes the draft guidance is a starting point for regulating IVDMIAs but expresses concern that if it is implemented as written, innovation will be stifled and access to tests will be impaired. Proposes a workshop to allow stakeholders the opportunity to develop a guidance document with the FDA, more formal rulemaking procedures, clarification on how the IVDMIA regulation will work in conjunction with CLIA, and clarification of the definition of IVDMIA. Requests that FDA define a process for the development of "Orphan IVDMIA Products" to ensure availability to small patient populations, and that the FDA allow a process within the developing framework for the continued improvement of tests and timely delivery to clinical laboratories.
Johnson & Johnson	Does not comment on FDA's authority to regulate IVDMIAs but makes several recommendations. States rulemaking is the appropriate procedure to introduce these kinds of changes. Requests a transition period to allow labs to adjust to new regulations and to permit continued availability of ASRs. Suggests that classification and regulation of LDTs be risk-based.
Knowledge Support & Action	Concerned that the draft guidance could be read to suggest that all LDTs are illegal, and that proposal as written could stifle investment or slow down innovative research efforts. Asks that FDA pay attention to input from labs. States that any areas of the draft guidance which might delay or undermine the value of new and innovative tests should be removed.
Life Sciences Management Group	Expresses various concerns with respect to draft guidance and proposes creation of registry of IVDMIAs instead, which could then inform regulations. States that FDA's draft IVDMIA and ASR guidances will reduce the kinds of LDTs that would be available, to the detriment of public health and contrary to FDA and NIH biomarker identification efforts. They will also depress investments in diagnostics. The guidance documents need to clarify the definition of IVDMIA, the relationship between GMPs and CLIA, how modifications of the test would be regulated, and what the device is that is being regulated. Whatever the FDA does, an adequate transition period is necessary. FDA should implement changes like these through rulemaking.
Marti Nelson Cancer Foundation	Supports FDA oversight of laboratory tests. Believes that CLIA regulation alone will allow exploitation of consumer. FDA should provide phase-in period and should regulate the clinical claims made for IVDMIAs that have not been previously FDA-regulated. Raises concerns that FDA does not have adequate resources for oversight, that good products will be withdrawn from the market, that CLIA and FDA regulations will conflict, that delays in marketing

	approval will inhibit investment and deter innovation, and that cost of tests will increase. Suggests that products already in clinical use and validated by a third party should be grandfathered or exempt from immediate compliance, that existing tests should not be labeled “experimental” because of insurance coverage concerns, that standards specific to different technologies be clarified, that a mechanism for provisional approval for IVDMIAs used for rapidly emerging infectious diseases be created, that classification standards of an IVDMIA as Class II or Class III be clarified, and that conflicts between CLIA and FDA be clearly reconciled.
Mayo Central Laboratory for Clinical Trials	Welcomes the draft guidance but feels it does not clearly define the new requirements. Suggests requirements for labeling, and inclusion and exclusion criteria for testing. Recommends that the distribution of the data in the test be published. Biological variability data should be part of the submission and included in the labeling. The algorithm in the calculation should be published.
Mayo Clinic Rochester	Requests clarification of definition of IVDMIAs, with accompanying examples. Asks about timelines for submitting test systems already in use, and questions whether FDA has adequate staffing to review submissions in timely manner. Asks whether supplemental submissions will be required if changes are made to a test system, how FDA plans to address inquiries from industry on determining specific classification of a test system, and how FDA plans to educate labs on how the new requirements relate to the old CMS requirements.
Mohr Davidow Ventures	Notes that funding for diagnostics research has historically been much lower than funding for drug research or other devices, and states that the draft guidance in its current form will lead to even less funding. Says that the draft guidance creates tremendous ambiguity and uncertainty. Unclear what types of laboratory services will be subject to regulation by FDA as IVDMIA, what level of regulation that would be, what the definition of IVDMIA is, what the regulatory path is, whether and how labs will comply both with FDA and CLIA requirements, how products or services deemed to be IVDMIAs will be labeled, and what the costs of compliance will be. To attract investors, companies will need more information than the proposed regulatory scheme provides.
National Breast Cancer Coalition Fund	Believes the draft guidance is a step in right direction of establishing more regulation of biomarker assays. Recommends that the FDA incorporate the best components of drug development to guide the development and validation of biomarker assays, review relevant federal law pertaining to biomarker assay oversight and recommend changes where needed, and establish rules for post-marketing surveillance of approved biomarker assays. Draft guidance needs more clarity about how the risk-based approach will be applied to diagnostic tests and whether the definition of clinical utility will be meaningful.
National Tay-Sachs & Allied Diseases Association, Inc.	Is very concerned with the draft guidance. Guidelines lack specificity in identifying which tests are subject to regulation or the problem being addressed. Simpler solution would be to create genetics specialty under CLIA. Guidance interferes with the practice of medicine and could lead to delays in receipt of lab results, which could lead to disease exacerbation or emotional turmoil for expectant Tay-Sachs carrier couples. Medical tests may become unavailable, remain frozen in their current state, become more expensive, or lose insurance coverage. The current guidance does not allow a transition period.
Ovarian Cancer National Alliance	Seeks clarification of benefits of the proposed regulation – what deficiencies is it meant to address? Unclear as to benefit of having FDA, rather than CMS, as regulatory body. Recommends that tests already in use not be pulled off the market as they are evaluated. Guidance is piece-meal approach rather than a big picture plan. Should be

	risk-based rather than technology-based. Regulation should encourage companies to develop tests. The regulatory process must be clear, predictable, and speedy.
Parent Project Muscular Dystrophy	Fears that the draft guidance will impede genetic research on Duchenne muscular dystrophy. Requests FDA withdraw the document and undertake formal rule-making.
Pfizer	Agrees that FDA has jurisdiction over IVDMIAs and that more oversight is needed. However, FDA should only regulate tests where complexity of the algorithm is such that a person skilled in the field would not be able to interpret the results without an algorithm. The risk-based approach is appropriate, but it is unclear how the FDA will apply it. Recommends that tests be allowed on market without FDA review, or with a lesser submission as a Class II device, if intended to be used as a supplement to physician's judgment or other tests. Once the test's performance as a supplementary information source is established, a new submission could enable it to be approved as a first line diagnostic; this approach would not restrict innovation. Suggests that FDA develop additional expertise in this area.
Prediction Sciences	Asserts that there are already barriers to innovation in this field; increased FDA regulatory requirements could further stifle innovation by increasing costs and time required to develop the tests. Smaller companies in particular will have a hard time finding investors. Continued regulation under CLIA would help alleviate financial burdens. If the Guidance is adopted, however, its language needs to be clearer to ensure proper classification of IVDMIAs.
Dr. Bruce Quinn, NHIC – CA Medicare Part B Contractor	States that Medicare can only pay for FDA-regulated tests, so ambiguity regarding FDA domain on a test is problematic for Medicare when making payment decisions. Would be helpful if a waiver statement were available. For example, test A might be submitted for clearance under this regulation and be cleared for marketing. Test B might be submitted as not falling under the regulation, but rather traditional ASR or homebrew testing, and FDA would give assent to that status. Also notes that FDA is coy in stating that it is merely restating existing practice to clarify it, when existing practice has been so vague.
Paul Radensky (law firm representing clinical laboratories/potential IVDMIA manufacturers)	Asserts that FDA must answer several questions before labs can be required to comply with the new regulatory burdens. It must provide a clearer definition of an IVDMIA, identify the medical device within the laboratory service, clarify the pre-market pathways to be followed, explain how to comply with QSRs, explain how labs can meet conflicting requirements of FDA and CLIA, and allow a transition time. FDA should also articulate what concerns it has about IVDMIAs, why CLIA and FTC regulatory controls are insufficient, and how the proposed regulations are the least burdensome approach. The FDA should proceed through Notice and Comment Rulemaking.
Research Advocacy Network	Requests that FDA explain the basis for its decision to issue the draft guidance. Notes that IVDMIAs are not all the same and should not all be treated the same way. Asks how FDA will distinguish between companies with adequate and sub-par research. Asks whether FDA will allow patients continued access to existing tests that are already scientifically validated; believes that these tests should be grandfathered in. Asks when a company has fulfilled its research obligations to demonstrate accuracy and validity. Asks whether IVDMIA developers that have already provided much data attesting to the utility of their tests will have to redo their clinical studies.

Dr. Jon Rosenblatt (health professional)	Asks for definition of “proprietary” and for provision of examples of assays that would be covered. Asks whether the IVDMA would almost always be computer generated and whether interpretations of lab reports and interpretive guides would be included. Asks for clarification of difference between laboratory-derived “consultative” report and the algorithm discussed in the draft. Notes that laboratories might not have the resources to conduct large scale studies that might be required to validate in-house developed IVDMIAs.
Save Babies Through Screening	States that the ASR and IVDMA Draft Guidances may have a negative impact on innovation, especially for diseases with lower incidences, and requests that FDA direct efforts towards promoting testing and research for disease rather than introducing requirements that may hinder them.
Helen Schiff (patient advocate)	Argues that biomarker tests must be rigorously regulated. The new FDA Guidance is an important step in the right direction. Neither CLIA, nor the FTC, nor any other agency in HHS has the experience, capability, or regulatory power to undertake this job. The arguments that FDA regulation of IVDMIAs will hinder development or is unfair are non sequiturs. We want to find out which IVDMIAs work and which do not, regardless of when they are developed.
Target Discovery	Echoes and supports points made by the Coalition for 21 st Century Medicine, of which it is a founder. Further states that FDA’s draft guidance has had chilling effect already on availability of venture capital for development of new LDTs. This investment environment needs to be changed in order to accelerate important innovations in biomarker research and the development of personalized medicine diagnostics.
Trimethylaminuria Foundation	Argues that FDA’s proposed regulations will significantly chill investment in personalized medicine. Forcing labs to function under both FDA guidelines and CLIA will significantly impair ability to produce new, effective testing methods and will eliminate much of the progress made in early detection and treatment of many diseases and disorders, such as Trimethylaminuria. In a dense regulatory environment, it may no longer be cost effective for labs to invest in research on uncommon disorders like Trimethylaminuria.
Stuart Hogarth, University of Cambridge, UK	Believes that FDA should regulate IVDMIAs. Notes that New York state’s requirements for clinical laboratories, which include pre-market review of in-house tests, is similar to 510(k) review by FDA, and has not been a major barrier to innovation. However, feels the guidance document could be broadened to cover all LDTs. This could result in a continuation of the uneven playing field, as well as confusion if the FDA investigates non-covered tests on an ad-hoc basis. Calls for a comprehensive, flexible approach to in-house tests. Suggests several regulatory tools that might be applied to ensure that FDA review is not unduly burdensome on either the Agency or the industry – third party review, orphan disease status, focus on truth-in-labeling, conditional licensing, post-marketing controls, multiple gatekeepers with different focuses, responsive regulation (where companies who play by the rules are given relative freedom but those who transgress come under greater scrutiny), and the review process employed by NY state.
Washington Legal Foundation	Believes the proposed regulations will be a setback for public health. There is no evidence that LDTs are inaccurate, and clinical labs are already subject to regulation by CMS. Additional FDA regulation would stifle innovation and impede access to LDTs. Labs are not operated as medical device manufacturers; they do not maintain the procedures and documents necessary for compliance with FDA’s QSR. If FDA regulations require existing tests to be labeled “investigational,” insurance reimbursement may be harder to obtain. Furthermore, the regulations are contrary to law for three reasons: 1) Congress has allocated regulatory authority to CMS, not FDA;

	<p>2) the Secretary of HHS confirmed that the regulatory authority lies with CMS, and 3) even if FDA does have regulatory authority, its manner of asserting it violates the Administrative Procedure Act by not engaging in notice and comment rulemaking. Lastly, raises First Amendment concerns about FDA interfering with communication of medical information between lab professionals and physicians.</p>
<p>XDx</p>	<p>Supports the intentions of the draft guidance but is concerned that in its current form, it is unclear how a clinical lab would comply with both FDA regulations and CLIA, and that the regulations will impede the development of new tests. Explains that the CLIA system is equally if not more effective in regulating LDTs. Notes potential confusion surrounding labeling requirements and requirements for modifications to tests. Suggests strengthening of CLIA regulations, or, if FDA continues to question CLIA oversight of IVDMIAs, that FDA limit its review to IVDMIA algorithms and associated clinical data, with laboratory operation remaining under CLIA review.</p>