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**VIA Electronic Submission** ([www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments))

Dockets Management Branch—HFA-305  
Food and Drug Administration  
5630 Fishers Lane—Room 1061  
Rockville, Maryland 20852

**RE: 2006D-0347**  
**Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on *In Vitro***  
**Diagnostic Multivariate Index Assays**

Dear Sir or Madam:

On behalf of Genomic Health, Inc. (“Genomic Health”), we are pleased to submit comments in response to the above-captioned draft guidance on In Vitro Diagnostic Multivariate Index Assays (IVDMIA)s(the “Draft Guidance”). Genomic Health is a licensed clinical laboratory, located in Redwood City, California, that conducts genomic research to develop clinically validated molecular diagnostics, such as the *Oncotype DX*<sup>TM</sup> Breast Cancer Assay, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy.<sup>1</sup> These diagnostic technologies generate information that physicians and patients can use in making treatment decisions. Genomic Health has a Certificate of Accreditation under the Clinical Laboratory Improvement Amendments (CLIA) and is accredited by the College of American Pathologists (CAP).

Genomic Health fully supports the Secretary’s goals to develop the information we need for personalized health care and to use the information correctly.<sup>2</sup> We applaud the Food and Drug Administration (“FDA”) for taking a leadership position in personalized medicine. At the same time, we are concerned that the Draft Guidance, if implemented as drafted, would not advance the Secretary’s goals.

Genomic Health endorses all of the comments responding to the Draft Guidance submitted by the Coalition for 21st Century Medicine, including the call for notice and comment rulemaking and for FDA to convene a public workshop prior to publication of a proposed rule. We believe the Coalition’s comments offer constructive solutions to advance the goals of personalized medicine while addressing key concerns we have identified from our review of the Draft Guidance. We shall not repeat the detailed points presented by the Coalition, but rather offer the following additional recommendations for your consideration:

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<sup>1</sup> Genomic Health’s comments supportive of certain approaches to regulation should not be considered an acknowledgement by Genomic Health that FDA has the authority to regulate laboratory services as medical devices. In addition, our reference to tests that may fit under FDA’s definition of an IVDMIA does not represent an admission by Genomic Health that the *Oncotype DX*<sup>TM</sup> Breast Cancer Assay is a device as that term is defined under Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 321(h)).

<sup>2</sup> Alex M. Azar, II, as Deputy Secretary of Health and Human Services. Remarks delivered to the President’s Council of Advisors on Science and Technology (Oct. 28, 2006) < <http://www.hhs.gov/agencies/speech/2006/061209.html>> (accessed Feb. 27, 2007).

1. If the FDA determines that regulation of IVDMIAs as medical devices is the most appropriate pathway to address concerns the Agency has about these assays, we would urge FDA to articulate clear and objective criteria that identify IVDMIAs and distinguish these assays from all other laboratory-developed tests that will remain subject to enforcement discretion and not required to comply with FDA regulations.
2. If FDA proceeds with regulation of IVDMIAs, the Agency should identify the algorithm (and any associated software or hardware) as the medical device subject to regulation.
3. FDA should allow a reasonable transition period following publication of any final policy on regulation of IVDMIAs to allow laboratories to come into compliance with the substantial new regulatory burdens that would be imposed, and FDA should not require laboratories to label IVDMIAs as “Investigational Use Only” during such transition period.
4. FDA’s regulation of any laboratory-developed tests should be risk-based and should allow for clearance/approval under the least burdensome means.
5. FDA should work through the Department of Health and Human Services to assure that clinical laboratories’ compliance with pre-market review and post-market control requirements under the Federal Food, Drug, and Cosmetic Act<sup>3</sup> do not conflict with compliance requirements under CLIA and that the regulatory burdens placed on laboratories are not duplicative or superfluous.

Further explanation of these recommendations and the rationale for proposing these is provided below.

**I. If FDA Determines that Regulation of IVDMIAs as Medical Devices is the Most Appropriate Pathway to Address Concerns the Agency Has About these Assays, We Would Urge FDA to Articulate Clear and Objective Criteria that Identify IVDMIAs and Distinguish these Assays from All Other Laboratory-Developed Tests.**

The term “In Vitro Diagnostic Multivariate Index Assay” is not set forth anywhere in the FFDCFA or in FDA’s regulations. Since the publication of the Draft Guidance, many stakeholders have expressed to FDA their concerns about the lack of clarity of the IVDMIA definition. Laboratories cannot determine which test services fit within the definition and which do not. The second and third criteria set forth in the Draft Guidance are inherently subjective,<sup>4</sup> which leaves laboratories uncertain as to whether their tests would or would not fall under FDA regulation.

For example, the algorithm that produces the Recurrence Score report from the *Oncotype DX* assay has been clearly presented in peer-reviewed, published reports of clinical studies that validated the clinical performance of the assay.<sup>5</sup> In addition, investigators completely unrelated

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<sup>3</sup> 21 U.S.C. § 301, *et seq.*

<sup>4</sup> These criteria are:

“2. 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; and

3. Report this result, which cannot be interpreted by the well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.” (Draft Guidance, at 3.)

<sup>5</sup> See Paik S, Shak S, Tang G, *et al.* A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004; 351:2817-26.

to Genomic Health independently validated the algorithm using a different assay platform.<sup>6</sup> A common sense reading of the Draft Guidance, particularly criterion 3, would suggest that this independent validation and level of transparency are sufficient to take the assay outside the definition of an IVDMIA. If this is what FDA seeks and intends, it should say so. If not, it is unclear what level of independent validation and transparency would be sufficient to avoid the IVDMIA label.

The lack of clarity around the definition of an IVDMIA has important implications for laboratories and those who fund the development of new tests in those laboratories. If a test is subject to FDA pre-market review and post-market controls, the cost of development and the ongoing cost of compliance with QSRs will be substantially higher and the time to commercial release significantly longer than would be the case under the CLIA pathway. Laboratories and their sponsors must be able to forecast accurately the likely costs and timeline to commercialization or they may find that projects must be halted mid-course for lack of funding. Uncertainty about the regulatory pathway will give funders pause before investing in novel tests. Higher costs and longer times to market will mean that sponsors will invest only in those tests that are less risky and/or have larger patient populations to justify the increased investment expenditures. As a result, physicians and patients will not realize the full promise of new genomic know-how and tests for rare disorders will go undeveloped.<sup>7</sup>

## **II. If FDA Proceeds with Regulation of IVDMIA's, the Agency Should Identify the Algorithm (and Any Associated Software or Hardware) as the Medical Device Subject to Regulation.**

Under the Draft Guidance, the key feature which identifies an IVDMIA is the presence of a computational algorithm. A laboratory-developed test that does not incorporate an algorithm to produce a reportable result will not fit the definition of an IVDMIA. Therefore, we would recommend that, if FDA proceeds with regulation of IVDMIA's, the Agency should define the "device" subject to regulation as the algorithm along with any associated software and hardware involved with running the algorithm. Under this definition, FDA regulation would comprise pre-market review (under a risk-based assignment to Class I, II, or III), labeling consistent with the intended use statements cleared or approved by FDA, compliance with QSRs, MDR reporting, registration, and listing.

Defining the algorithm as the medical device would address many questions and concerns that we and others have raised about how a clinical laboratory can simultaneously meet laboratory licensure and certification requirements under CLIA and state laws and fulfill FDA pre-market and post-market control regulations as a medical device manufacturer. Drawing a line between the CLIA-regulated laboratory service and the FDA-regulated medical device around the computational algorithm (and associated software/hardware) should eliminate most of the major concerns about conflict between CLIA and FDA requirements that have been raised in meetings with Agency staff. The clinical laboratory would perform pre-analytical, analytical and post-analytical steps under CLIA and state law, subject to test validation, personnel, quality system and proficiency testing requirements to which the laboratory has always been subject. There would be the added step that the laboratory would be acquiring and using an FDA-regulated device—the algorithm—the labeling and instructions for use of which would be incorporated into

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<sup>6</sup> Fan C, Oh DS, Wessels L, *et al.* Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 2006;355:560-9.

<sup>7</sup> Healy B. Too slow for cancer. *US News & World Report*. Jan. 9. 2006  
<[http://www.usnews.com/usnews/health/articles/060109/9healy\\_print.htm](http://www.usnews.com/usnews/health/articles/060109/9healy_print.htm)> (accessed Mar. 1, 2007)

the laboratory's procedure manuals. FDA inspectors evaluating compliance with QSRs would look at compliance with required controls as these pertain to the algorithm, but would not need to address the operations of the lab, which the CLIA/state/accrediting bodies cover in their inspections.

Defining the device as the algorithm would also make the regulatory requirements for modifications much clearer as these would follow well-established pathways under CDRH and OIVD guidance.

### **III. FDA Should Allow a Reasonable Transition Period Following Publication of Any Final Policy Regarding Regulation of IVDMIAs to Allow Laboratories to Come into Compliance with the Substantial New Regulatory Burdens that Would Be Imposed.**

Extending medical device jurisdiction to IVDMIAs represents a major change in FDA policy that will impose significant new burdens on clinical laboratories offering these tests. In addition, there remains significant confusion among stakeholders about what and how FDA intends to regulate under the IVDMIA initiative. Given these concerns, we would strongly urge FDA to allow clinical laboratories adequate time following release of any final policy document to come into compliance with the new rules. Fundamental fairness requires that such transition periods be allowed because laboratories cannot know until a final document is released who, what, how or when they will need to come into compliance.

We would also ask that the Agency not require laboratories offering IVDMIAs to label these as "Investigational Use Only" until after a final policy document is released and a reasonable transition period is completed. Many IVDMIAs, like the *Oncotype* DX Breast Cancer Assay, are well-established in clinical practice and are being covered by health plans and payers across the U.S. If FDA were to require that these tests be labeled for "Investigational Use Only" pending clearance or approval by FDA, then there is a high likelihood that health plans and payers would discontinue providing coverage for these tests to the detriment of patients.

### **IV. FDA's Regulation of Any Laboratory-Developed Tests Should Be Risk-Based and Should Allow for Clearance/Approval Under the Least Burdensome Means.**

When assessing the potential risks associated with a novel test for purposes of determining the appropriate pre-market review pathway and the extent of data required for clearance or approval, FDA should focus on the claims made by the sponsor. If a sponsor claims that a novel test reports a particular result, but makes no claim as to how the results may be used to make a diagnosis or to select treatment, FDA should not infer broader claims. Physicians order tests based upon their determination as to how they would use the information obtained from the test report in evaluating alternatives with an individual patient. That determination may be informed by the laboratory's claims, but also may be based upon other information available to the physician as well as the physician's own clinical experience. Rather than inferring claims that may involve greater risk and requiring the sponsor to clear higher regulatory hurdles, FDA could address these concerns through appropriate statements set out in labeling about the limitations of the test.

Claims that are limited to providing patient-specific information to physicians—to be used in conjunction with other patient-specific information when making a diagnosis or selecting among treatment options—involve only moderate risk because physicians do not act solely on the basis of information from these tests. If other information is contradictory, physicians explore further before making a diagnosis or making recommendations among treatment alternatives based on

knowledge of each patient's specific circumstances, preferences, and risk/reward calculus. Class II special controls should be sufficient to protect patients with these types of tests.

Claims that are binary in nature—yes/no determinations about diagnosis or treatment selection for conditions or diseases presenting a high risk—involve the highest level of risk because these are intended to direct patient management. Class III premarket approval controls are appropriate for these highest risk claims. This type of risk-stratified approach is consistent with the least burdensome provisions of the FFDCFA.

**V. FDA Should Work Through the Department of Health and Human Services to Assure that Clinical Laboratories' Compliance with Pre-Market Review and Post-Market Control Requirements Under the Federal Food, Drug, and Cosmetic Act<sup>8</sup> Do Not Conflict with Compliance Requirements Under CLIA and that the Regulatory Burdens Placed on Laboratories Are Not Duplicative or Superfluous.**

IVDMIA's are clinical laboratory test services. As such, they already are subject to substantial levels of regulation under federal and state law. CLIA is a comprehensive regulatory system covering the pre-analytic (including sample requisition and accession), analytic and post-analytic (including reporting) phases of laboratory testing. CLIA regulations include standards covering registration, personnel, facility administration, proficiency testing, quality systems, and enforcement.<sup>9</sup>

We are concerned that adding compliance with FDA regulations under the Medical Device Amendments to compliance with the clinical laboratory regulations under CLIA to which laboratories already are subject, will result in significant burdens and costs on clinical laboratories without any assurance of commensurate gains in the quality of services or information provided. The net result is likely to be that fewer tests will be developed and fewer enhancements and updates will be offered to those tests that are developed. Technology transfer of new know-how into improved patient care will be curbed.<sup>10</sup>

In addition, laboratories may face conflicting regulatory requirements, such as CLIA requirements that laboratories update information they provide to treating physicians to facilitate interpretation of test reports<sup>11</sup> versus FDA restrictions on promotion outside FDA-cleared/approved labeling.

Our recommendation that FDA identify the algorithm as the medical device would address many of these concerns. It would allow for a clear line between those elements of the test service that would remain under CLIA requirements and those components of the test that would be the

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<sup>8</sup> 21 U.S.C. § 301, *et seq.*

<sup>9</sup> 42 CFR Part 493.

<sup>10</sup> “Just because we have evidence about what should be done does not mean that we know how to change practice or policy . . . [W]hile potholes and gaps impede progress, **the true problem is that everyone is focused on their own kingdoms.** Bench scientist publish and expect clinical researchers to pick up their findings. They then move on to their next discovery. Clinical researchers complete trials with human subjects, and then expect physicians and patients to be familiar with the evidence. Meanwhile, many physicians and patients take the process for granted, and there are not enough people focused on whether the beginning of the road actually links directly to the end or if somewhere along the way discoveries are getting lost. \* \* \* **[There is a] ‘bottleneck’ in transforming good science into good medicine.**” Lisa Simpson, MD, former deputy director of AHRQ. Quoted in: Elliott VS. Translation frustration: When research doesn't reach. *AMNews*. Nov. 1, 2004. (emphasis added)

<sup>11</sup> 42 C.F.R. § 493.1291(e). *See also* 42 C.F.R. § 493.1445(e)(8), (9) (laboratory director responsibilities), 42 C.F.R. § 493.1457(c) (clinical consultant responsibilities).

device subject to FDA pre-market review and post-market controls. It would also address the concern identified above about conflicts between CLIA and FDA over communications between the laboratory and referring practitioners.

We would encourage FDA to work through HHS to identify areas of overlap and conflict between FDA regulations and CLIA regulations and to limit the burdens imposed on clinical laboratories to the least burdensome regulation necessary to assure the safety and effectiveness of the algorithm under the FFDCa and to assure accurate and reliable test services under CLIA.

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Genomic Health supports FDA's goal of working to assure that patients have access to timely, accurate and reliable testing that can improve patient outcomes and reduce healthcare resource utilization. We look forward to working with FDA to evaluate the most appropriate regulatory framework to promote development of innovative tests while assuring these are safe, effective, and made accessible to all via timely and efficient federal regulatory pathways. In response to the Draft Guidance, we respectfully make the following recommendations:

1. If the FDA determines that regulation of IVDMIAs as medical devices is the most appropriate pathway to address concerns the Agency has about these assays, we would urge FDA to articulate clear and objective criteria that identify IVDMIAs and distinguish these assays from all other laboratory-developed tests not subject to FDA regulations.
2. If FDA proceeds with regulation of IVDMIAs, the Agency should identify the algorithm (and any associated software or hardware) as the medical device subject to regulation.
3. FDA should allow a reasonable transition period following publication of any final policy regarding regulation of IVDMIAs to allow laboratories to come into compliance with the substantial new regulatory burdens that would be imposed, and FDA should not require that laboratories label IVDMIAs as "Investigational Use Only" during such transition period.
4. FDA's regulation of any laboratory-developed tests should be risk-based and should allow for clearance/approval and subsequent regulation under the least burdensome means.
5. FDA should work through the Department of Health and Human Services to assure that clinical laboratories' compliance with pre-market review and post-market control requirements under the Federal Food, Drug, and Cosmetic Act do not conflict with compliance requirements under CLIA and that the regulatory burdens placed on laboratories are not duplicative or superfluous.

We look forward to continuing our dialogue with the Agency on this important matter. If you have any questions about our comments, please contact me at 650-569-2298. Thank you for consideration of these comments.

Sincerely yours,

/s/

Randy Scott, Ph.D.  
Chairman and CEO