



Prediction Sciences
Personalized Medicine Today™

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket 2006D-0347 - Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays

Prediction Sciences looks forward to working with the FDA and hopes that the following comments will assist you in your proposed regulation of In Vitro Diagnostic Multivariate Index Assays.

A. The Guidance could stifle development.

Diagnostics provide much lower returns than drugs, even complex multivariate diagnostics that are very expensive to develop. This is due largely to the inequitable reimbursement structure that currently exists. Thus, there are already large barriers to innovation in this field. Increased FDA regulatory requirements, such as those proposed in the in vitro diagnostic multivariate index assays (IVDMIA) draft guidance, could further stifle innovation by substantially increasing both the costs and time required to develop multivariate diagnostics. Moreover, the proposed guidance reduces the ability of diagnostics companies to produce revenue from home-brew assays upon which they may rely to fund further data collection studies to be used for eventual FDA approval. The increased regulatory requirements arising from the proposed guidance will have a particularly negative impact on smaller diagnostics companies by reducing the early value of their multivariate diagnostic technologies, thereby making it more difficult to obtain outside financing (e.g., venture capital, angel investors, licensing deals, etc.). This puts them in the untenable position of needing financing to get FDA approval, but needing FDA approval to get financing. Continued regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) administered through the Centers for Medicare & Medicaid Services would help alleviate these burdens.

B. The language in the Guidance requires significant clarification to ensure proper classification of IVDMIA's.

The presumed goal of FDA regulation of IVD tests is to verify their analytical and clinical performance to ensure that they are safe and effective for patients. Assuming that the FDA concludes this is not possible under current CLIA regulations such that IVDMIA regulation is required, the language in the three criteria defining IVDMIA's in the draft guidance require significant clarification. Under the proposed language, compelling arguments can be made that current multivariate tests that the FDA presumably does not intend to regulate could be misclassified as IVDMIA's, and that new multivariate tests that the FDA presumably intends to regulate may be exempt. The following points and questions are raised using examples of breast cancer prognostic tests, which will likely be one of the first sets of assays to be tested

under the proposed guidance, although the same points apply to other disease areas. See the accompanying Table for a summary.

B.1. Criterion 1 reads: “[IVDMIA]s use clinical data -- including data from one or more in vitro assays and, in some cases, demographic data -- to empirically identify variables and to derive weights or coefficients employed in an algorithm.”

This criterion can be broken down into two separate requirements for designation as an IVDMIA. First, the test must include at least one in vitro assay. Second, the test must apply “weights or coefficients” to the variables in its algorithm. We argue that these requirements may prove to be quite ambiguous.

With regard to the first requirement, a treatment decision test that uses complex statistics to derive a weighted expression algorithm from multiple variables to produce a patient-specific score apparently would not be subject to IVDMIA regulation, as long as none of the variables comes from an in vitro assay. Why should inclusion of an in vitro assay be required to make the test subject to regulation, since the tests have the same potential effects on patients?

With regard to the second requirement, the presumed intent of the FDA is to regulate multivariate assays that apply complex calculations to multiple variables. The proposed guidance identifies these as algorithms that “derive weights or coefficients.” However, algorithms that use weights/coefficients can be very simple and easy to comprehend, even when in vitro assays are included. Thus, the current language may lead to misplaced regulatory requirements on current clinical guidelines, such as the Nottingham Prognostic Index (NPI)¹, which is currently used to help guide adjuvant breast cancer treatment decisions. The NPI includes an in vitro assay (tumor grade) along with two other variables (tumor size and grade) in the form of a weighted expression, so it appears to fully meet Criterion 1 for regulation as an IVDMIA.

Is it the intent of the FDA to regulate the usage of the NPI, and other similar clinical guidelines? Such guidelines are being developed by the academic community, so the FDA regulatory process likely is not envisioned.

Conversely, algorithms that do not contain weights/coefficients can be highly complex and difficult to comprehend, whether they include in vitro assays or not. For example, decision tree-based algorithms do not apply weights/coefficients to individual variables, but they can include hundreds, or even thousands, of decision nodes. In fact, decision trees are general function approximators with the same capabilities and complexities as artificial neural networks, and both can be far more complex than simple weighted expressions. Furthermore, algorithms that use weights/coefficients can be converted to complex decision trees that no longer require weights/coefficients.

If the algorithm for a multivariate in vitro test is developed using a decision tree or artificial neural network approach (or other complex informatic approach that does not explicitly use weights or coefficients) is it exempt from IVDMIA regulation? If the algorithm for a multivariate in vitro test is developed as a weighted expression, but it is then converted to a format that does not use weighting (e.g., a complex decision tree), is it exempt from IVDMIA regulation?

Current breast cancer treatment decisions already are based largely on multivariate tests, such as the above-described NPI. Other examples of multivariate treatment guidelines include the following: National Institutes of Health (NIH)², St. Gallen International Expert Consensus³, National Comprehensive Cancer Network (NCCN)⁴, and Adjuvant!⁵. All of these include in vitro assays (e.g., ER, PR, ERBB2, histologic/nuclear grade, etc.). It could be argued that the NIH, St. Gallen, and NCCN algorithms constitute “decision trees,” as opposed to being “weighted expressions,” thus exempting them from IVDMIA status. And Adjuvant! essentially uses a look-up table system with hundreds of entries estimated from historical data on tens of thousands of previous patients to derive a risk of recurrence score, which may constitute a highly complex decision tree. However, it is unclear whether these tests and/or tests with similar levels of complexity that are currently under development should face FDA scrutiny for clinical effectiveness.

In summary, the requirements in this criterion are ambiguously defined in their current form and do not seem well-suited to meet the FDA’s presumed goal. The resulting confusion would further exacerbate the already difficult situation described in Section A (above), creating an unreasonable burden on multivariate diagnostics companies trying to choose the correct developmental and regulatory pathways.

B.2. Criterion 2 reads: “[IVDMIAs] 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.”

All of the current breast cancer clinical guideline tests described above, as well as all of the commercial tests under development, meet the first requirement in this criterion, as they all calculate a patient-specific result (a raw score and/or a classification into a risk category). However, the phrases “independent derivation and confirmation” and “proprietary information” require clarification.

In theory, the published studies on which the current breast cancer clinical guidelines are based are available for others to independently derive and confirm the results (although not all of the raw data is necessarily available). Does this mean that if both the raw data and statistical methods used to develop an algorithm for a commercial multivariate test are made publicly available, for example through publication, that this test also would be exempt from IVDMIA regulation? If this is not the case, which seems probable, then it would be more appropriate for the FDA to regulate all tests, whether developed by academic or commercial groups, to independently ensure their clinical performance prior to release to physicians or the public independent of whether there is any proprietary information involved.

Again, the ambiguously defined phrases create an unreasonable burden on multivariate diagnostics companies trying to choose the correct developmental and regulatory pathways.

B.3. Criterion 3 reads: “[IVDMIA] 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.”

The language in this requirement also requires clarification. What constitutes a “well-trained health care practitioner”? Does this include nurses, surgeons, pathologists, oncologists, and/or oncologists with a research background, etc.?

What constitutes “prior knowledge of medicine” (examples below in order of increasing complexity)?

1. Ability to interpret a risk of recurrence percentage or a recurrence risk category provided by a multivariate test (e.g., low, medium, or high risk; or 10% chance of cancer recurrence within 10 years).
2. Knowledge of the prognostic power of individual variables within a multivariate test (e.g., lymph node status, tumor size, tumor grade, steroid hormone receptor status, etc.).
3. Specific knowledge of the techniques used to assay the variables (e.g., surgical techniques, histology, protein analysis by immunohistochemistry, DNA analysis by fluorescence in situ hybridization, RNA analysis by microarray or RT-PCR, etc.).
4. Knowledge of the literature and methods used to derive the complex decision trees, look-up tables, or weighting used to develop the algorithms?

In all likelihood, the “prior knowledge of medicine” of a “well-trained health care practitioner” would not exceed the second level listed above. As such, it is unlikely that these practitioners fully comprehend the analytical and statistical methods and subtleties used to derive even the current standard treatment guidelines. Rather, they rely on research experts in their field, such as those on the clinical practice guideline committees and/or biostatisticians, to provide the tests and keep them updated to ensure reliable clinical performance and effectiveness.

Assuming that the FDA does not intend to regulate current clinical guidelines, would other multivariate tests that only use features that are familiar to well-trained health care practitioners be exempt from IVDMIA regulation? Would tests that only use features that have established roles in the disease process according to the published literature be exempt from IVDMIA regulation? If clinical practice guideline groups decide on new in vitro assays to include in their multivariate tests based on level of evidence in the literature, is that in vitro assay and the resultant revised multivariate test exempt from IVDMIA regulation?

Again, the ambiguously defined phrases create an unreasonable burden on multivariate diagnostics companies trying to choose the correct developmental and regulatory pathways.

C. References to other guidance would be welcome to help ensure innovation.

If the FDA concludes that IVDMIA regulation is necessary, specific references to the following FDA procedures/guidance would be welcome within the IVDMIA guidance for clarification given the potential barriers to innovation stated above in Section A:

1. Ability to obtain regulatory approval of multiple assays in one IVDMIA submission (e.g., “Bundling Multiple Devices or Multiple Indications in a Single Submission,” FDA Document 1215, 11/26/2003).

2. Ability to use retrospective data in IVDMA regulatory submissions (e.g., “Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable,” FDA Document 1588, 4/25/2006).
3. Expedited, de novo, and real-time review procedures as they apply to IVDMIAs.
4. The pre-market notification (PMN)/510(k) process as it applies to regulatory approval of updated versions of IVDMIAs, including potential changes/additions to variables and/or weighting.

Table

Breast cancer prognostic tests/guidelines	Clinical data			Algorithm	Patient-specific result
	General	Demographic	In vitro assay(s)		
National Institutes of Health	lymph node status, tumor size, menopausal status	age	ER/PR, tumor grade	decision tree	classification
Ninth St. Gallen	lymph node status, tumor size, menopausal status, vascular invasion	age	ER/PR, ERBB2, uPA, PAI-1, tumor grade	decision tree	classification
National Comprehensive Cancer Network	lymph node status, tumor size, surgery type, menopausal status, vascular invasion	age	ER/PR, ERBB2, histologic type, tumor grade	decision tree	classification
Adjuvant! Breast Cancer	lymph node status, tumor size, comorbidity	age	ER/PR, tumor grade	look-up table (decision tree)	index
Nottingham Prognostic Index	lymph node status, tumor size		tumor grade	weighted expression	index and classification
Agendia: MammaPrint	lymph node status		70 mRNA levels (microarray)	weighted expression (correlation)	score and classification
Genomic Health: Oncotype DX	lymph node status		ER/PR, 21 mRNA levels (RT-PCR)	weighted expression	score and classification
Prediction Sciences: GeneRx for Breast Cancer	lymph node status	age	ER/PR, ERBB2, BCL2, MYC, p53	weighted expression	score and classification
AviaraDX: Breast Cancer Profiling (2-gene) test	lymph node status		ER/PR, 2 mRNA levels (RT-PCR)	weighted expression	score and classification

References

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Signed,



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