



The Pathologist's Message

IVDMIA (In Vitro Diagnostic Multivariate Assays) are emerging diagnostic vehicles growing in popularity for a wide variety of illnesses; in fact, many experts estimate that over 200 of these tests are in the development pipeline. IVDMIA harness multiple molecular and non-molecular markers to produce a diagnostic, prognostic and/or predictive index (value) for a patient.

IVDMIA seek to answer clinical problems not sufficiently addressed by current diagnostic testing by taking advantage of multiple antibodies/genetic markers simultaneously; the combination or algorithm used is not intuitively obvious and is frequently proprietary. IVDMIA commonly use PCR (Polymerase Chain Reaction) tests or gene expression microarrays, the results of which are integrated into an algorithm to organize and prioritize individual markers thereby producing a readily accessible result. A common example of this modality is the *Oncotype DX*® test (Genomic Health) that is used to help determine prognosis in women with breast cancer.

While physicians and patients welcome the potential clinical value of these tests, some IVDMIA testing models and associated marketing strategies have raised concerns. The main issue stems from the overall lack of transparency. In some cases, testing sites make specific diagnostic or prognostic claims yet provide the pathologist with little insight regarding the quality control or validation measures used to make these claims.

Like any new technology, IVDMIA offer risks and potential rewards for the patient and his/her pathologist. However, careful navigation of these new seas will lead to better healthcare decisions.

The pathologist has a responsibility to manage the risk to the patient by becoming familiar with these technological advances.

When a new test is identified or proposed perhaps by a colleague, the pathologist is required to know how the test is being performed, what answers the test is intended to offer (the predictive value), and the best way to seek those answers—regardless of where the test is performed. Uniquely skilled with the ability to analyze and integrate these test results, the pathologist must be the keeper and guardian of pathology information and the lab's quality. This role includes specimen selection and understanding, interpreting and integrating IVDMIA test results with previously performed clinical laboratory work-up and clinical information.

IVDMIA are powerful emerging tests that have the potential to answer significant clinical problems by integrating multiple molecular markers. The prevalent model of adoption and the pathologist's ability to integrate that information will determine the future relationship of this modality and the pathologist.

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Clinical Context

To understand the regulatory climate in which IVDMIA are emerging, a review of terms is helpful.

- **ASR (Analyte-Specific Reagent):** An ingredient to a test, regulated by the FDA, used to analyze the presence or absence of a specific entity in a test. For example, the immunohistochemical antibody used for the detection of certain viruses is considered an ASR. ASRs are components of a test, but cannot stand alone.^{3,5}
- **LDT (Laboratory Developed Test):** These tests are developed and validated internally by a laboratory and not intended for widespread sale or distribution. Many IVDMIA are LDTs, and as such, are regulated under CLIA. Under CLIA rules, most LDTs are considered Class I tests (low-risk). However, this regulatory classification may change. In a recent draft guidance, the FDA has suggested that due to their high patient risk nature, some LDTs, such as IVDMIA, should be regulated as Class II tests. Currently, clear guidelines to determine the difference between a “high-risk” and “low-risk” LDT do not exist, but some guidelines for ASRs have been published and may be applicable.^{3,4}
- **IVDMIA:** In its Draft Guidance for Industry, the FDA defines an IVDMIA as a device that combines the values of multiple variables using an interpretation function to yield a single, patient-specific result that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

IVDMIA are one of the early dividends of the human genome project. Although individual genetic and proteomic markers have diagnostic and prognostic relevance, the aggregate results obtained for multiple markers should in theory increase the diagnostic, prognostic, or theranostic power over that obtained from the results of one or just a few markers. IVDMIA offer the treating physician a synthesis of multiple results in a simplified form. In this age of mushrooming information, simplification and distillation of important facts that are needed to best treat patients is eagerly sought by those making treatment decisions.

Most available IVDMIA (and those in development) address gaps in information needed for making patient management decisions. For example, some IVDMIA attempt to subdivide diagnostic categories that show heterogeneity in clinical response (e.g., dividing breast cancer patients into low and high risk recurrence groups).

The future availability of IVDMIA may hinge on how they are classified by regulatory organizations. While they are currently regulated under CLIA, the FDA will likely exert greater authority over these tests. The debate is ongoing and the FDA has not released a final guidance on this class of assays. The degree of regulation will likely influence the speed of market introduction. One key difference between CLIA and FDA oversight is that the FDA requires clinical efficacy, validation and utility while CLIA emphasizes quality in laboratory testing and analytic validation.

Due to the complexity of IVDMIA, pathologists and clinical geneticists are likely to be asked by clinicians to help interpret the results obtained from these assays as they relate to patient management. Therefore, the pathologist must understand the role of these tests in the overall care of the patient, and how they relate to other testing modalities.

Technology Overview

Increasingly sophisticated data analysis tools now make it possible to screen thousands of potential markers to find a subset or subsets of biomarkers which can predict a disease state, determine the likelihood of disease progression, or calculate the probability of responding to a therapy or other important medical information.

IVDMIA are sometimes referred to as ‘black box’ assays. They use raw data obtained for a number of analytes and apply them to an algorithm to generate an index for the purpose of diagnosing, prognosticating, or treating disease. While in some cases the specific markers or levels of gene expression may be disclosed and the relative weight given to different variables may be provided, the exact method to replicate the test elsewhere is often not disclosed, therefore making the test proprietary. A good example of this algorithmic approach is *OncoType DX*® in which breast cancer recurrence predictions are based on the results of a 21-gene RT-PCR assay (16 analytes and 5 controls).

Examples of IVDMIA as identified by the FDA include: gene expression profiling assays for breast cancer prognosis or organ rejection, products/systems that predict disease risk by integrating results from multiple immunoassays, and tests that predict risk or diagnose disease by integrating age, sex, and genotype results from multiple genes.

The most commonly used primary methods to determine the raw data for IVDMIA are RT-PCR (Reverse Transcriptase Polymerase Chain Reaction Amplification) and Gene Expression Microarrays. RT-PCR uses reverse transcriptase and traditional PCR, to determine the level of expression of a gene, generally using quantitative real-time PCR (qPCR). In gene expression microarrays, multiple gene sequences located on the same surface (often called a “chip”) are analyzed simultaneously. A patient sample is compared to a reference, and after hybridization, a scanner and imaging software determine the presence and level of targeted sequences.

Vendors: Currently, there are three FDA-cleared IVDMIA's. The first cleared, MammaPrint® (Agendia, 2007) is a 70-gene assay that categorizes patients with Stage I/II, lymph node negative breast cancer into “low” and “high” risk for distant metastasis. The PathWorks Tissue of Origin Test® (PathWorks Diagnostics) was FDA approved in 2008. This test utilizes approximately 1,500 genes in a gene expression microarray system to determine the most likely primary site for a metastatic tumor by way of its gene expression. This test will also be available as an *In Vitro* Diagnostic kit, and thus, available to be run in any CLIA-certified laboratory. A third test, cleared by the FDA in October 2008 is AlloMap (XDx, Brisbane, CA). This test uses a multi-gene expression microarray to predict heart transplant rejection.

In addition, a number of independent laboratories offer IVDMIA's that are not FDA cleared; *Oncotype DX*® is among them. These products are offered under the umbrella of a CLIA certified laboratory. Based on the FDA Draft Guidance for IVDMIA's, it is unclear whether these laboratories will be able to continue to offer these tests without additional validation and approval. The current guidelines suggest that if the test is high-risk, the test may be subject to additional scrutiny and therefore pre-market approval by the FDA. Currently, *Oncotype DX*® is marketed directly to oncologists and patients.

Impact on Current Pathology Practice: Being the primary keeper of both pathologic specimens and information for patients, the pathologist has a unique role in understanding these techniques as they relate to best practices. Pathologists are in the ideal position to assimilate the results of these tests along with other laboratory and clinical information for a given patient.

These tests will likely be available in multiple formats with varying degrees of pathology interaction.

Acceleration/Deceleration Triggers to Adoption: Numerous forces will influence the adoption of IVDMIA's including:

- Currently, these tests are expensive to develop and to perform clinically, but these costs are shrinking.
- In light of the FDA's most recent draft guidance, it is likely that FDA approval will be required for any tests that make specific and significant claims to prognosis, treatment sensitivity, and other important patient information. IVDMIA assays fall into this category of tests. In February 2007, the FDA assigned Class II status to MammaPrint. Class II status requires pre-market approval.
- However, many private laboratories that intend to introduce IVDMIA's may circumvent FDA review for acceptance by instead relying on research results to determine test validity. This latter model is the method currently used by Genomic Health, whose laboratory is regulated by CLIA, state laws, and the CAP as its accrediting body.
- Recent legislative activity and increasing regulation will likely slow the introduction of IVDMIA's in the market. Two significant bills include:
 1. As a senator, President Obama (D-IL) introduced a bill in the Senate in 2006 that sought to establish a working group that includes a representative from the FDA, to evaluate molecular testing.¹
 2. The late Senator Kennedy (D-MA) authored a bill, also in 2006 that proposed to require pre-market analysis for all lab-based tests including IVDMIA's. This legislation would close the CLIA-approved versus FDA approved route for new tests.²

Depending on the vendor model used, IVDMIA's could have a significant impact on current pathology practice:

- **Clinical Impact:** Pathologists should ideally be able to interpret tests that are performed both within and outside their laboratories. IVDMIA's are potentially problematic in that sense, since closed algorithms do not allow pathologists to easily understand or interpret how the IVDMIA result is obtained.
- **Financial Impact:** The potential impact depends on the particular IVDMIA. If the IVDMIA is one that can be performed in any CLIA-certified pathology laboratory (e.g., PathWorks Assay), it could produce an additional revenue stream. However, if the IVDMIA can only be performed by the lab that developed the IVDMIA (e.g. *Oncotype DX*) then it may take services away from pathology laboratories.
- **Operational/Procedural Impact:** Laboratories will need to become familiar with how specimens are handled and processed when various IVDMIA assays are ordered by clinicians. For example, an IVDMIA might require high quality mRNA and consequently laboratories will need to gain the knowledge and experience necessary to properly process frozen tissue for optimal RNA isolation.
- **Business Model:** There are divergent business models for IVDMIA's. One model seeks to supersede the results of the laboratory and another intends to integrate with the results of the laboratory. It is important to recognize the benefits and limitations of the various IVDMIA's even if they are performed extramurally since the pathologist is likely to have a role in the assimilation of the data produced.

Acceleration/Deceleration Triggers to Adoption: (continued)

- Pathology laboratories may need additional expertise in molecular or other techniques in order to capture this business.
- Intellectual property related to these assays may prevent their broad dissemination to most pathology laboratories.
- A lack of reimbursement to pathologists for the pre-analytical aspects of IVDMIA testing (e.g. selecting a block for analysis) may inhibit adoption.

For More Information/References:

For additional information on device classifications: <http://www.fda.gov/cdrh/devadvice/3132.html>

1. www.dnapolicy.org/resources/Obama_Genomics_Personalized_Medicine_Act_2006.pdf
2. www.govtrack.us/congress/bill.xpd?bill=s110-736
3. Guidance for Industry and FDA Staff—Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (Rockville, MD: FDA, Center for Devices and Radiological Health, 2007).
4. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—Multivariate Index Assays (Rockville, MD: FDA, Center for Devices and Radiological Health, 2007).
5. 21 CFR 864.4020 (a)