



The Development and Utility of In Vitro Diagnostic Multivariate Index Assays (IVDMIA) in Regards to Breast Cancer

John H. Irlam, DO

In Vitro Diagnostic Multivariate Assays (IVDMIA) are emerging testing technologies utilizing multiple molecular and non-molecular markers to produce diagnostic and prognostic information by way of predictive index values. Currently, these tests use reverse transcriptase polymerase chain reactions (RT-PCR) and gene expression microarrays to determine the presence and level of expression of a specific gene sequence. IVDMIA then manufacture a score based on a proprietary formulator algorithm that attempts to answer a specific question. Possible clinical questions that they aim to answer include presence of disease, likelihood of progression, or the likely response to current treatment modalities.

Recurrent problems in the treatment of cancer allow for a possible use of new technologies, such as IVDMIA. For example, the current mainstays in the treatment of stage I/II, node-negative, estrogen receptor-positive breast carcinomas include resection, local radiation, and hormonal therapy. However, up to 65% of patients with invasive breast cancer do not demonstrate nodal disease at the time of diagnosis,¹ and without this, it may not be clear by current clinical and pathologic methods which patients would benefit from chemotherapy.

In this clinical scenario, some have turned to IVDMIA as the earliest attempts to fill the gaps in personalized medicine. MammaPrint[®] (Avandia, 2007) is a Food and Drug Administration (FDA)-approved, oligonucleotide microassay (examining 70 predictive genes) that is performed on fresh-frozen tumor samples.² Patients less than 61-years-old are then placed into low- and high-risk categories for distant metastasis. Studies have demonstrated a 10-year overall survival rate of 69% for patients with high-risk tumors and 88% for patients with low-risk tumors.³ Another example is Oncotype DX[®], a non-FDA approved diagnostic test offered by a CLIA-certified laboratory. This test analyzes 21 genes, including 16 cancer-related genes and five reference genes.⁴ Based on expression of these genes, patients are categorized as having a low, intermediate, or high risk of recurrence. Retrospective analysis has demonstrated that 93.2% of patients in the low-risk group were free of distant recurrence at 10 years compared with 69.5% of high-risk patients.⁵ Additional FDA-approved IVDMIA include the PathWorks Tissue of Origin Test[®] (PathWorks Diagnostics) and AlloMap[®] (XDx, Inc.).

While the true benefits of IVDMIA have yet to be defined, this emerging technology holds great promise in answering the most vexing clinical questions by harnessing the power of multiple molecular markers. As this technology develops and more testing

becomes available, the pathologist will assimilate these findings into other diagnostic tools to best personalize the diagnosis and prognosis for the patient.

[Read the full Perspectives on Emerging Technologies \(POET\) report](http://www.cap.org/POET), written by John W. Turner, MD, FCAP, at www.cap.org/POET.

References

1. Ghafoor A, Jemal A, Ward E et al. Trends in breast cancer by race and ethnicity. *CA Cancer J Clin.* 2003;53:342-355.
2. Van de Vijver MJ, He YD, van't Veer LJ et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med.* 2002; 347:1999-2009.
3. Buyse M, Loi S, van't Veer L et al. Validation and clinical utility of a 70-gene prognostic signature for women with node negative breast cancer. *J Natl Cancer Inst.* 2006;98:1183-1192.
4. Oncotype DX Overview. Genomic Health, Inc. www.oncotypedx.com/PatientCaregiver/OncoOverview.aspx?Sid=1. Accessed September 22, 2009.
5. 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;351:2817-2826.