

National Breast Cancer Coalition Fund  
Comments on  
FDA's Draft Guidance on  
In Vitro Multivariate Diagnostic Assays  
March 5, 2007

Founded in 1991, the National Breast Cancer Coalition Fund is the nation's leading grassroots advocacy organization dedicated to ending breast cancer.

NBCCF recognizes the tremendous potential that biomarker research has to impact risk assessment for the prevention and early detection of breast cancer, and for the clinical care of those diagnosed. However, despite enormous investment and decades of research, there have been few successes and many disappointments thus far.

With this in mind, the National Breast Cancer Coalition Fund (NBCCF) convened its first *Strategic Consensus Conference: Shaping the Future of Biomarker Research in Breast Cancer to Ensure Clinical Relevance*<sup>1</sup> in November 2005. Participants included 50 world experts representing five key stakeholder groups: consumers; practicing clinicians; academic researchers; industry and federal regulatory/research agencies.

Consensus was developed on five general principles that served as the framework for six priority areas and eighteen recommendations. The five principles focus on the need for research on, and clinical use of, biomarkers to be patient-centered and aimed at substantially improving patient outcomes. In other words, for biomarker assays to be clinically useful, their

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<sup>1</sup> National Breast Cancer Coalition Fund, Strategic Consensus Report. Shaping the Future of Biomarker Research in Breast Cancer to Ensure Clinical Relevance. November 13-15, 2005, Philadelphia, PA.

use must reliably result in marked improvement in patient outcomes (chiefly survival) that are balanced with quality of life (minimal toxicity and no overtreatment). Ultimately, a clinically useful biomarker will accurately identify those individuals likely to benefit from specific interventions and those who will probably will not benefit fro those interventions. The other principles call for biomarker research to be conducted in a socially responsible environment that fosters innovation, where resources are shared as part of a social network, and where stakeholders abide by mutually agreed standards and guidelines.

The Consensus Panel identified six priority areas and 18 specific recommendations:

<b>Consensus Priorities and Recommendations</b>
<p><b>Priority 1.</b> Develop and adopt standards and guidelines for the different stages of the “bench to bedside” continuum to ensure that only biomarkers with clinical utility make their way into routine clinical practice.</p> <p><i>Recommendation 1A.</i> Incorporate the best components of drug development to guide the development and validation of biomarker assays.</p> <p><i>Recommendation 1B.</i> Expand and encourage adoption of guidelines for the publication of biomarker study results.</p> <p><i>Recommendation 1C.</i> Maintain and update current guidelines for clinical use of biomarkers and ensure their implementation.</p> <p><i>Recommendation 1D.</i> Develop standards to encompass clinical methodologies for biomarker measurement and reporting.</p> <p><b>Priority 2.</b> Improve access to biological specimens including associated clinical data and research study information.</p> <p><i>Recommendation 2A.</i> Establish a central registry of existing and new specimens</p> <p><i>Recommendation 2B.</i> Prioritize the use of biological resources.</p> <p><i>Recommendation 2C.</i> Ensure that additional data are collected even after a biomarker appears to have been validated.</p> <p><i>Recommendation 2D.</i> Improve access to information on biomarker research studies.</p> <p><b>Priority 3.</b> Strengthen the role of regulatory agencies, particularly the FDA, in ensuring the responsible and evidence-based clinical use of biomarkers.</p> <p><i>Recommendation 3A.</i> Review relevant federal law pertaining to biomarker assay oversight and recommend changes where needed.</p> <p><i>Recommendation 3B.</i> Establish rules for post-marketing surveillance of approved biomarker assays.</p> <p><i>Recommendation 3C.</i> Revise and streamline the consent process for collecting and using specimens for biomarker studies.</p>

*Recommendation 3D.* Centralize the Institutional Review Board (IRB) process to expedite biomarker validation.

**Priority 4.** Promote synergistic collaboration across research disciplines and among industry, academia, and consumer advocates.

*Recommendation 4A.* Development of biomarker assays and new therapies must be in tandem.

*Recommendation 4B.* Encourage multidisciplinary collaborations to conduct biomarker evaluation studies.

**Priority 5.** Educate all stakeholders, including clinicians and consumers, in all aspects of biomarker research and use.

*Recommendation 5A.* Educate the public about evidence-based use of biomarkers and the role of regulatory agencies with regard to biomarker assays.

*Recommendation 5B.* Educate physicians about evidence gaps

*Recommendation 5C.* Educate patients about the levels of evidence for available biomarker and treatment options.

**Priority 6.** Enact legislation to protect patients against discrimination on the basis of biomarker information.

*Recommendation 6A.* Strong, enforceable legislation should be enacted to protect consumers from discrimination on the basis of their biomarker studies.

Priority area number three is: ***strengthening the role of regulatory agencies in ensuring the responsible and evidence-based clinical use of biomarkers.***

The Panel expressed that “the current regulatory framework for cancer biomarker oversight is insufficient to serve the best interests of consumers. It permits the clinical use of assays that are not reviewed by the FDA and the widespread use of FDA-reviewed assays for non-approved indications”.

Further, the Panel expressed that “even in the case of FDA-approved biomarkers assays, there is not assurance that the biomarker has demonstrated clinical utility”. Furthermore, it stated that “the scope of FDA review should be expanded to include clinical utility as defined through the consensus process, as well as extended to tests currently under the authority of CLIA”.

The Panel expressed considerable concern regarding the premature or inappropriate (not evidence-based) use of biomarker assays. Such use

wastes health care dollars and can lead to negative physical and psychological consequences in affected consumers.

Specific recommendations of direct relevance to the draft guidance and the FDA are:

1A: Incorporate the best components of drug development to guide the development and validation of biomarker assays

3A: Review relevant federal law pertaining to biomarker assay oversight and recommend changes where needed

3B: Establish rules for post-marketing surveillance of approved biomarker assays

The National Breast Cancer Coalition Fund believes that the draft guidance is a step in the right direction as it attempts to exercise more significant regulatory oversight of biomarker assays to ensure clinical relevance. This should lead to evidence-based use. However, the scope of the draft guidance is too narrow and the document itself is surprisingly brief. There needs to be a comprehensive approach that creates a clear path moving forward, with definitions and criteria that reflect the key issue: impact on patient outcomes. The technology being used, and business considerations are certainly relevant and important to the development and market availability of diagnostic tests. However, both these are secondary to clinical utility and cannot be the driving force behind the guidance. Lastly, there needs to be more clarity about how the risk-based approach mentioned in the draft guidance will be applied to diagnostic tests, and more importantly, whether the definition of clinical utility will be meaningful and consistent with that endorsed by the Strategic Consensus Panel.

