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The potential for complex biomarkers known as IVDMIAs (In vitro diagnostic multivariate index assays) to change the face of breast cancer treatment is tremendous. For too long we have been plagued with a one size fits all approach to treatment. Even though many women are cured with surgery they have to suffer through radiation, chemotherapy, and 5 years of hormonal treatment because there is no way to know with certainty what treatment a woman really needs, IF ANY. While this treatment strategy has had a small impact on breast cancer mortality, it has meant that many women have been NEEDLESSLY exposed to the lethal and life altering effects of all these modalities. Just to name some of the worst ones: leukemia, cardiomyopathy, endometrial cancer, stroke,

pulmonary embolism, infertility, lymphedema, chemobrain, and loss of libido.

So we welcome a new technology that has the potential to customize our treatments. To give us only what we need. To even tell us WHICH chemotherapy, hormonal treatment, monoclonal antibodies, or small molecule will be OPTIMAL for our specific tumors. And we know that in the future IVDMIA's will also have the potential to find breast cancer earlier than is now possible and to do a better job than the Gail model at determining who is REALLY at high risk for getting breast cancer.

Nevertheless, it is very important to be aware of the pitfalls that have plagued biomarker research over the years. In almost half a century of breast cancer biomarker research only TWO biomarkers have proved to be of clinical value: ER and Her2. The significance of what PR means is still disputed. We know for a fact that problems with assays have led to erroneous assessments, less than optimal treatment, and most importantly, premature loss of many lives.

Unfortunately, recent studies indicate that there are still problems, for example, with accurate ER and Her2 assays. For example the cut point for ER positivity varies from 1 to 25% of cells with estrogen receptors. A recent study showed that 20% of Her2 tests were not accurate. As many have said, a treatment is ONLY AS GOOD as its biomarker, and hence they too need to be rigorously regulated.

One of the most important recommendations of the National Breast Cancer Coalition's Strategic Consensus Report on Breast Cancer Biomarkers is "to incorporate the best components of drug development to guide the development and validation of biomarker assays." This new FDA Guidance for IVDMIAs is an important first step in that direction. It will assure that IVDMIAs are: 1) examined before they are marketed, 2) that their results are reproducible by an independent body, 3) that they are tested for accuracy and 4) that they have clinical relevance. The writing of the IVDMIA label, as with new drugs, must be over seen by the FDA to ensure that there are no false claims and that the results of an INDMIA assays are understandable to both doctors and patients. It is clear to me that neither CLIA, the Federal Trade Commission, nor any other

agency in HHS has the depth of the experience, the capabilities, or the resources to undertake such a job nor do they have the regulatory power.

One need only look to the Ova Check experience to see why this kind of regulatory power is so important. Ova Check was developed as a blood test for the early detection of ovarian cancer in high risk women by Correlogic, a private company, in partnership with scientists from the FDA and the NCI. However, the FDA said that it would not allow Ova Check to be marketed until it published clinical evidence that it WORKED in patients. Keith Baggerly, a bioinformatics specialist at MD Anderson, when trying to replicate the study, found, among other problems, that test results were influenced by the order in which the assay was run. According to an article by David Ransohof in the Journal of the National Cancer Institute Ova Check had not been properly validated its finding in an independent data set and there was a possible problem with overfitting and bias. Three years later, it has still not been approved to be marketed, confirming its problems were serious. If it was up to CLIA or the Federal Trade Commission

Ova Check would have been marketed-because they do not have the power to stop it. And we all know how hard it is to get something off the market once it is on. Not to mention the irreparable damage it would have done to women.

To me the arguments that FDA regulation of IVDMIAs will hinder development and commercialization, or that this new regulation is unfair, are non sequiturs.

Don't we want to find out which IVDMIAs work and which ones don't, regardless of when they were developed or by whom? If anything will hold up development in this field it will be the premature marketing of more Ova Checks. As we see this is not just a matter of "colorful characters" or fly by night companies as suggested in a recent GAO report. Reputable scientists can make honest mistakes.

As an advocate I think we need to introduce rigor and oversight into the biomarker field and I think the FDA Guidance on IVDMIAs is an important step in that regard. I certainly don't follow the logic that when IVDMIAs are homebrews

they should not be regulated by the FDA. My logic leads in the other direction. All biomarkers, including homebrews, when used in the CLINIC should be regulated by the FDA. Otherwise we leave the successful commercialization of IVDMIAs to companies who write the best press release, do the most advertising or try and court advocacy groups.