Commentary: Hormone Receptor Testing in Breast Cancer: A Distress Signal from Canada

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Recent events in Canada underscore substantial problems with estrogen receptor (ER) testing by immunohistochemistry (IHC) in breast cancer [1, 2]. In 2005, a woman there was diagnosed with invasive lobular carcinoma. Her tumor was tested for ER expression by IHC in a laboratory managed by Eastern Health, the provincial health care provider in Newfoundland and Labrador. The results were negative, which is unusual for this type of tumor, so her physicians had it retested in another laboratory. The new IHC results came back positive, and the discrepancy led Eastern Health to investigate the accuracy of testing in Newfoundland and Labrador. The new IHC results came back positive, and the discrepancy led Eastern Health to investigate the accuracy of testing in Newfoundland and Labrador. Eventually, over 2,000 originally ER-negative cases were retested in another laboratory in Ontario, and nearly 40% were found to be ER-positive. An official inquiry was convened in July 2007, to determine the scope and causes of the problem, and to develop policies to prevent it from happening in the future (Commission of Inquiry on Hormone Receptor Testing at http://www.cihrt.nl.ca/transcripts.html). The conclusions of this inquiry are still forthcoming.

In current clinical practice, ER testing is mandatory in all newly diagnosed breast cancers, and accurate results are critical in determining the use of adjuvant hormonal therapy. This type of therapy significantly improves the outcome of many patients with ER-positive tumors, but it is ineffective with ER-negative disease. For this reason, most of the erroneous ER-negative patients in Newfoundland and Labrador were not treated with hormonal therapy, and some were almost certainly harmed because of it. This tragic outcome was avoidable and raises several urgent questions that should concern all of us: How did it happen? Is it happening elsewhere? What is being done to prevent it?

There are many well-known problems associated with measuring proteins by IHC, particularly proteins requiring quantified results such as ER [3, 4]. Some problems involve preanalytical issues unrelated to IHC itself, such as delayed or inadequate fixation of tissue, allowing proteins to degrade. Others are analytical in nature, such as the use of diverse reagents with unequal sensitivities [5–8], or antigen-retrieval procedures that inadequately re-expose proteins masked during fixation [4]. Most IHC assays rely on enzymatic detection systems with very rapid kinetics that are difficult to control,
and it is very challenging to quantify results in an accurate and reproducible manner [9]. Postanalytical events may also contribute in the sense that tumors with very low levels of receptors (e.g., 1%–10% positive cells) may respond to hormonal therapy [6, 7, 10], and some laboratories use arbitrary definitions of positive that are too high (e.g., >10% positive cells). Fastidious oversight by highly experienced and knowledgeable personnel is required to recognize, resolve, and avoid these problems, and some or all of them may have contributed to the debacle in Canada.

Unfortunately, the problem with ER testing by IHC is not restricted to Newfoundland and Labrador. Perhaps the best evidence for this comes from the United Kingdom National External Quality Assessment Service (NEQAS). This organization has conducted and published the results of several studies on the accuracy and reproducibility of evaluating ER by IHC based on proficiency testing of 150 laboratories in 26 countries worldwide [4, 11–14]. The results identified error rates in some laboratories rivaling those in Newfoundland and Labrador, as well as the major technical problems causing them. The U.S. does not participate in NEQAS, and information regarding the accuracy of ER testing in this country is hard to find. Although many laboratories in the U.S. participate in proficiency testing offered by the College of American Pathologists (CAP), many do not, and the evaluation of ER by the CAP is less comprehensive than that of the NEQAS, so detailed results are not available. However, there is compelling anecdotal evidence suggesting that problems in the U.S. are also substantial. For example, in a recent large international clinical trial comparing hormonal therapies in receptor-positive breast cancer, a subset of >100 patients was enrolled with ER-negative/progesterone receptor (PgR)-positive tumors based on local laboratory results from several countries, including the U.S., who was a major contributor to the trial [15]. Repeat testing in an expert central laboratory revealed a 69% false-negative rate for ER in this subset of patients. Furthermore, there was a 44% false-negative rate for PgR in the group of >1,200 ER-positive/PgR-negative patients enrolled based on local laboratory results, so the problem is larger than ER alone. While far from being scientific, the false-negative rate of IHC testing for both receptors in my consulting practice over the past 10 years is about 30%, which is similar to that of other experienced consulting pathologists I have spoken with on this issue.

Given the critical need for accurate ER and PgR results in all patients with breast cancer, and the widespread difficulty obtaining them, it is clear that something must be done to remedy the problem. On one hand, it should be relatively easy to resolve because several comprehensively validated IHC methods have been published for other laboratories to emulate [5–7, 10, 16, 17]. On the other hand, it is remarkably difficult to persuade laboratories on a global scale to adopt the same methods, or to rigorously standardize and validate their own. A few years ago, a similar widely publicized predicament regarding human epidermal growth factor receptor (HER)-2 testing in breast cancer led to the development of rigorous guidelines by the CAP and the American Society of Clinical Oncology (ASCO) [18], and laboratories in the U.S. must soon comply with these guidelines to maintain CAP accreditation. The CAP and ASCO are also aware of the need to improve ER and PgR testing, and they are in the process of developing enforceable guidelines for these biomarkers as well. However, CAP accreditation is currently not required in the U.S. for laboratories to conduct these tests, and most laboratories are not CAP accredited. The situation is similar in other countries and it will take considerable resources, education, and persistence to achieve universal compliance in the use of assays that are comprehensively standardized and validated in an equivalent manner.

Ultimately, however, it is unrealistic to expect that even perfect tests for ER and PgR alone, by IHC or any other methods, will be sufficiently powerful to predict the response of all breast cancer patients to hormonal therapy because the biology involved is so complex. New more powerful predictors are needed, and they will most likely be based on multiple biomarkers. In this regard, there are many promising new approaches on the horizon at varying stages of development and validation, including oncoype DX® (Genomic Health, Inc., Redwood City, CA, http://www.genomichealth.com) [19, 20], the HOXB13/IL17BR gene ratio [21–23], and estrogen-regulated gene signatures determined by microarrays [24], to name a few. Hopefully, these and other approaches will lead to significant improvements in predicting response to hormonal therapies, and it will be important for them to avoid making the same mistakes concerning proficiency and standardization that have plagued ER, PgR, and HER-2 testing by IHC.

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