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Control/Tracking Number: 20-LB-1980-SABCS
Activity: Late Abstract
Current Date/Time: 9/29/2020 9:12:13 PM

Introduction and clinical validation of metrology standards for immunohistochemistry (IHC); new tool for standardization of estrogen receptor (ER) IHC Assay in Breast Cancer

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Abstract:
Traceability of measurement to a higher order reference standard is a foundation of laboratory testing. There is as yet no method for creating reference standards for cellular proteins in situ in an analogous fashion as for soluble analytes. At present, IHC laboratories produce results for breast cancer hormone receptors without connection to a reference standard. Not surprisingly, high rates of testing variation as well as discrepancies among IHC laboratories have been reported. To address this need, we developed a system of measurement traceability using a linked fluorescein tag for creating reference standards for any cellular analyte and, as a first test, validate it for estrogen receptor (ER) testing. In this study, the newly developed ER standard defines and compares the thresholds separating “high positive”, “low positive”, and “negative” tests according to updated ASCO/CAP guidelines as detected by clinical IHC laboratories in a national external quality assessment survey. This reference standard utilizes NIST Standard Reference Material (SRM) 1934 as a universal IHC standard. We calculated ER concentration based on a linked fluorescence measurement traceable to NIST SRM 1934 as each ER is linked to a single fluorescein, and fluorescein concentration equals ER concentration. Each laboratory’s lowest detected ER concentration (i.e. “limit of detection”, LOD) was compared to their results with 80 tumor samples enriched for triple negative breast cases. For the Canadian Immunohistochemistry Quality Control (CIQC) ER proficiency testing run, calibrator sets with peptides for the SP1, EP1, and 6F11 epitopes were created. The various concentrations were pipetted onto histology slides used by CIQC to place its 80-case breast cancer tissue microarray. These slides were stained by participating laboratories using their routine ER IHC protocols and returned to the CIQC. For the purpose of this study, Histology Score and ASCO/CAP categorical scoring recommendation was used for the readout. Results with SP1 clone are reported here because it was employed by overwhelming majority of laboratories. A total of 3,038 readouts were included in the analysis. Most IHC laboratories had a LOD between 10,000 – 25,000 molecules ER per microbead. Highly

sensitive ER assays (low LODs) detected more positive cases while those with poorly sensitive assay detected fewer. The LOD correlated with the percent positive cases (R^2= -.767, p < 0.0001, Spearman Correlation) as well as with cumulative individual laboratory Histology Score (R^2= -.612, p < 0.0001, Spearman Correlation). The tumor samples accounting for this difference were principally “low positive” (ASCO/CAP classification) while ER-high positive tumors were less affected. Although the concept of a non-quantitative IHC LOD has been introduced with critical assay performance controls (iCAPCs, e.g. germinal center cells in the tonsil for ER), there were no tools until now to actually measure LOD for ER IHC testing. With the calibrators introduced here, it is now possible to measure the LOD for ER IHC assays. Furthermore, our data show that ER low positive and some cases of ER high positive breast cancers are highly affected by the variability of analytic sensitivity between clinical IHC laboratories. These data argue for the urgent need to standardize testing to a defined analytic sensitivity range, which is now possible for the first time. Beyond inter-laboratory standardization, known measured LOD also enables: i) methodology transfer from clinical trials to clinical laboratories; ii) determination of optimal analytical sensitivity to produce assays with highest clinical and analytical validity, and iii) daily monitoring of analytical sensitivity for each tested IHC slide.

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Author Disclosure Information:

E.E. Torlakovic: None. **S.R. Sompuram:** Salary; Author; Boston Cell Standards LLP. Receipt of Intellectual Property Rights / Patent Holder; Author; Yes. Ownership Interest (stock, stock options, or other ownership interest excluding diversified mutual funds); Author; Yes. **K. Vani:** Salary; Author; Boston Cell Standards LLP. Receipt of Intellectual Property Rights / Patent Holder; Author; Yes. Ownership Interest (stock, stock options, or other ownership interest excluding diversified mutual funds); Author; Yes. **L. Wang:** None. **A.K. Schaedle:** Salary; Author; Boston Cell Standards. **P.C. DeRose:** None. **S.A. Bogen:** Salary; Author; Boston Cell Standards LLP. Receipt of Intellectual Property Rights / Patent Holder; Author; Yes. Ownership Interest (stock, stock options, or other ownership interest excluding diversified mutual funds); Author; Yes.

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