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the tissue phenomics company

CDx Development: Robust Assay Development with a More Accurate Cut Point to Stratify Patients

Merrimack Pharmaceuticals is using Definiens technology to identify candidate Companion Diagnostics across their oncology pipeline. Trying to predict response to treatment with their monoclonal antibodies blocking the HER family of receptors, Merrimack successfully established assays to determine the receptor numbers on a cell by cell basis. This allows them to comprehensively and consistently assess tumor heterogeneity and identify subgroups of patients that may differ in their response to treatment.

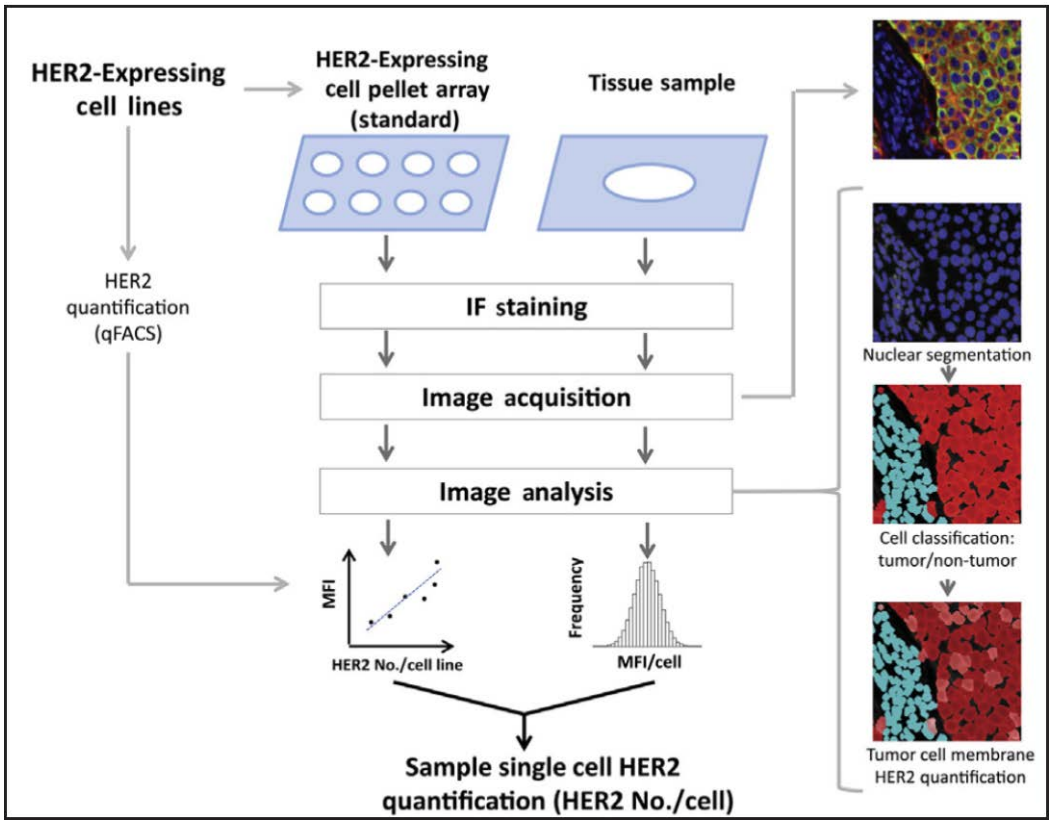
Study Synopsis

What problems needed to be solved?

- A mechanistically relevant scoring method for a novel IHC assay had to be determined.
- The limited dynamic range of the chromogenic IHC assay had to be expanded.

What was employed to solve the problem?

- A standard curve array was used to standardize the assay and the clinical samples used for quantitation.
- Immunoflourescent IHC was used to increase the ability to quantitate the limited dynamic range of the assay.
- Definiens image analysis was employed to quantitate images.



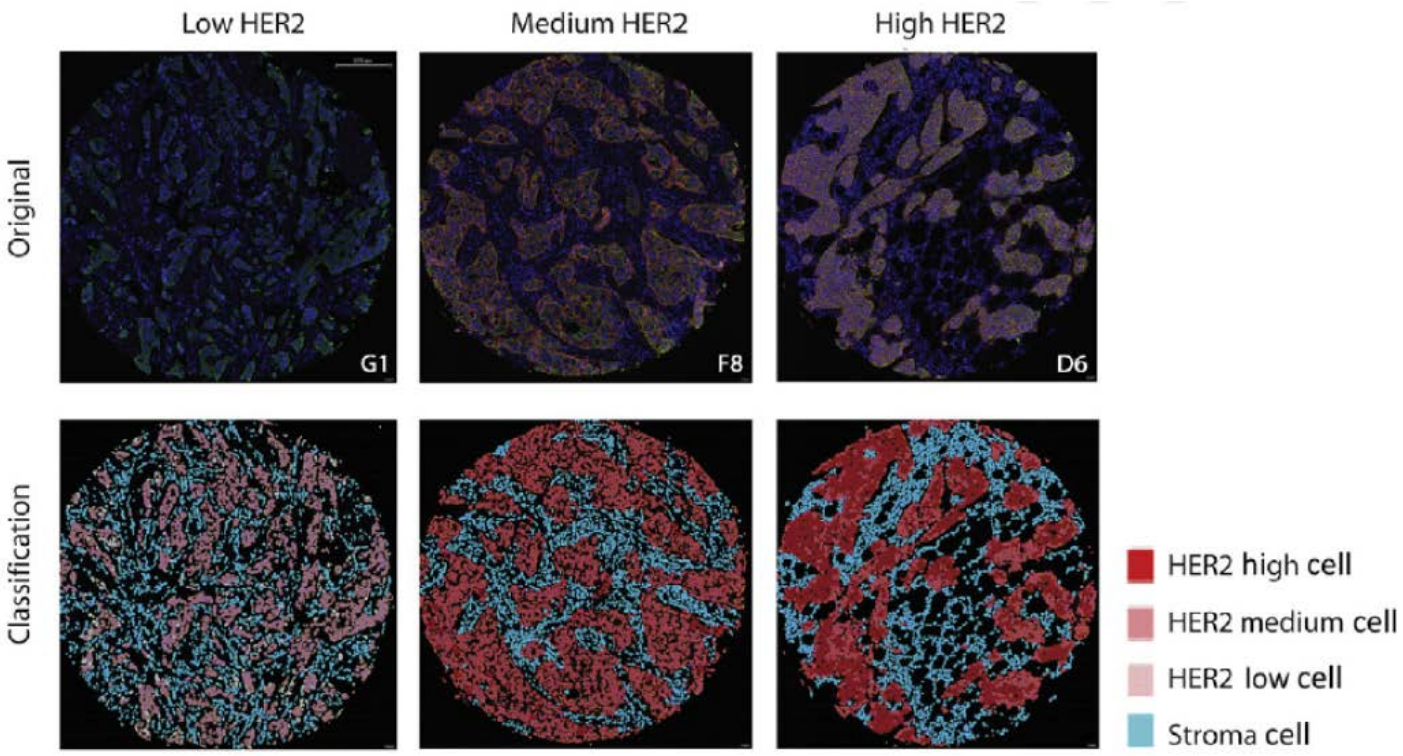
Schematic overview of the quantitative immunofluorescence (IF)

Benefits

- A clinically relevant scoring modality was determined that would not have been detectable by traditional chromogenic staining and pathology scoring.
- This new scoring modality was translated into a chromogenic IHC assay optimized for pathologist scoring around the clinically relevant cutpoint.
- Significant improvement in identifying more qualified patients for treatment.

Implications

- The study illustrates how better assays can result from approaching IHC assay development and IHC quantification with advanced image analysis in tandem.
- The level of standardization and validation achieved is exemplary for the rigorous IHC assays needed in CDx development.
- The methodology is transferable to similarly assess other membrane markers than the HER family of receptors.



A breast disease TMA was stained with HER2 (red), cytokeratin (green), and DAPI (blue). Representative TMA cores at low (G1), medium (F8), and high (D6) HER2 expression are shown with the corresponding cell segmentation and classification.

Additional Information

The findings have been published in The American Journal of Pathology:
Onsum et al.; Am J Pathol. Sep 11, 2013; DOI: 10.1016/j.ajpath.2013.07.015