

#1115: Identification of HER2 ultra-low based on an artificial intelligence (AI)-powered HER2 subcellular quantification from HER2 immunohistochemistry images

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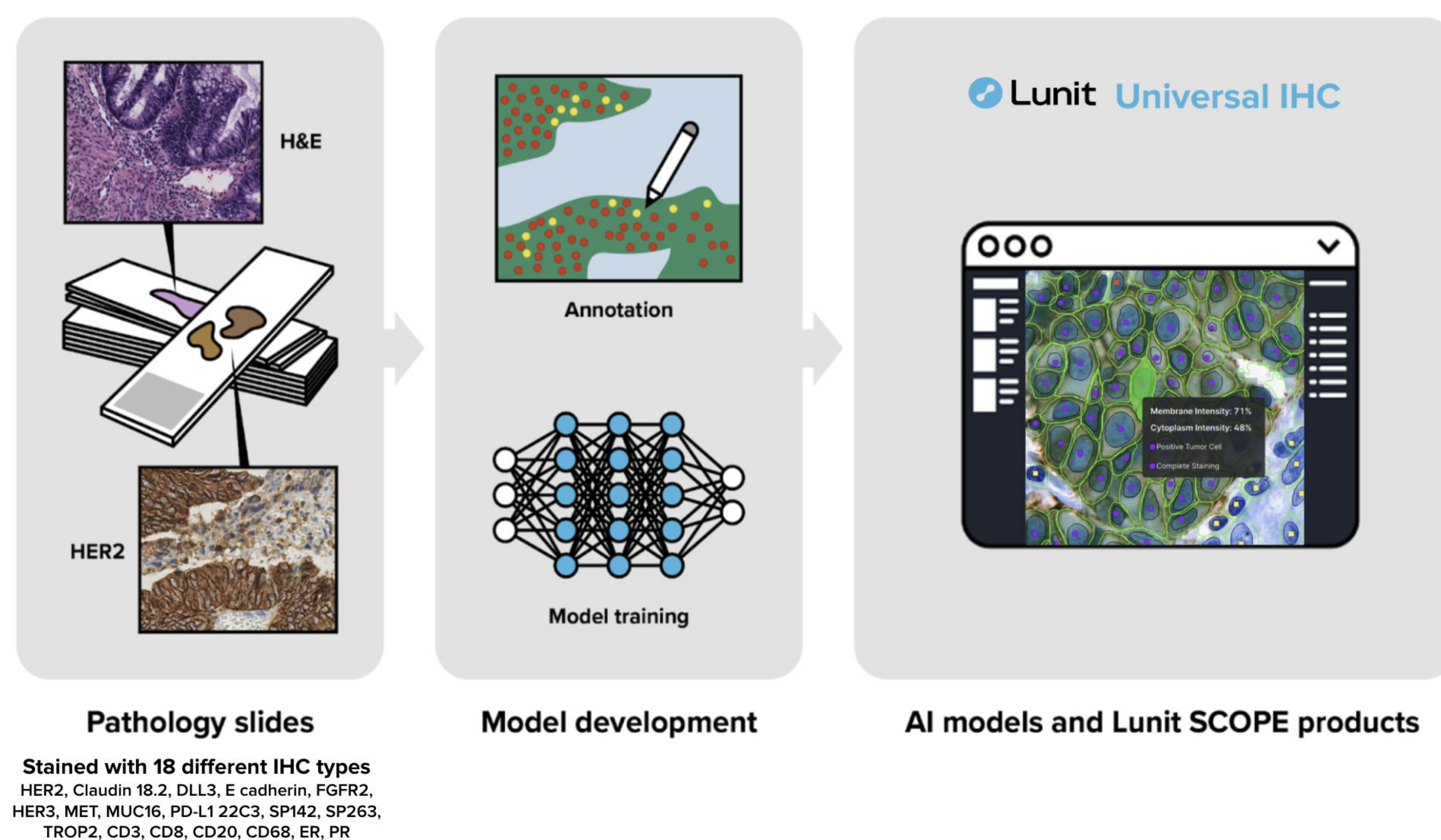
Background

- HER2-targeted antibody-drug conjugates (ADCs) can effectively target tumor cells even in HER2-low breast cancers (1+ and 2+/no amplification).
- HER2-targeted ADCs may be efficacious even in patients with ultra-low HER2 expression, faint/barely perceptible and incomplete staining in <10% of tumor cells, classified as HER2 score 0 according to ASCO/CAP guidelines.
- We developed an AI-based whole-slide image (WSI) analyzer for immunohistochemistry (IHC)-stained slides, exploring a cutoff differentiating between true HER2 negative versus HER2 ultra-low.

Methods

- An AI-based IHC WSI analyzer was developed using 6,188 WSIs, from various cancers, stained by 18 types of IHC including HER2, annotated by 153 pathologists.
- The model predicts cells as tumor cells or non-tumor cells, and generates HER2 expression continuous score (HER2ecs, 0-100%), quantifying IHC staining intensity of membrane, nucleus, cytoplasm, and membrane+cytoplasm separately for each cell (**Fig. 1**).
- A total of 401 HER2 IHC WSIs were acquired from Samsung Medical Center (n=275), Kyung Hee University Hospital (n=78), and Commercial Biobank (n=48), scored as 0 (n=347) and 1+ (n=54) by pathologists, for HER2ecs scoring.

Figure 1. Development of the AI-powered IHC analyzer



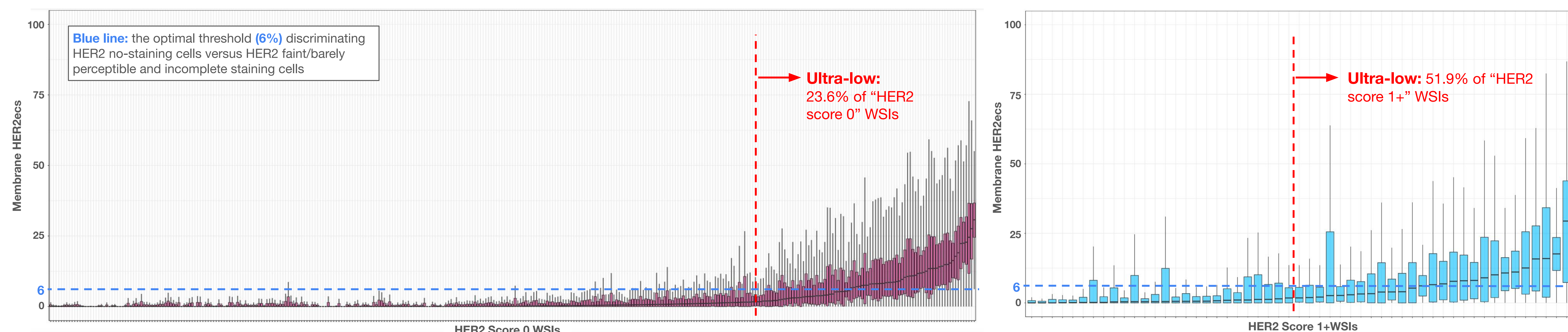
Conclusion

- Among WSIs scored as HER2 score 0 by pathologist, AI-powered subcellular-level analysis enables identification of 23.6% as HER2 ultra-low, which is defined by AI-HER2-weak or higher membrane-specific HER2 expression $\geq 10\%$.
- Clinical validation of the AI-powered HER2 ultra-low definition is warranted.

Results

- In total, 67,169,114 tumor cells and 119,113,886 non-tumor cells from 401 WSIs were successfully evaluated.
- Comparing HER2 score 0 versus 1+ by pathologists, mean HER2ecs of nucleus (1.7% vs 4.1%), cytoplasm (6.5% vs 12.9%), and membrane (3.6% vs 8.2%) were comparable (**Fig. 2**).
- In HER2 score 0 WSIs, membrane HER2ecs of tumor cell was $3.6 \pm 7.8\%$ (mean $\pm$ standard deviation), while that of non-tumor cell was $0.9 \pm 2.9\%$ ($p < 0.001$ vs. tumor cell), suggesting, even in HER2 score 0 cases, tumor cell exhibits HER2 expression beyond non-specific HER2 staining intensity.

Figure 2. Distribution of membrane HER2ecs of tumor cells in HER2 score 0 and 1+ WSIs



- Based on our internal validation dataset, membrane-specific HER2ecs of 6.0% was the optimal threshold discriminating HER2 no-staining cells versus HER2 incomplete and faint/barely perceptible cells (AI-HER2-weak) per ASCO/CAP guideline.
- Among HER2 score 0 by pathologists, when applying this cutoff, the proportion of WSIs showing AI-HER2-weak or higher membrane-specific HER2ecs in over 10% of all tumor cells was 23.6% (82/347) (**Fig. 3**). Interestingly, the proportion of WSIs above this cutoff among those with a HER2 score 1+ by pathologists was 51.9% (28/54), which is comparable to 52.3%, objective response rate of trastuzumab deruxtecan in HER2-low patients in DESTINY-Breast04.

Figure 3. Ultra-low rate of HER2 by Lunit's criteria in HER2 score 0 WSIs

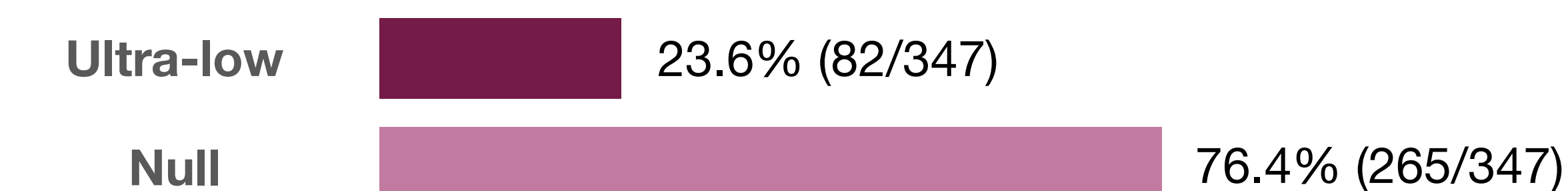


Figure 4. Heatmap of example cases

