

7P-Independent validation of HER2DX *ERBB2* mRNA score to predict HER2-positive (HER2+), HER2-low and HER2-0 status in breast cancer

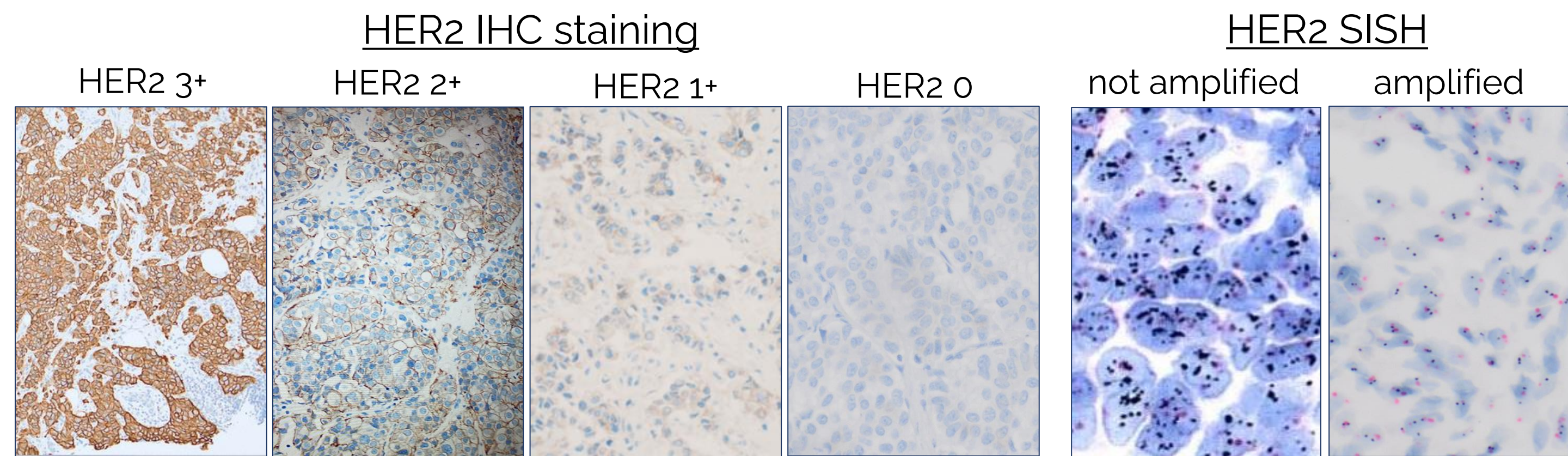
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Background

- HER2DX *ERBB2* mRNA score captures the dynamic range of *ERBB2* expression in both HER2-negative and HER2+ breast cancer (BC).
- In a previous study¹, *ERBB2* mRNA score predicted clinical HER2+ status with high performance in the validation dataset (n=353; AUC=0.96).
- Here, we evaluated the ability of HER2DX *ERBB2* mRNA to predict HER2+, HER2-low (HER2 1+ and 2+/SISH not amplified), and HER2-0 status (**Fig. 1**).

Fig 1. Examples of HER2 status determination by immunohistochemistry (IHC) and silver in situ hybridization (SISH)



Methods

- Standardized HER2DX was evaluated centrally on formalin-fixed paraffin-embedded tumors from 1,149 samples with HER2+ (n=1,029) vs. HER2-negative status (n=120).
- We trained a new *ERBB2* cutoff (by means of decision trees) to predict HER2-low (n=73) versus HER2-0 (n=47) status and tested in an independent validation dataset of 110 HER2-negative tumors with known HER2-low (n=60) and HER2-0 (n=50) status.
- To quantify the diagnostic performance: area under the ROC curve (ROC AUC), global accuracy, positive (PPV) and negative predictive value (NPV) were calculated.

Fig 2. Training and validation cohorts

Validation of the HER2DX *ERBB2* cutoff

**HER2+
N=1,029**

**HER2-negative
n=120**

- HER2-low n=73
- HER2-0 n=47

Training of the HER2-low *ERBB2* cutoff

**HER2-negative
n=110**

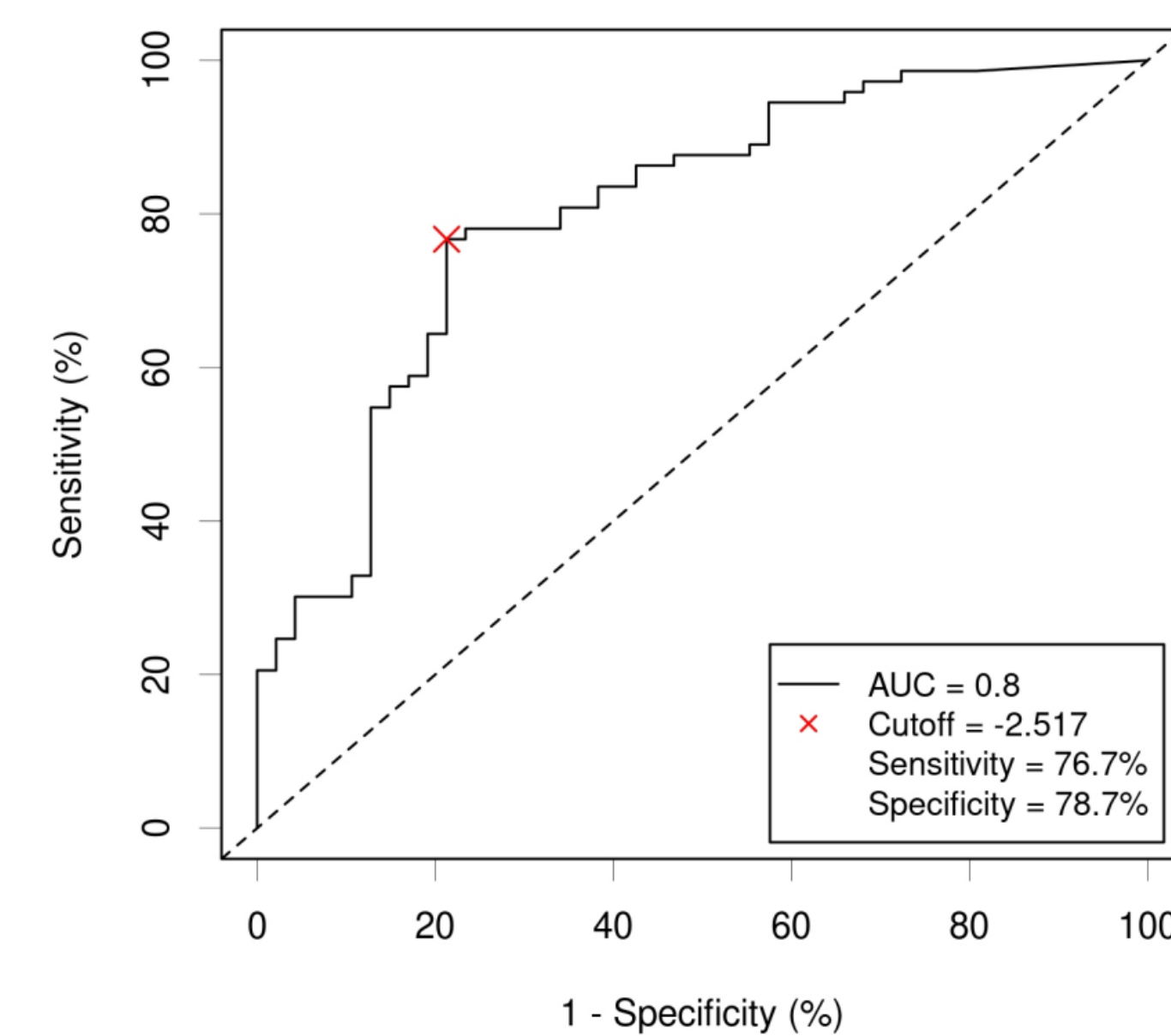
- HER2-low n=60
- HER2-0 n=50

Validation of the HER2-low *ERBB2* cutoff

Results

- In the HER2+ and HER2-negative dataset (n=1,149), the ROC AUC of *ERBB2* mRNA expression to predict HER2+ status was 0.98 (**Fig. 3a**)
- The mean *ERBB2* expression (in log base 2) in HER2+ and HER2-negative disease was 1.41 and -2.41, respectively (14.1-fold difference) (**Fig. 3b**)
- Of note, 0.8% of HER2-negative cases were identified as *ERBB2*-positive and 9.9% of HER2+ cases were identified as *ERBB2*-negative (**Fig. 3c**)
- In the HER2-negative training dataset (n=120), the ROC AUC of *ERBB2* mRNA expression to predict HER2-low vs. HER2-0 status was 0.80, and a new cutoff was identified with 77.5% accuracy (68.5% PPV and 84.9% NPV). (**Fig. 4**).

Fig 4. Identification of a HER2-low cutoff



- In the independent validation HER2-negative dataset (n=110), the ROC AUC of *ERBB2* mRNA expression was 0.77. With the new *ERBB2* cutoff, the overall accuracy to predict HER2-low and HER2-0 cases was 65.5% (66.7% PPV and 64.9% NPV) (**Fig. 5a-b**).
- Finally, in the two HER2-negative cohorts, the mean *ERBB2* mRNA expression (in log base 2) in HER2-low and HER2-0 disease was -1.86 and -2.72, respectively (1.8-fold difference) (**Fig. 5c**)

Fig 3. Validation of the HER2DX *ERBB2* cutoff

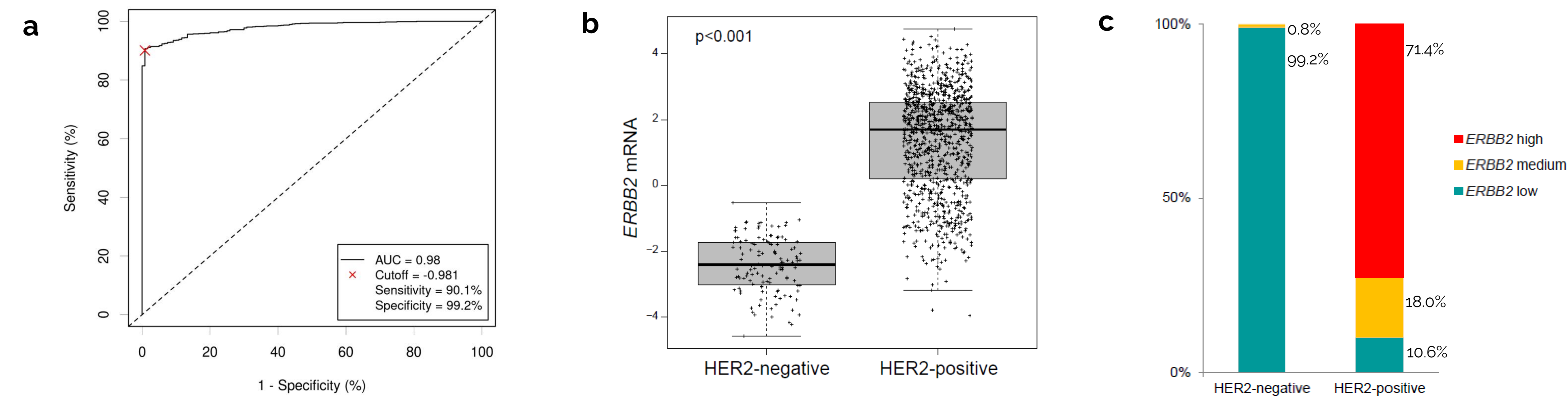
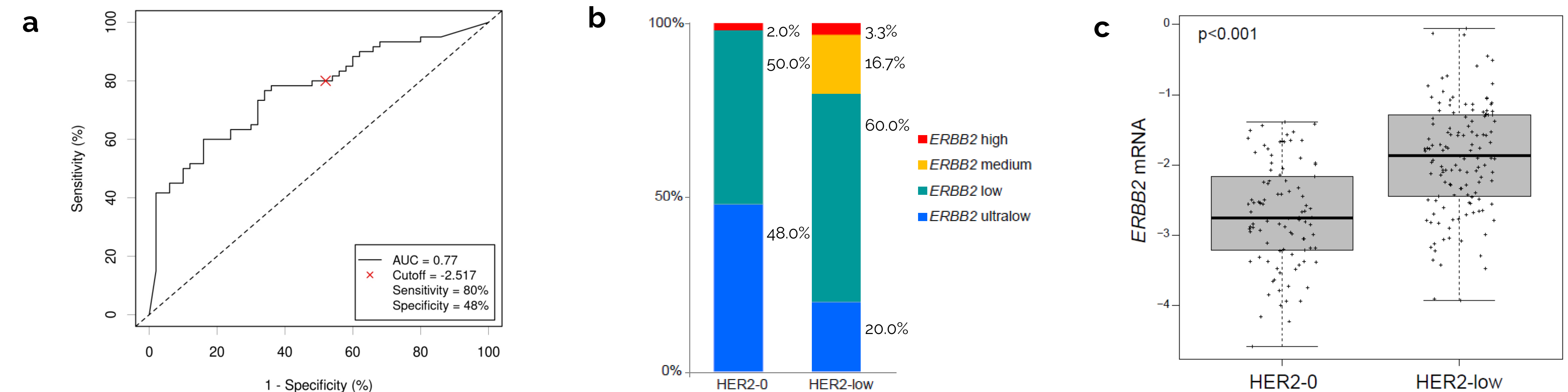


Fig 5. Validation of the HER2-low cutoff



Conclusion

The standardized HER2DX *ERBB2* mRNA score predicts the clinical status of HER2 (positive, low and zero) in BC.

References

References: 1. Prat A et al. Ebiomedicine, 2022 Jan; 75: 103801

COI: The first author does not have conflicts of interest.

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