

Increasing Inclusion in AD Clinical Trials By Using Biomarker Cutoffs Specific to Individuals' Race and Ethnicity

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Clinical Trials

Methodology

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Deriving race and ethnicity-specific biomarker cutoffs is essential to eliminating trial underrepresentation. Currently, using cutoffs based on non-Hispanic white populations creates a systemic screening barrier that reduces generalizability.

INTRODUCTION

The 2018 NIA-AA Research Framework¹ shifted the definition of Alzheimer’s Disease from symptom-focused to pathology-focused.

While this improves diagnostic specificity, the AHEAD 3-45² and Bio-Hermes³ studies showed that racial and ethnic subpopulations had lower amyloid pathology than non-Hispanic whites, despite similar clinical symptoms.

The A4 study⁴ also demonstrated lower inclusion rates in these minority groups.

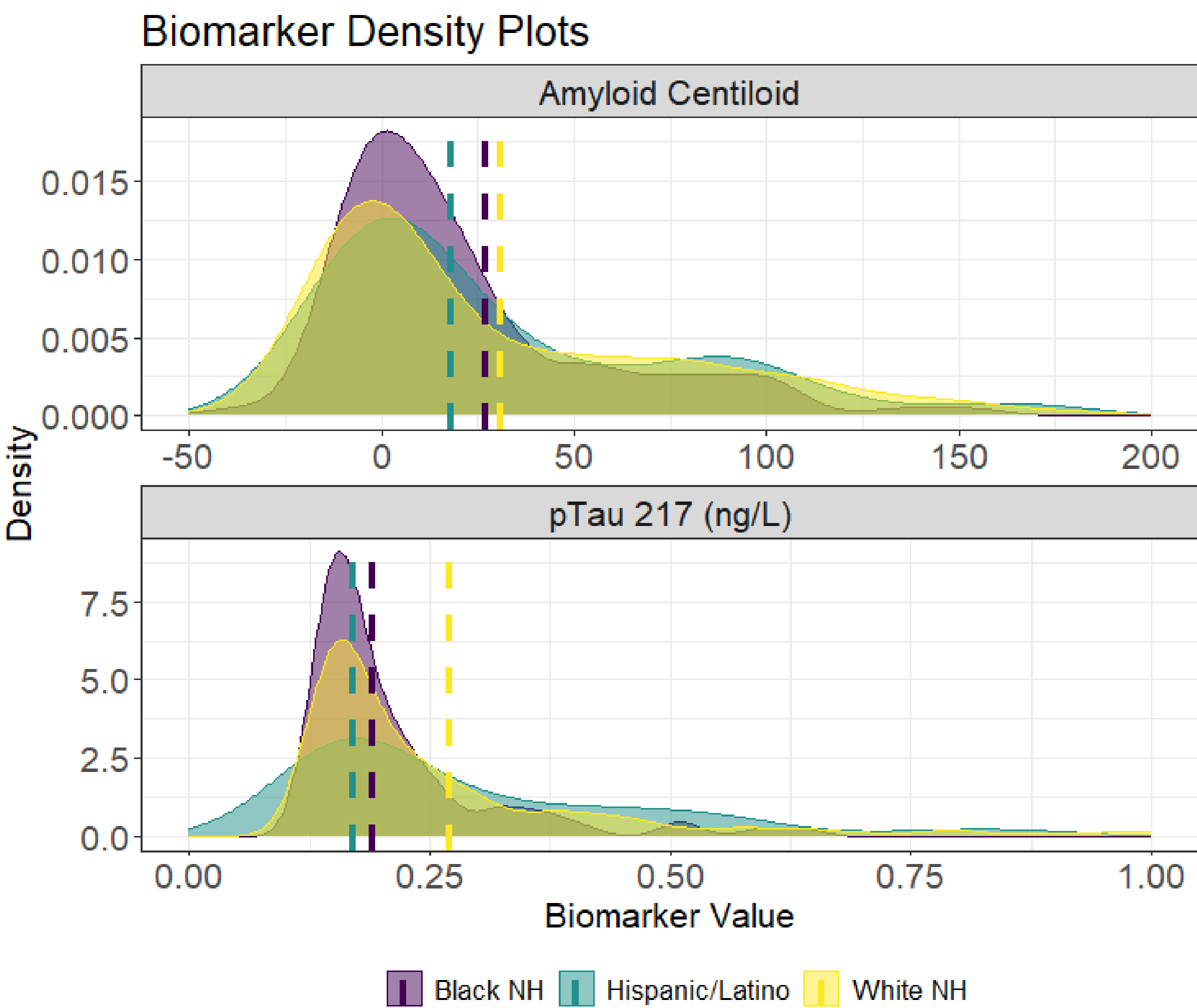
This bias ultimately reduces the generalizability of clinical trial results.

METHODS

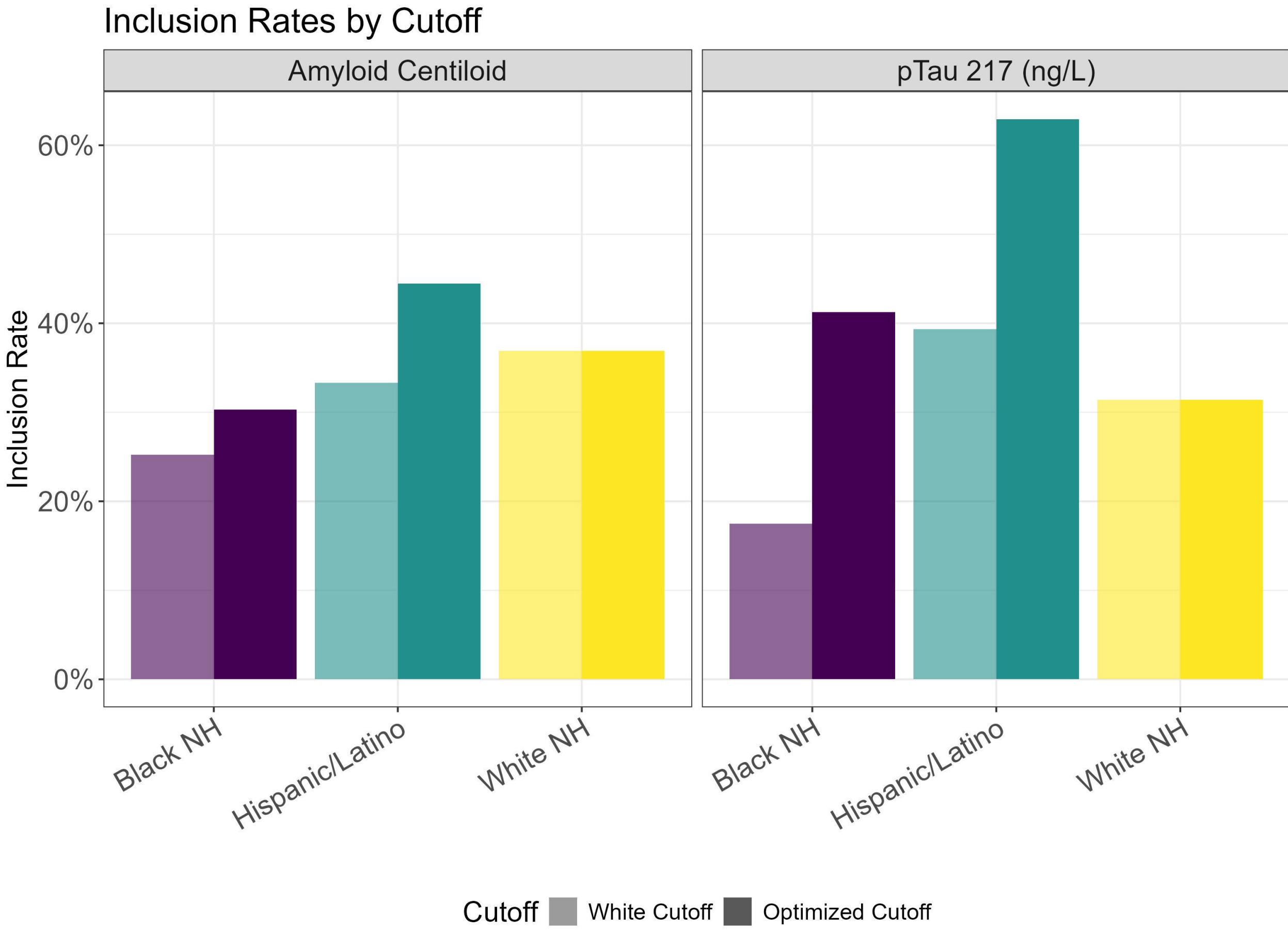
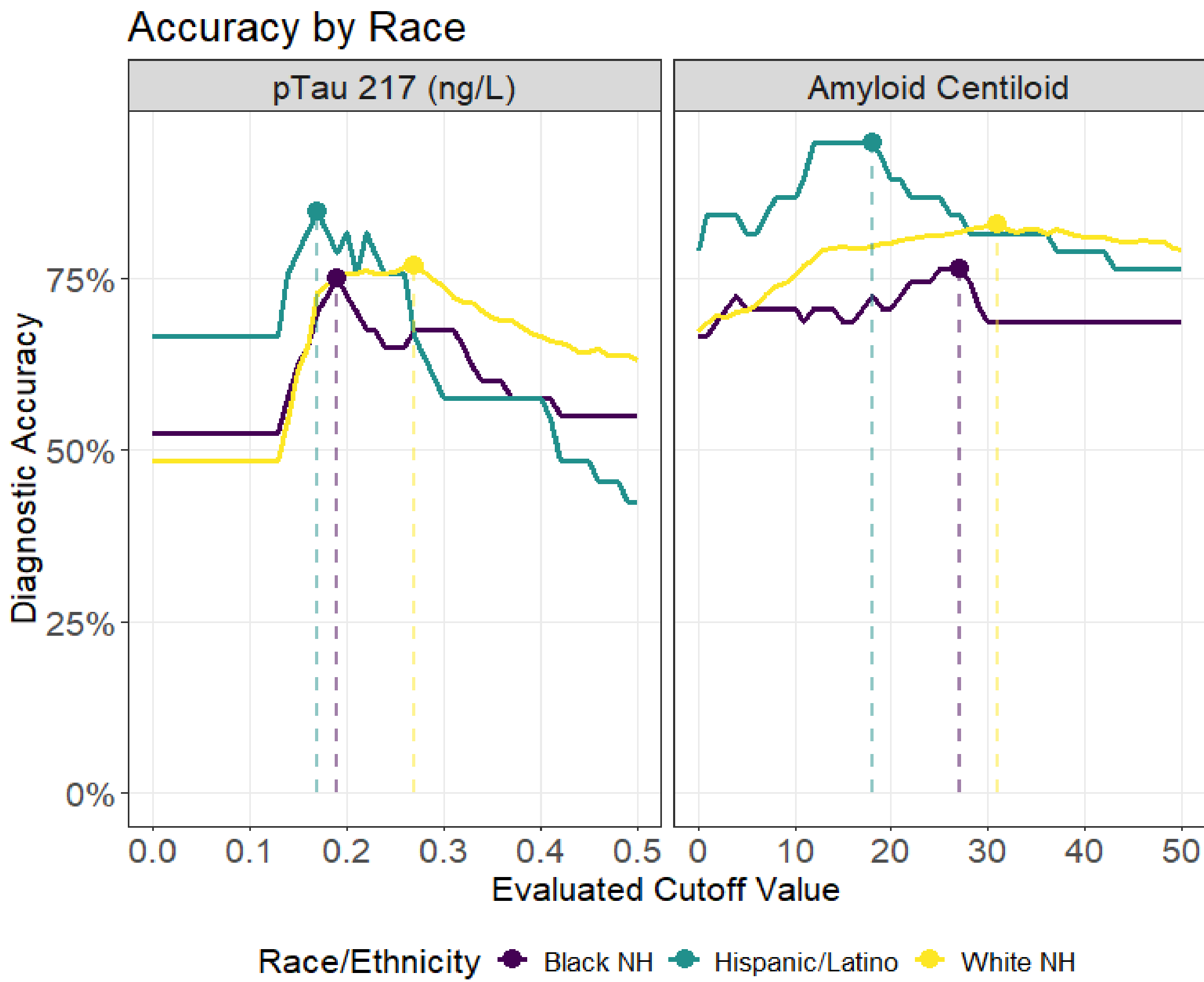
- Used the **Bio-Hermes biomarker database** from the Global Alzheimer’s Platform (GAP)³
- Populations:**
 - Non-Hispanic white
 - Black or African American
 - Hispanic or Latino individuals.
- Diagnostic accuracy based on:
 - True Positive:** ApoE carriers with MCI or confirmed AD
 - True Negative:** Healthy ApoE non-carriers
- Cutoff for amyloid positivity determined by maximizing accuracy by race
 - Accuracy defined as:
$$\frac{\text{True Positives} + \text{True Negatives}}{N}$$

N is the number of subjects evaluated.
- Used **centiloid** and plasma **p-tau217 (U/mL)**.

RESULTS



Cutoffs for black and Hispanic individuals were lower than white individuals for both amyloid centiloid values and for plasma p-tau217. For white individuals, the centiloid cutoff was 31 (83% accuracy) and the plasma p-tau217 cutoff was 0.27 (77% accuracy); for black individuals, the cutoffs were 27 (77% accuracy) and 0.19 (75% accuracy); for Hispanic individuals, the cutoffs were 18 (95% accuracy) and 0.17 (85% accuracy). By using the lower thresholds for blacks and Hispanics, amyloid increased in the MCI cohort by 100% positivity in blacks and 60% in Hispanics. Amyloid positivity in the Probable AD cohort increased by 17% in blacks and 26% in Hispanics.



DISCUSSION

While effort is being put into recruiting more representative populations, ethnic and racial minorities will continue to be underrepresented because of cutoffs derived primarily from non-Hispanic white populations. By deriving cutoffs specific to race or ethnicity, reduced screen failure will reduce cost and burden of recruitment in minority populations, and increased representativeness will allow more generalizable clinical trials.

REFERENCES

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³Mohs, Richard C et al. “The Bio-Hermes Study: Biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease.” *Alzheimer's & dementia : the journal of the Alzheimer's Association* vol. 20,4 (2024): 2752-2765. doi:10.1002/alz.13722

⁴Sperling, Reisa A., et al. "The A4 Study: Stopping AD Before Symptoms Begin?" *Science Translational Medicine* 6.228 (2014): 228fs13.

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