

Identifying Eligible Candidates for Alzheimer’s Disease–Modifying Treatment with the Digital Clock and Recall

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KEY RESULT: A 3–minute DCR combining cognitive, amyloid, and functional–impairment scores identified DMT–eligible Alzheimer’s disease with AUC 0.90 and NPV 0.89

Background

Rapid identification of patients eligible for Alzheimer’s disease (AD) disease–modifying treatments (DMTs) is a bottleneck for both real–world prescribing and clinical–trial enrollment. Confirming eligibility requires evidence of cognitive impairment **and** amyloid pathology, driving high screen–failure rates and costly, burdensome downstream testing.

A brief digital cognitive assessment that concurrently estimates DCR Cognition Score (DCS), amyloid–positivity risk (APR), and functional impairment probability (FIP) may reduce screen failures and downstream testing burden.

We evaluated whether the 3–minute **Digital Clock and Recall (DCR)** can identify individuals with MCI or mild dementia due to AD by integrating the results of three DCR–derived machine–learning algorithms, i.e., DCS, APR, and FIP.

Methods

Participants. Data were obtained from 594 participants in the prospective, multisite Bio–Hermes–001 study organized by the Global Alzheimer’s Platform Foundation.

Assessments. Participants completed the DCR, MMSE, RAVLT, FAQ, and an Aβ–PET scan: 378 cognitively unimpaired (CU) and 216 with MCI or mild dementia who were Aβ+ on PET (the “DMT–eligible” group).

Models. Three pretrained ML models estimated DCS¹, APR¹, and FIP² from subsets of 2,000+ multimodal, process–based DCR features, including drawing metrics, temporal–spatial and pressure features of stylus manipulation, speech and acoustic features, and demographics.

Analysis. A random–forest model using these three inputs was trained with nested leave–one–out cross–validation to identify the DMT–eligible group; evaluable subjects were split 70/30 into training and testing sets. Performance was assessed with sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

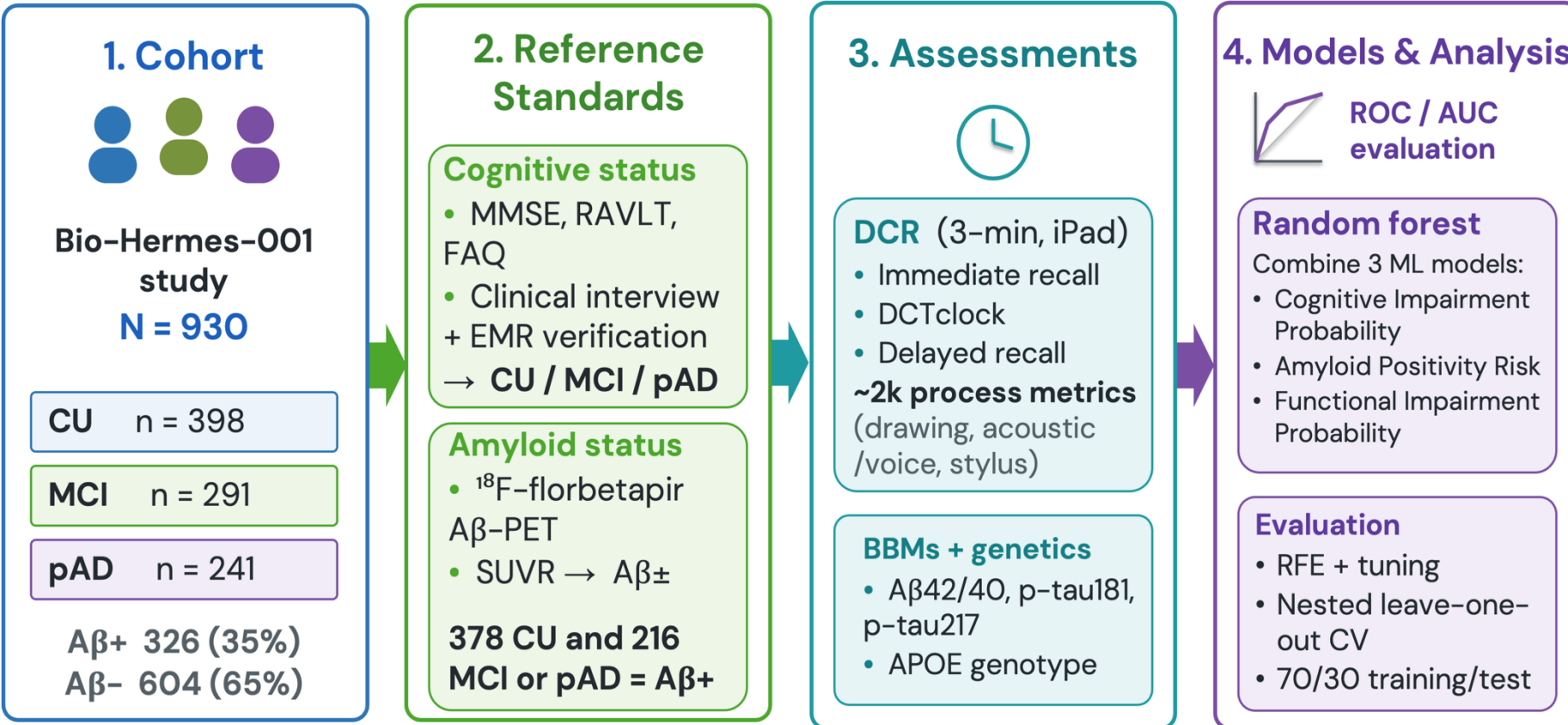


Figure 1. Bio–Hermes–001 study flow^{1,2}.

Metric	Aβ– (n=604)	Aβ+ (n=326)	Statistical Test
Age (years), Mean ± SD	70.75 ± 6.66	74.24 ± 6.15	T=–7.83, p<0.001
Gender (%F)	354 (59)	174 (53)	X²=0.003, p=0.95
Years of education	15.51 ± 2.61	15.39 ± 2.89	T=0.7, p=0.49
Ethnicity – Not Hispanic	536 (89)	288 (88)	X²=4.5, p=0.11
Hispanic	61 (10)	28 (9)	–
Not Reported	7 (1)	10 (3)	–
Race – White	507 (84)	293 (90)	X²=12.8, p=0.026
Black	76 (13)	28 (9)	–
Asian	11 (2)	5 (1)	–
Other / Unknown	10 (2)	0	–
Cognitively Unimpaired (%)	314 (52)	84 (26)	X²=0.09, p=0.77
PiB SUVR, Mean ± SD	1.00 ± 0.09	1.42 ± 0.22	T=–39.9, p<0.001

Table 1. Bio–Hermes–001 study population characteristics by amyloid–PET status².

Digital Clock & Recall (DCR)

The DCR is a ~3–minute, iPad–based assessment: a digital Clock–Drawing Test (Command + Copy) plus 3–word Immediate and Delayed Recall. It captures 2,000+ process–based features, including drawing, spatial, timing, voice/speech, and stylus manipulation metrics.

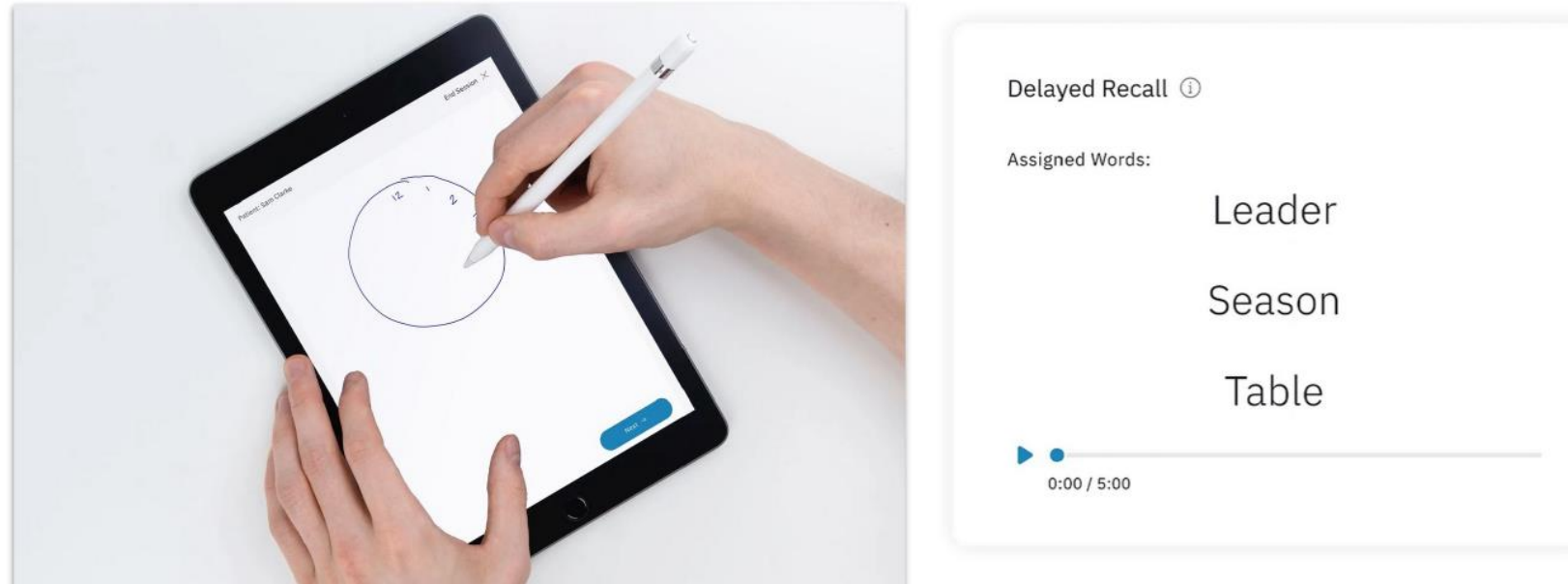


Figure 2. The DCR: digital clock drawing (left) with 3–word Immediate and Delayed Recall (right), on an iPad using an Apple Pencil.

Three distinct ML models derived three probabilities from these multimodal process features obtained during DCR performance:

DCS (DCR Cognition Score), **APR** (amyloid–positivity risk), and **FIP** (functional impairment probability). A random–forest model then combined these to flag DMT–eligible individuals, i.e., amyloid–positive MCI or mild dementia.

Multimodal Machine–Learning Pipeline

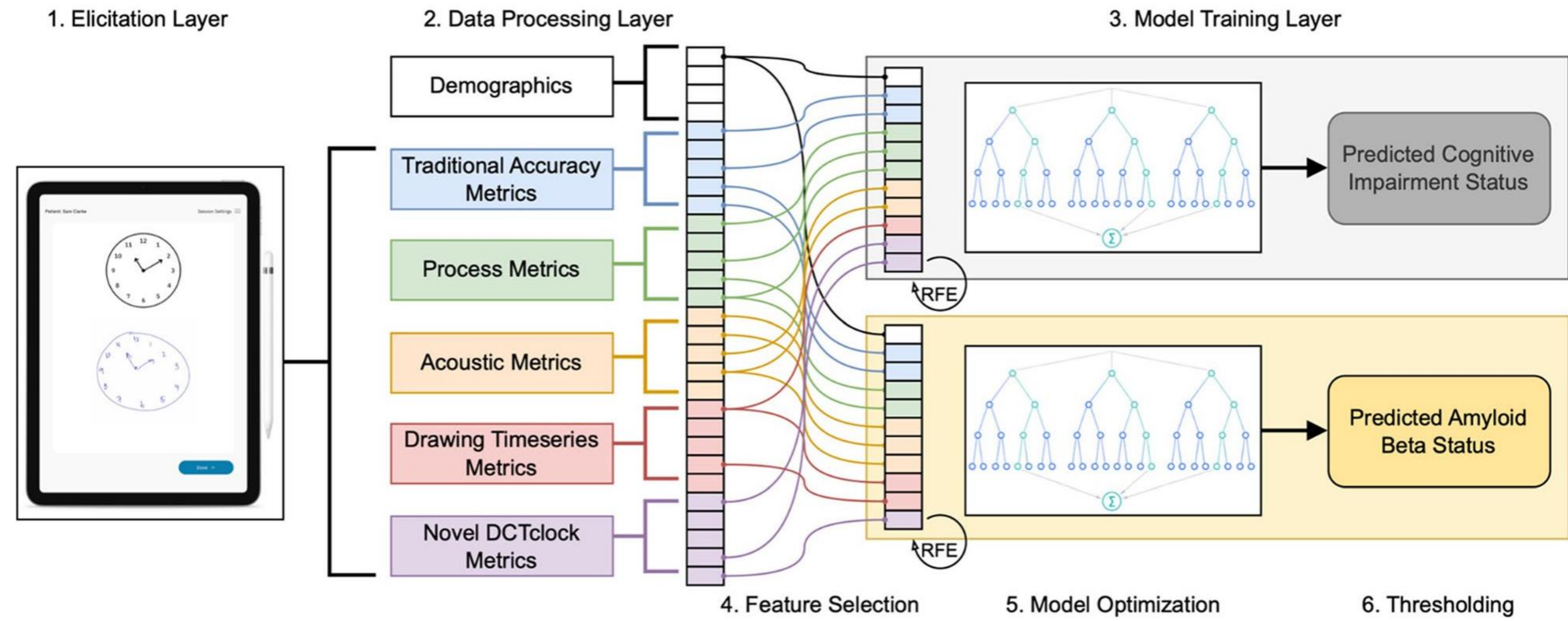


Figure 4. Multiplexed machine–learning (ML) pipeline for simultaneous cognitive, biomarker, and functional assessment (not shown) using the DCR ^{2,3}.

DCR–enabled Clinical Pathway

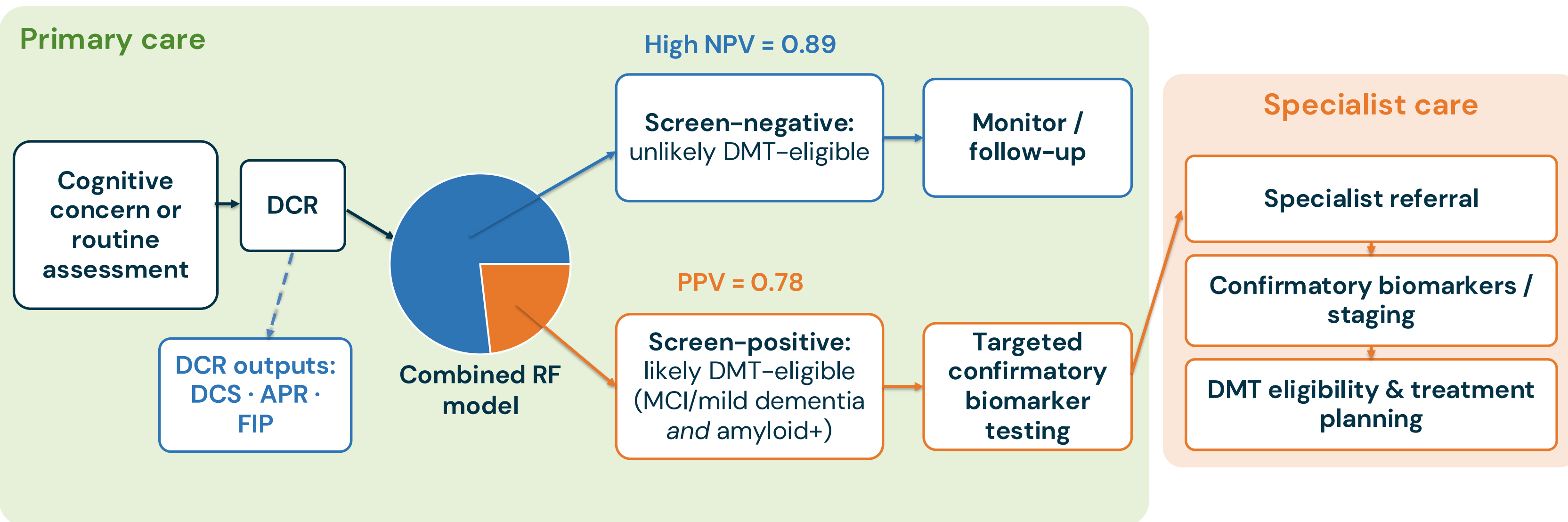


Figure 5. **DCR–enabled pathway.** As a frontline primary–care assessment, the DCR triages patients by DMT–eligibility — prioritizing biomarker confirmation for likely–eligible cases and ruling out others. APR, amyloid–positivity risk; DCS, DCR Cognition Score; FIP, functional impairment probability; RF, random forest.

Results

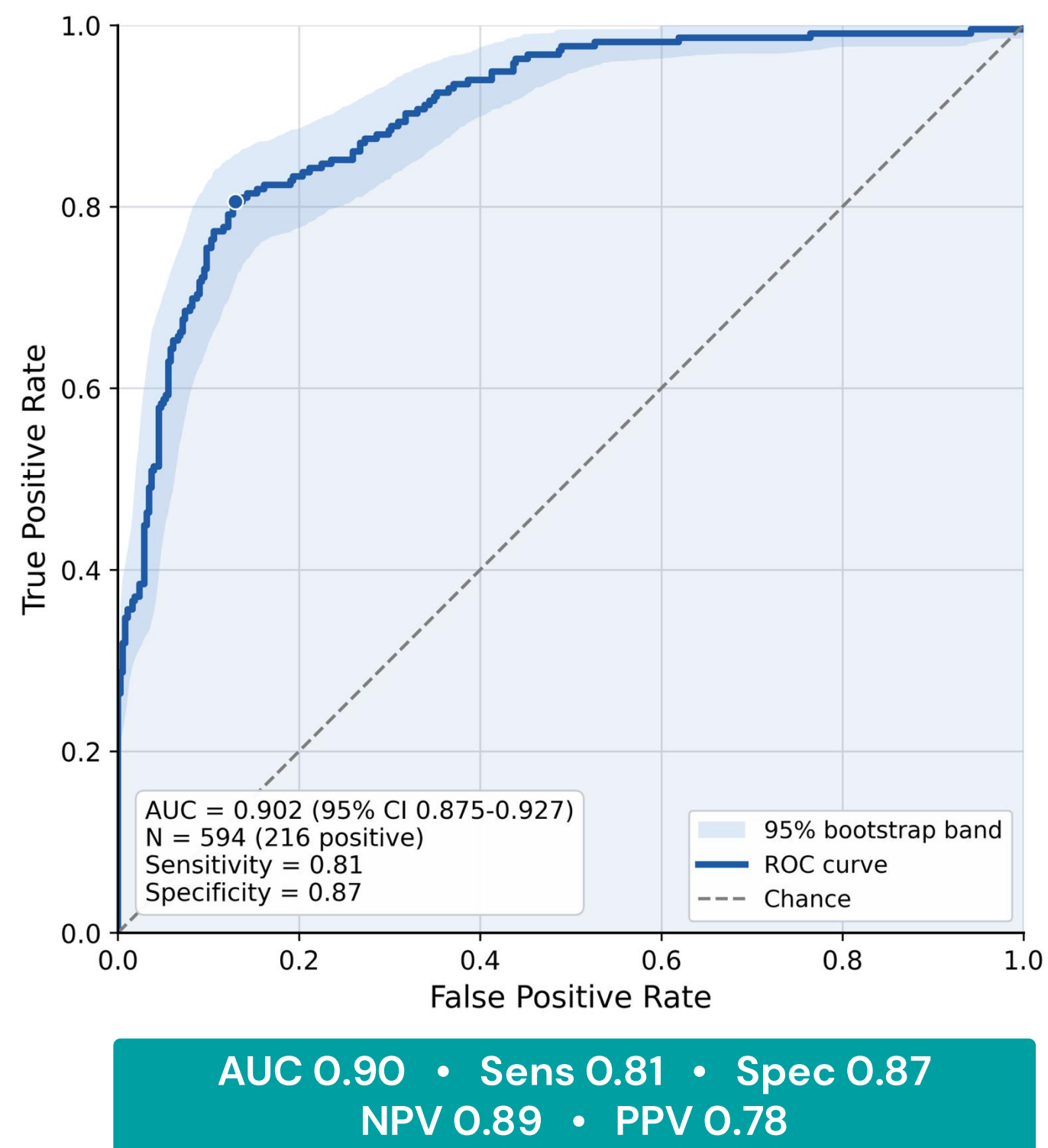


Figure 3. Random forest model combining DCS, APR, and FIP differentiates CU from DMT–eligible participants (AUC = 0.90).

Discussion

- In the Bio–Hermes–001 cohort, a random–forest model combining three DCR–derived machine–learning models estimating the probabilities of cognitive impairment, amyloid–positivity, and functional impairment distinguished cognitively unimpaired adults from **DMT–eligible** participants with strong accuracy (AUC 0.90).
- High NPV (0.89)** means DCR–negative individuals are unlikely to be DMT–eligible, supporting efficient rule–out and reducing screening failures.
- High specificity (0.87)** limits false positives that trigger unnecessary confirmatory testing.
- By integrating cognitive, biomarker, and functional estimates into a single 3–minute assessment, the DCR provides a **feasible, rapid, and scalable** tool to support both clinical trial recruitment and real–world treatment decisions.
- Because the DCR is already deployed in large health systems at the primary–care level, it can serve as a **frontline digital assessment** tool that streamlines DMT–eligibility determination and reduces demand on specialty memory clinics.

Conclusions

- The 3–minute DCR, integrating its multimodal insights into **cognition, pathology, and function**, identified likely DMT–eligible early symptomatic Alzheimer’s disease (MCI or mild dementia with amyloid positivity) with strong accuracy.
- Its high NPV enables **confident rule–out** of unlikely–eligible patients **at the point of care**, directly targeting the high screen–failure rates (~75–80%) and costly/invasive PET/CSF confirmation that bottleneck anti–amyloid prescribing and trial enrollment.
- The DCR suits the **emerging stepwise pathway** — digital cognitive triage → blood–biomarker confirmation → PET/CSF only when needed — aligned with 2025 practice guidance and FDA–cleared plasma assays; prior work shows it is non–inferior to blood biomarkers and, combined with them, approaches CSF–level accuracy ².
- As a **primary–care–ready** tool already deployed across large health systems, the DCR can streamline DMT–eligibility determination and ease demand on capacity–constrained specialty memory clinics.
- Future work should assess prospective, **longitudinal deployment** and the **real–world impact** on enrollment speed, screen failure reduction, and timely access to emerging AD therapies.

References

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