# Supplementary Material

Supplementary Table 1. Comparison in CI of AUCs between plasma p217+tau and imaging biomarkers in discriminating cognitive decliners from cognitively stable individuals

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Outcome measure: status of CDR-SB slope | | | | |
| Test | P217+tau | Tau Me PET | Tau Te PET | Tau MetaT PET | Amyloid PET |
| AUC | 0.83 | 0.71 | 0.79 | 0.77 | 0.76 |
| *p* value  (of p217+tau AUC vs PET AUC) |  | 0.058 | 0.502 | 0.274 | 0.236 |
|  | Outcome measure: status of MMSE slope | | | | |
| Test | P217+tau | Tau Me PET | Tau Te PET | Tau MetaT PET | Amyloid PET |
| AUC | 0.74 | 0.69 | 0.72 | 0.73 | 0.76 |
| *p* value  (of p217+tau AUC vs PET AUC) |  | 0.478 | 0.816 | 0.960 | 0.679 |

Data are presented as biomarker AUC and *p* values from DeLong test. Plasma p217+tau’s prognostic performance is non-inferior to the ones for tau and Aβ PET in the cognitively impaired group. *CI* cognitively impaired at baseline; *MMSE* mini-mental state examination; *CDR-SB* clinical dementia rating sum of boxes; *Me* mesial temporal ROI; *Te* temporoparietal ROI; *MetaT* meta-temporal composite region.

Supplementary Table 2. Cost estimation in the CU group if a blood test costed one fifth of a PET scan

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | T+Me | T+Te | T+MetaT | A+ |
|  | Cost based on PET screening alone: | | | |
| PET screening Cost | *﻿﻿* *﻿10950z ($)* | *﻿﻿* *﻿15643z ($)* | *﻿﻿* *﻿11732z ($)* | *﻿﻿* *﻿5866z ($)* |
|  | ﻿ Cost based on p-tau pre-screening followed by PET of pT+: | | | |
| p-tau pre-screening  +  PET screening Cost | *﻿﻿* *﻿7552z ($)* | *﻿﻿* *﻿10980z ($)* | *﻿﻿* *﻿7238z ($)* | *﻿﻿* *﻿4338z ($)* |
| Saving | *31%* | *30%* | *38%* | *26%* |

Binary tau PET (T-/T+) and Aβ PET (A-/A+) groups based on previously reported established cut-off points: 20 CL for A+, 1.18 SUVR for T+Me, 1.24 SUVR for T+Te, 1.19 SUVR for T+MetaT. Cost estimated assuming 300 participants required per trial arm. Plasma p217+tau threshold defined by Youden’s Index to detect A+ or T+: ﻿97.8 fg/ml for detecting T+Me, ﻿104.5 fg/ml for T+Te, ﻿97.8 fg/ml for T+MetaT ﻿and ﻿100.3 fg/ml for A+. Cost of blood test: z, Cost of PET scan: 5z

Supplementary Table 3. Cost estimation in the CI group if a blood test costed one tenth of a PET scan

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | T+Me | T+Te | T+MetaT | A+ |
|  | Cost based on PET screening alone: | | | |
| PET screening Cost | *﻿5175z ($)* | *﻿5381z ($)* | *﻿5017z ($)* | *﻿5412z ($)* |
|  | ﻿ Cost based on p-tau pre-screening followed by PET of pT+: | | | |
| p-tau pre-screening  +  PET screening Cost | *﻿4939z ($)* | *﻿4906z ($)* | *﻿4454z ($)* | *﻿4897z ($)* |
| Saving | *﻿5%* | *﻿9%* | *﻿11%* | *﻿10%* |

Cost-savings of P217+tau pre-screening in MCI or mild dementia when a blood test costs one tenth of a PET scan. Binary tau PET (T-/T+) and Aβ PET (A-/A+) groups based on previously reported established cut-off points: 20 CL for A+, 1.18 SUVR for T+Me, 1.24 SUVR for T+Te, 1.19 SUVR for T+MetaT. Cost of blood test: z, Cost of PET scan: 10z

Supplementary Table 4. Cost estimation in the CI for biomarker groups binarized based on 80% sensitivity thresholds to detect a positive CDR-SB slope

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **No screening** | **pT+** | **T+Me** | **T+Te** | **T+MetaT** | **A+** |
| **a)** | CDR-SB slope  Mean ± SD | 0.8 ± 1.32 | 1.39 ± 1.51 | 1.13 ± 1.47 | 1.23 ± 1.5 | 1.21 ± 1.49 | 1.14 ± 1.47 |
| Estimated trial number per arm | 647 | 288 | 411 | 355 | 369 | 403 |
|  | | | | | | | |
| **b)** |  | | Plasma p-tau screening alone: | PET screening alone: | | | |
| Number to screen with same modality | — | 467 | 544 | 505 | 520 | 598 |
| *Screening Cost\** | — | *467z ($)* | *2719z ($)* | *2523z ($)* | *2601z ($)* | *2988z ($)* |
|  | | | | | | | |
| **c)** |  | | | ﻿ Plasma p-tau pre-screening followed by PET of pT+: | | | |
| Number of pT+ to PET scan | — | — | 481 | 477 | 457 | 456 |
| Number to pre-screen with p217+tau | — | — | 604 | 565 | 582 | 762 |
| *p-tau pre-screening +*  *PET screening Cost\** | — | — | *3010z ($)* | *2948z ($)* | *2867z ($)* | *3042z ($)* |

Binary p217+tau (pT-/pT+), Aβ (A-/A+), and tau (T-/T+) groups created using 80% sensitivity thresholds to detect positive CDR-SB slope in CI group: *﻿*129.8 fg/ml for pT+, 46 CL for A+, 1.05 SUVR for T+Me, 1.16 SUVR for T+Te, 1.11 SUVR for T+MetaT. **a)** *Estimated trial number per arm* power analysis with primary end point of 30% slowing decline on CDR-SB in CI with 90% power, 0.05 alpha. **b)** ﻿*Number to screen with same modality* estimated based on observed prevalence: 0.62 for pT+, 0.76 for T+Me, 0.70 for T+Te, 0.71 for T+MetaT, and 0.67 for A+. **c)** p217+tau threshold set to 80% sensitivity to detect A+ or T+. *Number to pre-screen with p217+tau* and *Number of pT+ to PET scan* estimated based on observed prevalence and predictive value of p217+tau positivity. Observed prevalence of pT+ ﻿for T+Me 0.69, for T+Te 0.71, for T+MetaT 0.63 and for A+ 0.60. ﻿PPV of p217+tau ﻿for T+Me 0.88, for T+Te 0.80, for T+MetaT 0.88 and for A+ 0.88. *CDR-SB* Clinical Dementia Rating Sum of Boxes. *PPV* positive predictive value. \*Cost per trial arm, assuming a PET scan costs five times a blood test (cost of blood test: z, cost of PET scan: 5z)