# Supplementary Material - Table 1.

**Supplementary Material -Table 1.** **Overview of the number of subjects changing their neuropsychological classification between defined groups over the follow-up of the study**.

|  |  | **Final neuropsychological classification** | | | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **NMC** | **SMC** | **MCI** | **OD** | **AD** |
| **Baseline neuropsychological classification** | **NMC (N=74)** | 39 | 29 | 3 | 1 | 2 |
| **SMC (N=163)** | 26 | 113 | 14 | 4 | 6 |
| **MCI (N=98)** | 0 | 0 | 31 | 7 | 60 |
| **OD (N=3)** | 0 | 0 | 0 | 3 | 0 |
| **AD (N=141)** | 0 | 0 | 0 | 0 | 141 |

AD: Alzheimer’s disease; CN: cognitively normal; MCI: mild cognitive impairment; NMC: no memory complaints; OD: other dementia; SMC: subjective memory complaints.  
Sum of the numbers in each row (differentiated by cognitive status) equals to the number of individuals for each neuropsychological classification at baseline in **Table 1**.

# Supplementary Material - Table 2.

**Supplementary Material -Table 2. Diagnostic performance of U-p53AZ and Aβ-PET to detect AD status versus non-AD as defined at baseline neuropsychological diagnosis.**

|  | **Baseline** | |
| --- | --- | --- |
| **Metrics** | **U-p53AZ** | **Aβ-PET** |
| AD individuals | 141 | 128 |
| Non-AD individuals | 338 | 294 |
| AUC (95% CI) | 98.5% (97.6-99.5%) | 80.9% (76.4-85.4%) |
| Accuracy | 96.5% | 72.0% |
| Sensitivity (95% CI) | 95.0% (90.0-98.0%) | 81.3% (73.4-87.6%) |
| Specificity (95% CI) | 97.0% (94.6-98.6%) | 68.0% (62.4-73.3%) |
| NPV (95% CI) | 97.9% (95.7-98.9%) | 89.4% (85.4-92.4%) |
| PPV (95% CI) | 93.2% (88.2-96.2%) | 52.1% (47.5-56.8%) |

AD: Alzheimer’s disease; AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

Parameters were calculated through maximizing the Youden’s J.

# Supplementary Material - Table 3.

**Supplementary Material - Table 3**. **Diagnostic performance of U-p53AZ to differentiate AD neuropsychological status versus CN or MCI as defined at baseline neuropsychological diagnosis**.

|  |  |  |
| --- | --- | --- |
| **Metrics** | **AD vs CN**  141 vs 237 | **AD vs MCI**  141 vs 98 |
| AUC (95% CI) | 99.8% (99.6-100.0%) | 95.7% (92.8-98.5%) |
| Accuracy | 98.1% | 93.7% |
| Sensitivity (95% CI) | 96.5% (91.9-98.8%) | 95.0% (90.0-98.0%) |
| Specificity (95% CI) | 99.2% (97.0-99.9%) | 91.8% (84.5-96.4%) |
| NPV (95% CI) | 98.5% (96.5-99.4%) | 97.7% (95.4-98.9%) |
| PPV (95% CI) | 98.0% (92.5-99.5%) | 83.3% (72.0-90.7%) |

AD: Alzheimer’s disease; AUC: area under the curve; CI: confidence interval; CN: cognitively normal; MCI: mild cognitive impairment; NPV: negative predictive value; PPV: positive predictive value.  
Cut-offs for **Table 3** are different from the ones used in **Table 2** and are based on the maximal Youden’s J on the specific AUC. They constitute a separate analysis for the specified subset.

Parameters were calculated through maximizing the Youden’s J.

# Supplementary Material - Table 4.

**Supplementary Material - Table 4**. **Association of U-p53AZ status and amyloid status to the diagnostic group**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Diagnostic group** | | | | |
|  | **Categories, N** | **CN**  **(N=207)** | **MCI**  **(N=31)** | **CD progressors (N=29)** | **AD progressors (N=68)** | **AD (N=141)** |
| **U-p53AZ status** | Low | 206 | 19 | 28 | 3 | 2 |
| Intermediate | 1 | 11 | 1 | 57 | 5 |
| High | 0 | 1 | 0 | 8 | 134 |
|  | **Categories, N** | **CN (N=202)** | **MCI**  **(N=30)** | **CD progressors (N=23)** | **AD progressors (N=36)** | **AD (N=128)** |
| **Amyloid status** | Negative | 139 | 9 | 7 | 5 | 16 |
| Uncertain | 11 | 1 | 2 | 1 | 4 |
| Moderate | 16 | 6 | 3 | 2 | 7 |
| High | 32 | 7 | 7 | 13 | 38 |
| Very high | 4 | 7 | 4 | 15 | 63 |
|  |  |  |  |  |  |  |

AD: Alzheimer’s disease; CD: cognitive decline; CN: cognitively normal; MCI: mild cognitive impairment.

# Supplementary Material - Table 5.

**Supplementary Material - Table 5. Diagnostic performance of U-p53AZ and Aβ-PET to differentiate neuropsychological AD versus non-AD individuals as defined at the last available diagnosis.**

|  | **Final diagnosis** | |
| --- | --- | --- |
| **Metrics** | **U-p53AZ** | **Aβ-PET** |
| AD individuals | 209 | 164 |
| Non-AD individuals | 270 | 258 |
| AUC (95% CI) | 99.0% (98.2-99.8%) | 83.5% (79.5-87.5%) |
| Accuracy | 95.6% | 77.0% |
| Sensitivity (95% CI) | 97.6% (94.5-99.2%) | 79.9% (72.9-85.7%) |
| Specificity (95% CI) | 94.1% (90.6-96.6%) | 75.2% (69.5-80.3%) |
| NPV (95% CI) | 98.0% (95.3-99.1%) | 82.0% (77.0-86.2%) |
| PPV (95% CI) | 93.1% (89.3-95.6%) | 72.5% (67.8-76.8%) |

AD: Alzheimer’s disease; AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

Parameters were calculated through maximizing the Youden’s J.

# Supplementary Material - Table 6.

Supplementary Material - Table 6. Time-dependent prognostic performance of U-p53AZ and Aβ-PET (CL) to predict neuropsychological AD in non-AD participants at different timepoints following baseline assessment.Time-dependent ROC curves were determined using subsets of individuals with unambiguous disease status at the specified timepoints. The table below also depicts the number of individuals available at each given timepoint.

| **Timepoint, months** | **36** | **54** | **72** | **90** |
| --- | --- | --- | --- | --- |
| **AD, N**  U-p53AZ (N=209)  Matched Aβ-PET (N=164) | 194  154 | 201  158 | 203  159 | 205  161 |
| **Non-AD, N**  U-p53AZ (N=280)  Matched Aβ-PET (N=258) | 210  196 | 150  140 | 112  106 | 75  69 |
| **Censored non-AD, N**  U-p53AZ  Matched Aβ-PET | 75  72 | 128  124 | 164  157 | 199  192 |
| **AUC (95% CI)**  U-p53AZ  Matched Aβ-PET | 98.4% (97.3-99.5%)  87.2% (83.3-91.1%) | 99.3% (98.7-99.9%)  90.0% (86.4-93.7%) | 99.3% (98.7-99.9%)  91.4% (88.0-94.9%) | 99.3% (98.6-100.0%)  92.8% (89.3-96.2%) |
| *P*-value | <0.001 | <0.001 | <0.001 | <0.001 |

AD: Alzheimer’s disease; AUC: area under the curve; CI: confidence interval.

AUC values were compared by DeLong test.

# Supplementary Material - Table 7.

Supplementary Material - Table 7. **Table with Cox proportional hazard models statistical parameters.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **AD Events** | **C-statistic** | **AIC** | **Model *P*-valb** |
| Reference modela (N=294) | 36 | 0.940 | 261.9 | - |
| U-p53AZ (N=338) | 68 | 0.933 | 574.6 | - |
| U-p53AZ (sub-population with complete risk factors) (N=294) | 36 | 0.953 | 292.8 | 0.3539 |
| U-p53AZ + Aβ-PET + age + *APOE* ε4 + gender (N=294) | 36 | 0.945 | 261.6 | 0.2568 |
| Aβ-PET + age (N=294) | 36 | 0.864 | 308.2 | <0.0001 |
| U-p53AZ + Aβ-PET + age (N=294) | 36 | 0.943 | 261.3 | 0.1641 |

AD: Alzheimer’s disease; AIC: Akaike information criterion.

a Reference model: U-p53AZ + Aβ-PET + age + *APOE* ε4

b Relative to reference model

# Supplementary Material - Table 8.

Supplementary Material - Table 8. **Table reporting Cox proportional hazard models for AD onset, unadjusted and adjusted for different risk factors (U-p53AZ, Aβ-PET, age, APOE ε4, and gender).**

|  | **U-p53AZ** | | **Aβ-PET (CL)** | | **Age** | | ***APOE* ε4** | | **Gender** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **HR** | ***P*** | **HR** | ***P*** | **HR** | ***P*** | **HR** | ***P*** | **HR** | ***P*** |
| Reference modela (N=294) | 2.10 | <0.0001 | 1.01 | 0.0155 | 1.08 | 0.0106 | 1.80 | 0.2323 | - | - | |
| U-p53AZ (N=338) | 2.15 | <0.0001 | - | - | - | - | - | - | - | - | |
| U-p53AZ with complete risk factors (N=294) | 2.12 | <0.0001 | - | - | - | - | - | - | - | - | |
| U-p53AZ + Aβ-PET + age + *APOE* ε4 + gender (N=294) | 2.23 | <0.0001 | 1.01 | 0.0407 | 1.07 | 0.0135 | 2.10 | 0.1394 | 1.80 | 0.1331 | |
| Aβ-PET + age (N=294) | - | - | 1.02 | <0.0001 | 1.09 | 0.0007 | - | - | - | - | |
| U-p53AZ + Aβ-PET + age (N=294) | 2.04 | <0.0001 | 1.02 | < 0.0001 | 1.08 | 0.0096 | - | - | - | - | |
| Normalized modelb (N=294) | 2.92 | <0.0001 | 1.66 | 0.0155 | 1.79 | 0.0106 | 1.80 | 0.2323 | - | - | | |

AD: Alzheimer’s disease; CL: centiloid level; HR: hazard ratio.

a Reference model: U-p53AZ + Aβ-PET + age + *APOE* ε4

b Normalized model: U-p53AZ + Aβ-PET + age + *APOE* ε4. Normalization of continuous variables (U-p53AZ, age, and Aβ-PET [CL]) into standard scores by subtracting the mean from each value and dividing by the standard deviation for direct HR comparison

# Supplementary Material - Figure 1.

**Supplementary Material - Figure 1**. **Flow of the subjects included in the study**.

Diagram

Description automatically generated

NA: Not available; Neg: Negative; Pos.: Positive; U.: Uncertain.

# Supplementary Material - Figure 2.

**Supplementary Material - Figure 2**. **Association of U-p53AZ and Aβ-PET categories (CL-based brain imaging) to classify individuals in different neuropsychological diagnostic groups**. A) Distribution of U-p53AZ categories among neuropsychological classifications. B) Distribution of Aβ-PET categories (CL-based) among neuropsychological classifications.

Chart, bar chart

Description automatically generated

Chart, bar chart

Description automatically generated

AD: Alzheimer’s disease; CD: cognitive decline; CN: cognitively normal; MCI: mild cognitive impairment; NMC: no memory complaints; SMC: subjective memory complaints.

In 3B, for each neuropsychological classification the cumulative percentage of the amyloid categories “Moderate”, “High” and “Very high” is shown in place of the individual ones.