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Sysmex Corporation

【Overview presentation】

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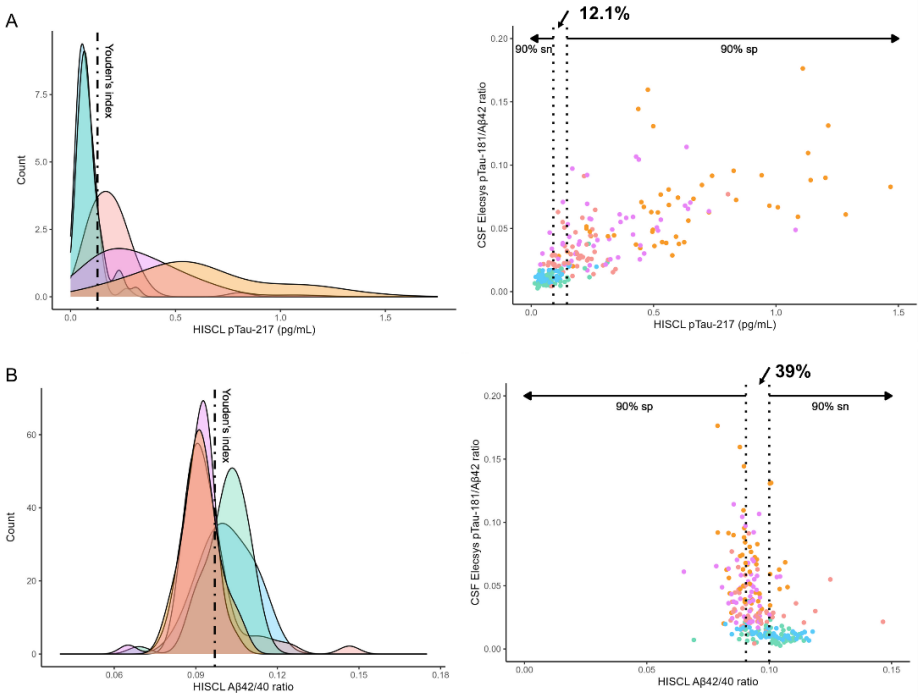
High diagnostic performance of the random-access HISCL pTau-217, Aβ42 and Aβ40 plasma assays in detecting amyloid pathology across clinical stages

Authors	Inge M.W. Verberk[1], Thomas Claessen[1, 2], Daniel Antwi-Berko[1], Hans Heijst[1], Azzam Aladdin[1], Yuko Sasaki Mori[3], Roman Boeer[4], Argonde C. van Harten[1, 2], Charlotte E. Teunissen[1] [1] Neurochemistry Laboratory, Laboratory Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands [2] Alzheimer Center Amsterdam, Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands [3] Sysmex R&D Center Europe GmbH [4] Sysmex Europe SE
Overview presentation	**Objectives** Alzheimer's disease (AD) blood biomarkers detecting cerebral amyloid-beta (Aβ) pathology are being implemented in clinical and trial settings. Plasma assays on high-performing automated random-access platforms are considered particularly relevant for implementation. Sysmex developed phosphorated (p)Tau-217, Aβ42 and Aβ40 assays on their random-access HISCL™-5000/HISCL™-800 platform, which we sought to validate for their potential to detect Aβ pathology. **Methods** We selected plasma samples across clinical stages from the Amsterdam Dementia Cohort: subjective cognitive decline (SCD; 50 Aβ-, 50 Aβ+), mild cognitive impairment (MCI; 50 Aβ-, 50 Aβ+) and AD-dementia (50 Aβ+). Groups were age/sex-matched (average±SD age 66±5.6y, 40%Female). Samples were measured on the HISCL™-5000 in duplicates for pTau-217, Aβ42 and Aβ40, and

	on the Lumipulse (pTau-217, Aβ42, Aβ40) and Simoa (Aβ42, Aβ40) as benchmark. Mann-Whitney U and ROC-AUC analyses were conducted. **Results** Average coefficient of variation for duplicate measurements was <3.5% for all three HISCL assays. HISCL pTau-217 levels were increased in the Aβ+ compared to the Aβ- groups, with a stepwise increase in levels from SCD Aβ+ to MCI Aβ+ to AD-dementia (all: p^{FDR}<0.01). HISCL plasma Aβ42/40 levels were decreased in the Aβ+ compared to the Aβ- groups (p^{FDR}<0.001), with no difference between the Aβ+ groups. HISCL pTau-217 and Aβ42/40 discriminated Aβ+ from Aβ- with ROC-AUC=0.93 (95%CI: 0.90–0.96), and ROC-AUC=0.80 (95%CI: 0.74–0.86) respectively. Results in the intermediate ranges bounded by 90%-specificity and 90%-sensitivity thresholds were 12.1% for pTau-217 and 39% for Aβ42/40 (Figure 1). DeLong's p=0.02 To benchmark these novel clinical findings, ROC-AUC to discriminate Aβ+/Aβ- in this same cohort was slightly better for HISCL pTau-217 than for Lumipulse pTau-217 than (DeLong's p=0.02, ΔAUC=0.03), and was better for HISCL Aβ42/40 than for Lumipulse Aβ42/40 and Simoa Aβ42/40 (both: DeLong's p≤0.02; ΔAUC=0.08 and ΔAUC=0.13, respectively). **Conclusions** HISCL™-5000/HISCL™-800 plasma pTau-217 and Aβ42/Aβ40 were validated as robust and accurate tests to asses Aβ pathology across the clinical continuum. These random-access assays could aid in streamlining clinical decision-making.

Sysmex Corporation
1-5-1 Wakinohama-Kaigandori, Chuo-ku, Kobe 651-0073,Japan
Tel 81-78-265-0500 Fax 81-78-265-0524

	 **Figure 1. A)** Data distribution of HISCL pTau217 levels as measured across the AD clinical continuum and in comparison to CSF pTau181/Aβ42 values are presented. The Youden's cutoff of 0.128 pg/mL resulted in 87.2% sensitivity and 88.8% specificity. Cutoffs set at <0.099 pg/mL to achieve 90% sensitivity and at >0.416 pg/mL to achieve 90% specificity resulted in 12.1% values falling in the intermediate range, PPV of 93% and NPV of 83%. **B)** Data distribution of HISCL Aβ42/40 levels as measured across the AD clinical continuum and in comparison to CSF pTau181/Aβ42 values are presented. The Youden's cutoff of 0.097 resulted in 84.7% sensitivity and 72.0% specificity. Cutoffs set at >0.100 to achieve 90% sensitivity and at <0.091 to achieve 90% specificity resulted in 39% values in the intermediate range, PPV of 86% and NPV of 76%.
Session	Developing Topics: Biomarkers (Tuesday-0311)

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Tel 81-78-265-0500 Fax 81-78-265-0524