

The Alzheimer's Association Quality Control Program

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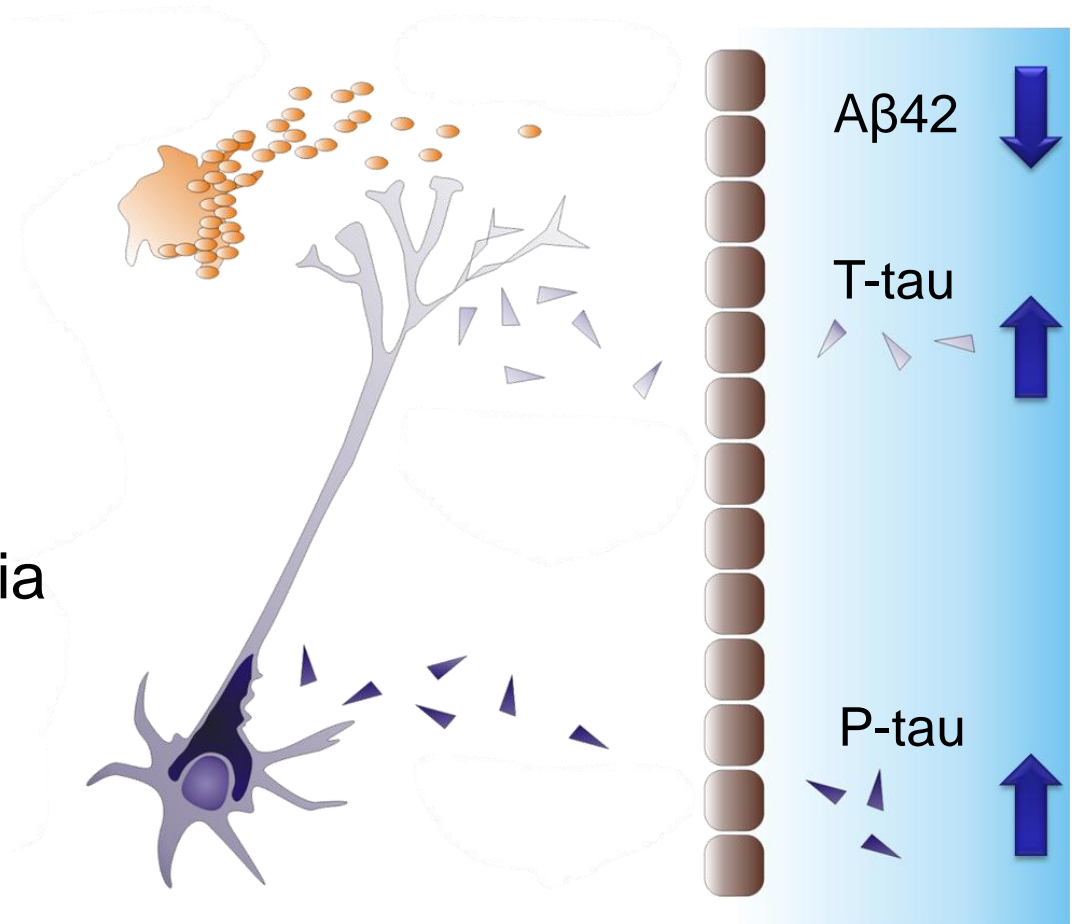
Sahlgrenska University Hospital

Göteborg/Mölndal, Sweden

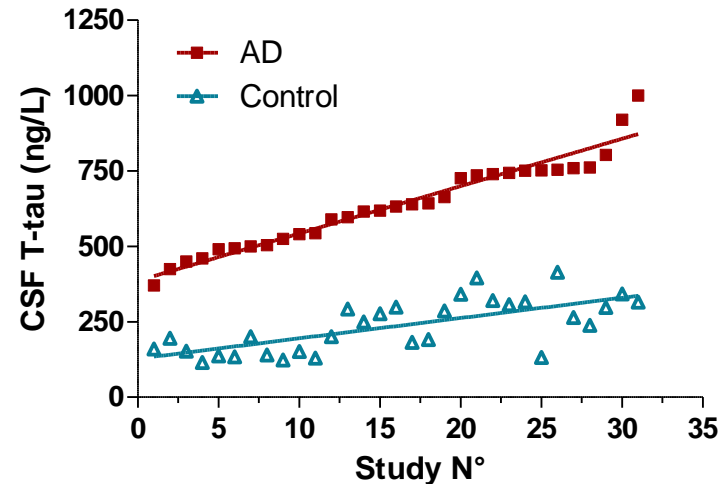
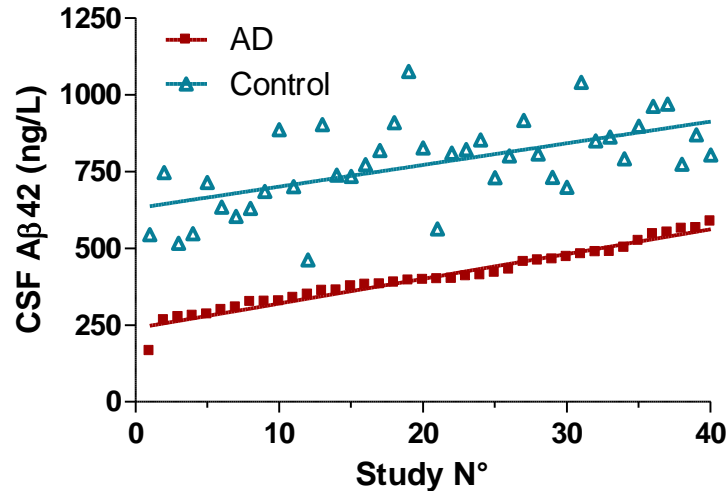
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CSF AD biomarkers

- Research
- Clinical trials
- Clinical practice
- New diagnostic criteria



Biomarker variability

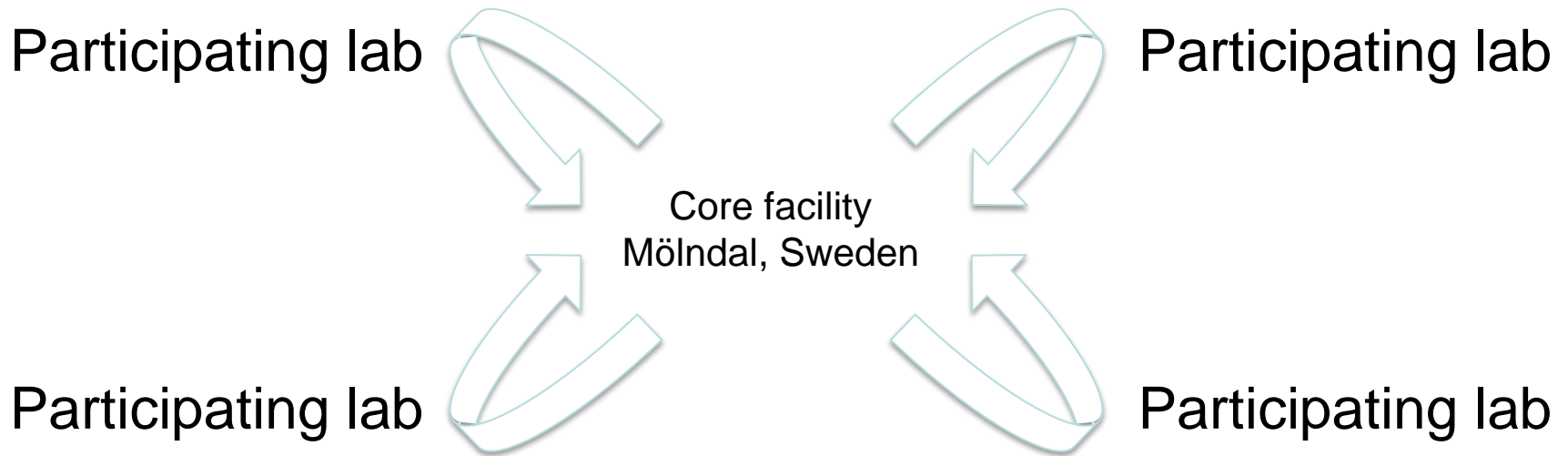


- **Varying absolute levels** between studies
- **Stable relative differences** between patients and controls
- Problem for **universal cut-offs and reference ranges**

Aims of the QC program

- Identify and monitor differences among labs
- Facilitate standardization of measurements
- Facilitate global implementation of AD biomarkers to support optimal patient management

Program overview



2009-1A
2009-1B

2010-2A
2010-2B

QC-L

QC-L

2010-3 2010-4 2011-5 2011-6 2011-7 2012-8

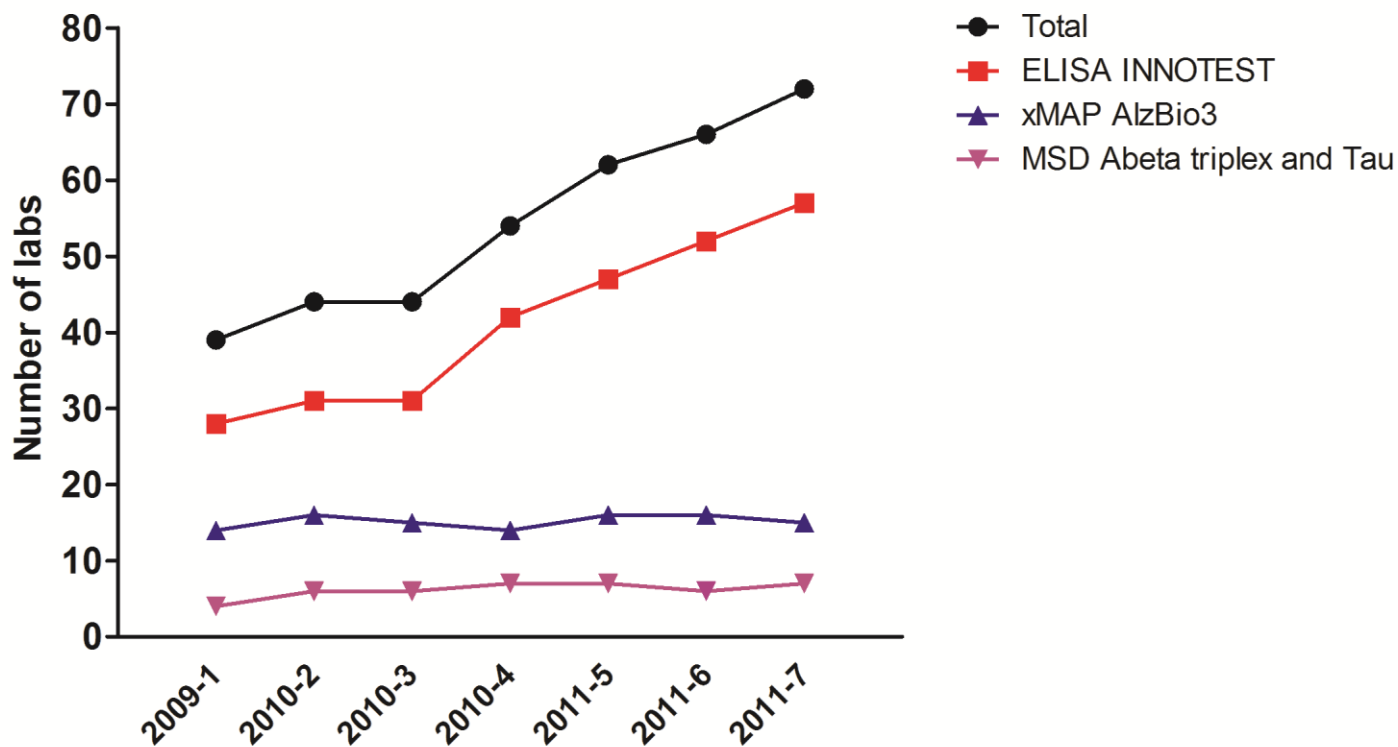
Rounds 1-2: Mattsson N et al, **The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers.** *Alzheimer's & Dementia* 2011;7:386-395

Rounds 3-8: manuscript in preparation

A world map with a blue background and grey landmasses. Yellow stars are placed on the map to indicate the locations of the 35 countries that have ratified the Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW). The stars are distributed as follows: 10 in North America (USA and Canada), 15 in Europe, 3 in Australia (Western, Southern, and Eastern), 1 in South America (Brazil), 2 in Asia (Japan and South Korea), and 4 in Africa (Morocco, Tunisia, Egypt, and Sudan).

The Sahlgrenska Academy

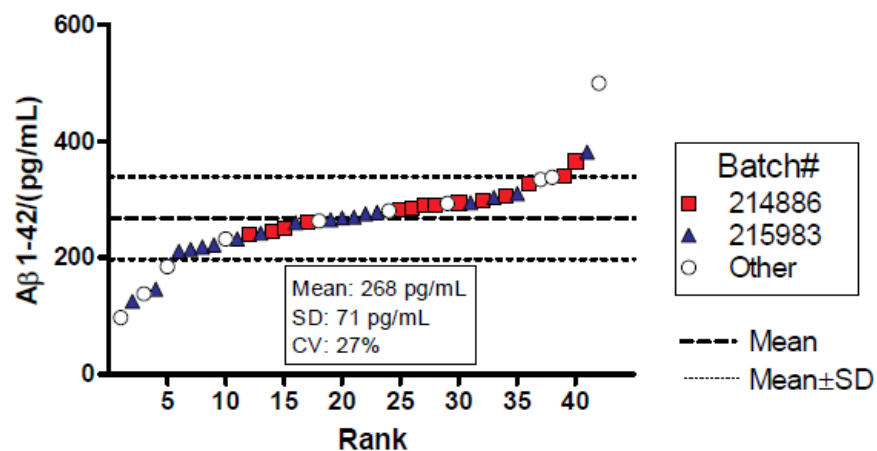
Labs and techniques



Example: results round 6

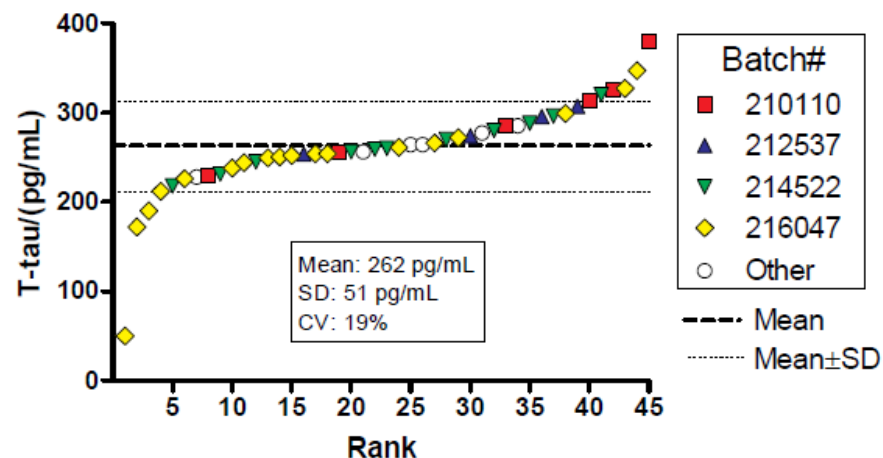
Summary A β 1-42 2011-6(INNOTEST)

2011-6A



Summary T-tau 2011-6(INNOTEST)

2011-6A



A β 42

Alzheimer's Association QC program for CSF

Longitudinal evaluations

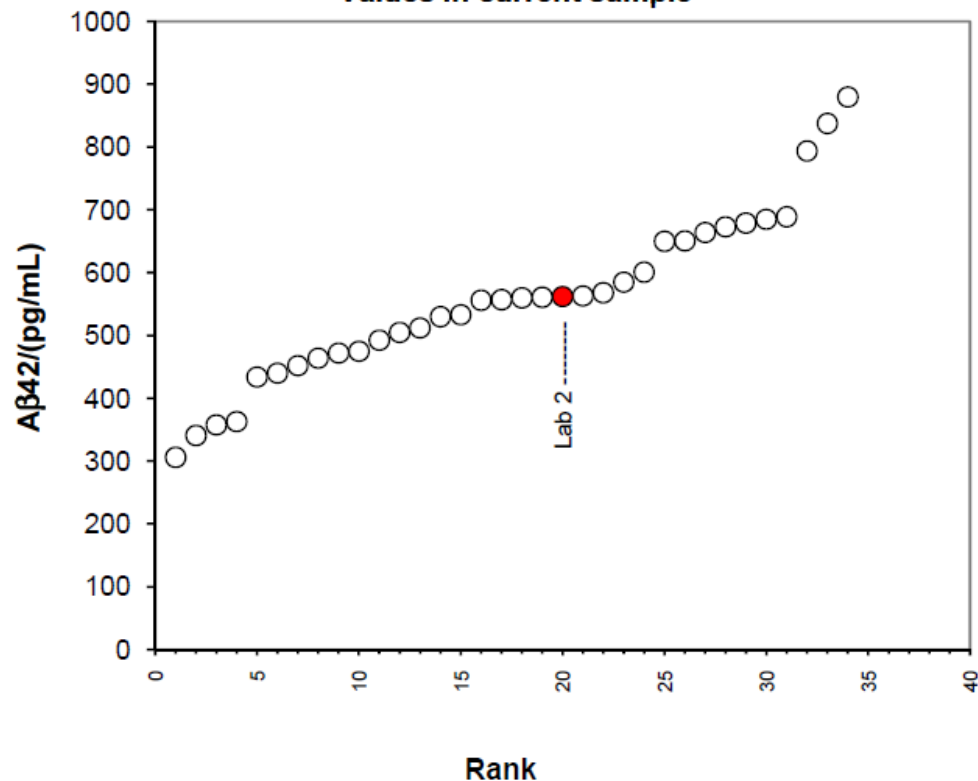
Göteborg (Lab 2)

Round:	2010:4 QC-L
Result:	562 pg/mL
Method:	INNOTEST

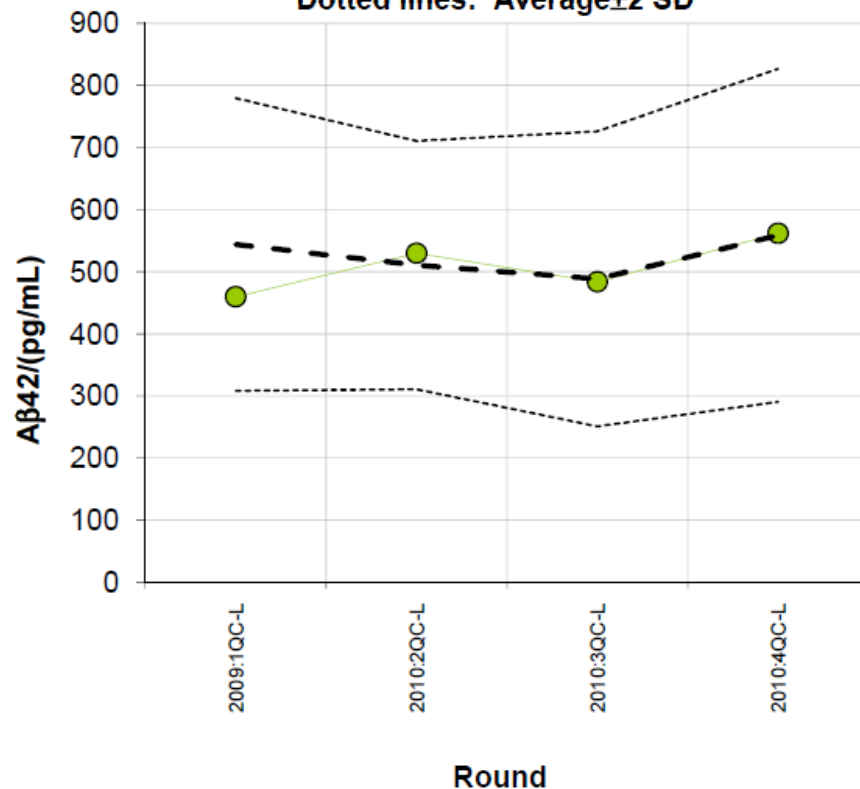
All 34 labs in this round

Mean:	559 pg/mL
SD:	134 pg/mL
CV:	24%

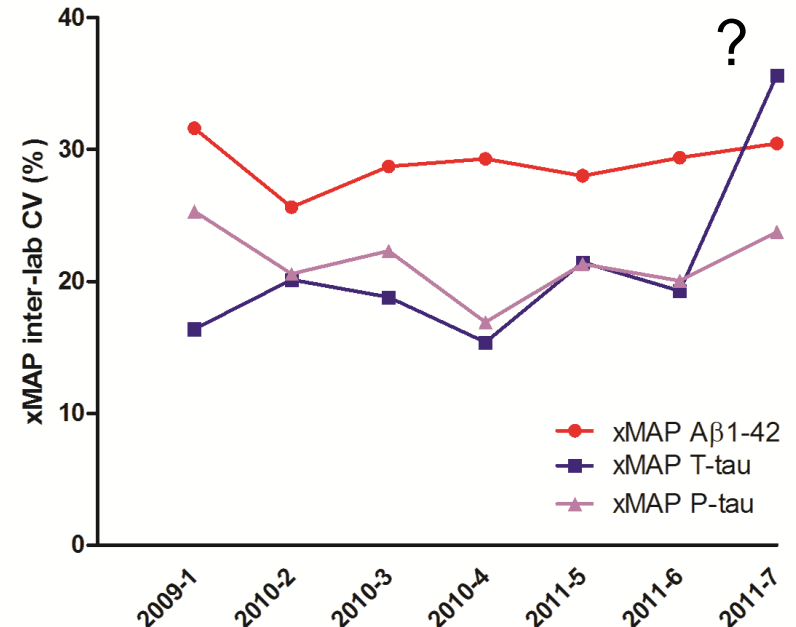
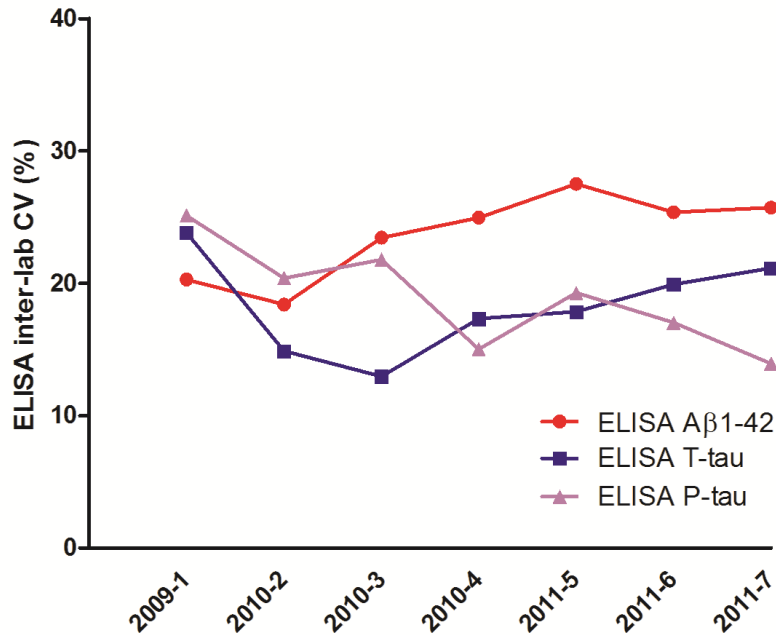
Values in current sample



Longitudinal QC-sample
Dotted lines: Average \pm 2 SD

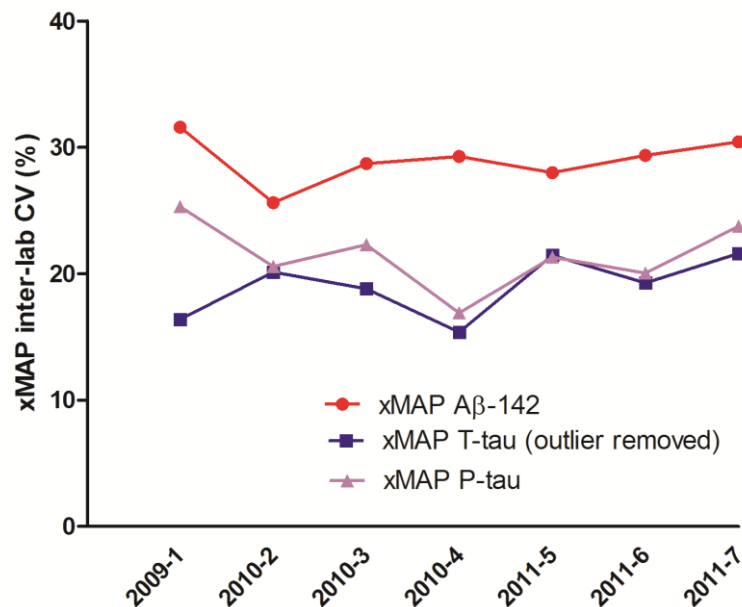
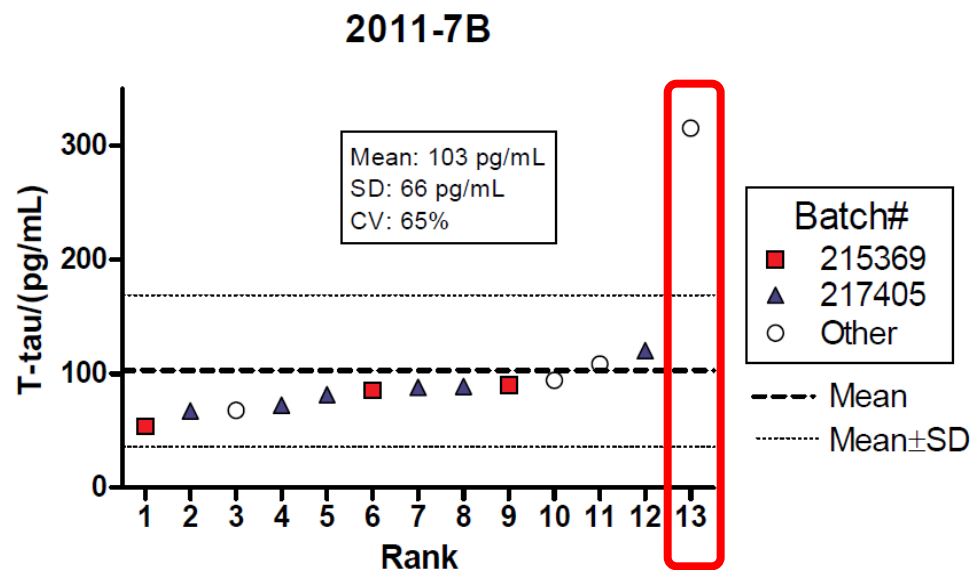


Inter-lab CVs rounds 1-7



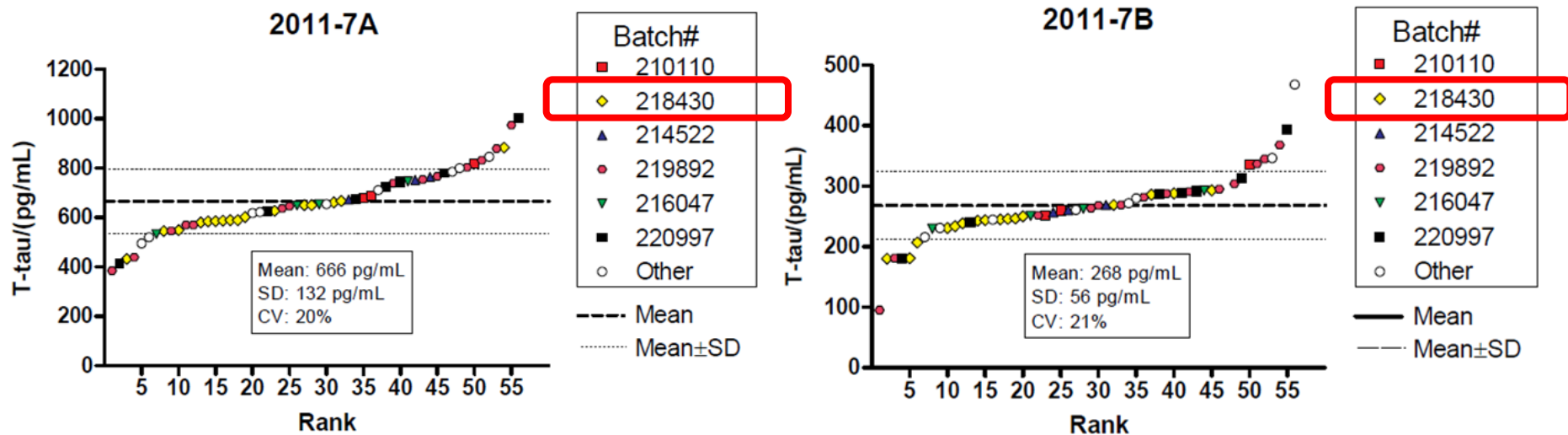
P-tau: reduction over time?

Influence of outliers



The laboratory is alerted and may revise procedures

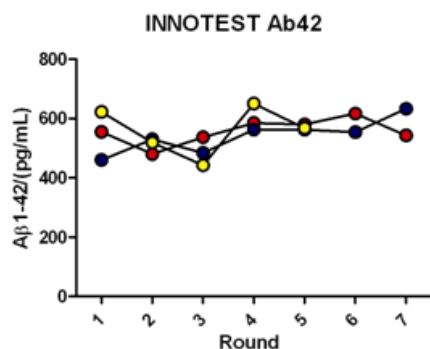
Influence of batches?



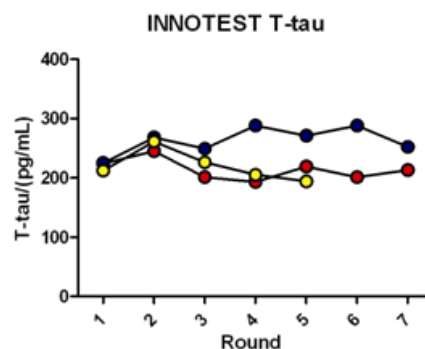
The QC program monitors batches of analytical kits and allows detection of batch-dependent variability

Low variability among reference labs

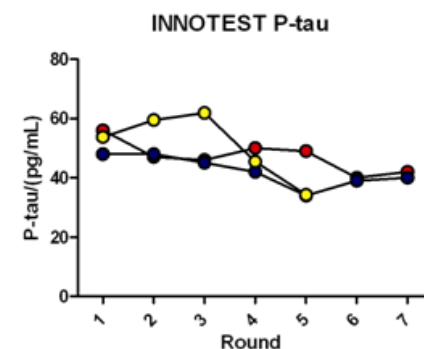
Amsterdam, Erlangen, Ghent, Mölndal, Philadelphia



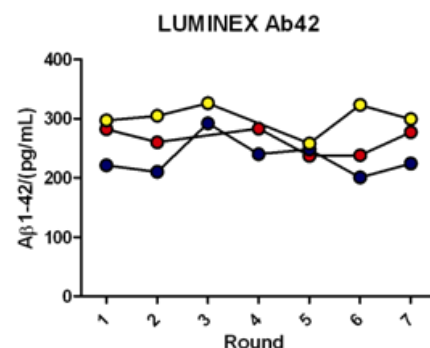
Mean/(pg/mL)	546	510	487	599	570	586	586
SD/(pg/mL)	47	15	27	26	5	32	45
CV%	15	5,2	9,8	7,6	1,6	7,6	11



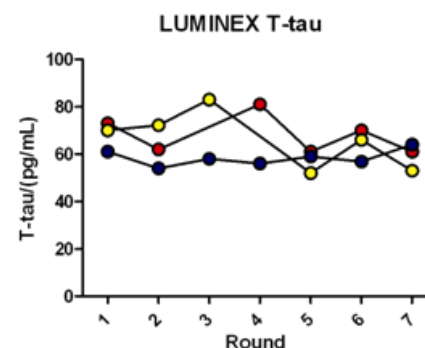
Mean/(pg/mL)	220	258	225	229	228	245	233
SD/(pg/mL)	7,2	11	24	52	39	62	28
CV%	3,3	4,6	11	23	17	25	12



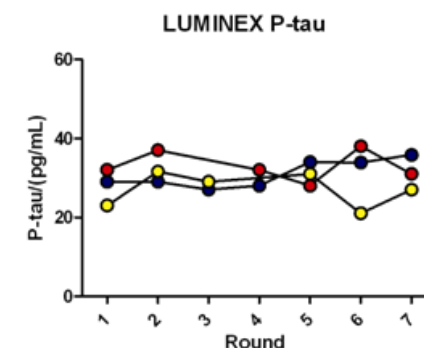
Mean/(pg/mL)	53	52	51	46	39	40	41
SD/(pg/mL)	4,1	6,9	9,5	4,0	8,6	0,7	1,4
CV%	7,9	13	19	8,8	22	1,8	3,5



Mean/(pg/mL)	267	258	309	262	248	254	267
SD/(pg/mL)	40	47	24	30	11	63	39
CV%	15	18	7,8	12	4,2	25	14



Mean/(pg/mL)	68	63	71	69	57	64	59
SD/(pg/mL)	6,2	9,1	18	18	4,7	6,7	5,7
CV%	9,2	15	25	26	8,2	10	9,6



Mean/(pg/mL)	28	33	28	30	31	31	31
SD/(pg/mL)	4,6	4,1	1,4	2,8	3,0	8,9	4,4
CV%	16	13	5,1	9,4	9,7	29	14

Confounding factors

Preanalytical	Sample handling
	Assay kit handling and storage
Analytical	Laboratory Equipment <ul style="list-style-type: none"> • Calibration • Detection instrument • Pipetting
	Analyst <ul style="list-style-type: none"> • Competency • Familiarization with the Method • Forward/Reverse Pipetting • Reagent handling

Postanalytical	Data handling <ul style="list-style-type: none"> • Analyzing singlets/duplicates • Decisions for rejecting data • Type of curve fitting used • Software for data calculation
	Documentation <ul style="list-style-type: none"> • Test Procedure Instructions • Minimal Method Optimization
Kit Manufacturing	Reagents <ul style="list-style-type: none"> • Source of reference standard • Buffer-composition • Lot-lot variability • Vendor-vendor variability • Quality controls

QC program checklist

INSTRUMENTATION, EQUIPMENT AND LAB TECHNICIANS

ASSAY: Standards (calibrators) and QC system

1	Calibrators diluted from stock in separate polypropylene tubes	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
2	Calibrators (standards) and samples analyzed in duplicates	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
3	Calibrators (including no. of calibrators) prepared according to kit insert	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
4	Internal control samples used for quality control	Yes (pooled CSF) <input type="checkbox"/>	Yes (other, e.g., spiked samples) <input type="checkbox"/> No <input type="checkbox"/>

ASSAY: Conditions

1	The test procedures in the kit inserts are followed without any deviation	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
2	Polypropylene plates used for pre-incubation (A β 1–42)	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3	If yes, polypropylene plate used for both standards and CSF samples	Yes <input type="checkbox"/>	No <input type="checkbox"/>

ASSAY: Data analysis and run acceptance

1	Plate reader settings: 450 nm, endpoint	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2	Standard curve calculated using the 4 parameter logistic equation	Yes <input type="checkbox"/>	No, specify equation: <input type="text"/>
3	QC samples vortexed before analysis	Yes <input type="checkbox"/>	No, specify: <input type="text"/>

ASSAY: Reagents

1	Kits stored following kit insert: ELISA plate at +2–8°C; standards at < -20°C	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
2	Assay components (standards, plate and reagents) only from the same kit box	Yes <input type="checkbox"/>	No, specify: <input type="text"/>
3	Kit used within expiry date given provided by the manufacturer	Yes <input type="checkbox"/>	No, specify: <input type="text"/>

Future prospects

- Identify confounding factors
- Inter-laboratory, intra-laboratory and assay related error sources
- Alert outliers → revise procedures
- Alert kit producers → improve kit stability
- Certified reference materials and methods

Proposed role of the QC program in further CSF biomarker standardization

Reference methods

GCBS with partners, including the IFCC working group (to be formed)

Use reference methods to set biomarker levels in **reference materials**

- Pilot batches by GCBS with partners including the IFCC working group
- Large-scale production by IRMM

Supply

reference material to assay producers by IRMM (non-profit)

Certification of methods and materials by IFCC

Collaboration with other research consortia including JPND

The QC program

The optimal system to monitor and evaluate the progress of the global standardization efforts

alzheimer's  association®

the compassion to care, the leadership to conquer


Institute for Reference
Materials and Measurements

 **IFCC**
International Federation
of Clinical Chemistry
and Laboratory Medicine

 **JPND**
research
EU Joint Programme – Neurodegenerative Disease Research

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the compassion to care, the leadership to conquer

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