Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Duke-Margolis Center for Health Policy | Virtual Meeting

May 24-25, 2022

Duke | MARGOLIS CENTER *for* Health Policy

Welcome and Overview | Day 2

Mark McClellan

Director, Duke-Margolis Center for Health Policy

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Meeting Agenda (Day 2)

12:00 pm Welcome and Overview

12:10 pm Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

1:50 pm Break

2:05 pm Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

3:30 pm Session 5: Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

4:15 pm Closing Remarks

4:25 pm Adjournment

All times listed in EDT

Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

12:10 pm – 1:50 pm EST

Steve Ryder

Chief Medical Officer

Rallybio Inc.

Duke | MARGOLIS CENTER for Health Policy

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More
May 24th and 25th 2022
Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

Use of Imported Clinical Assessment Tools in Rare Disease: A Case Study

Steve Ryder
Chief Medical Officer
Rallybio

Contributors: David Thompson, Tino Melian, Kenji Fujita and Colleagues

Disclosure

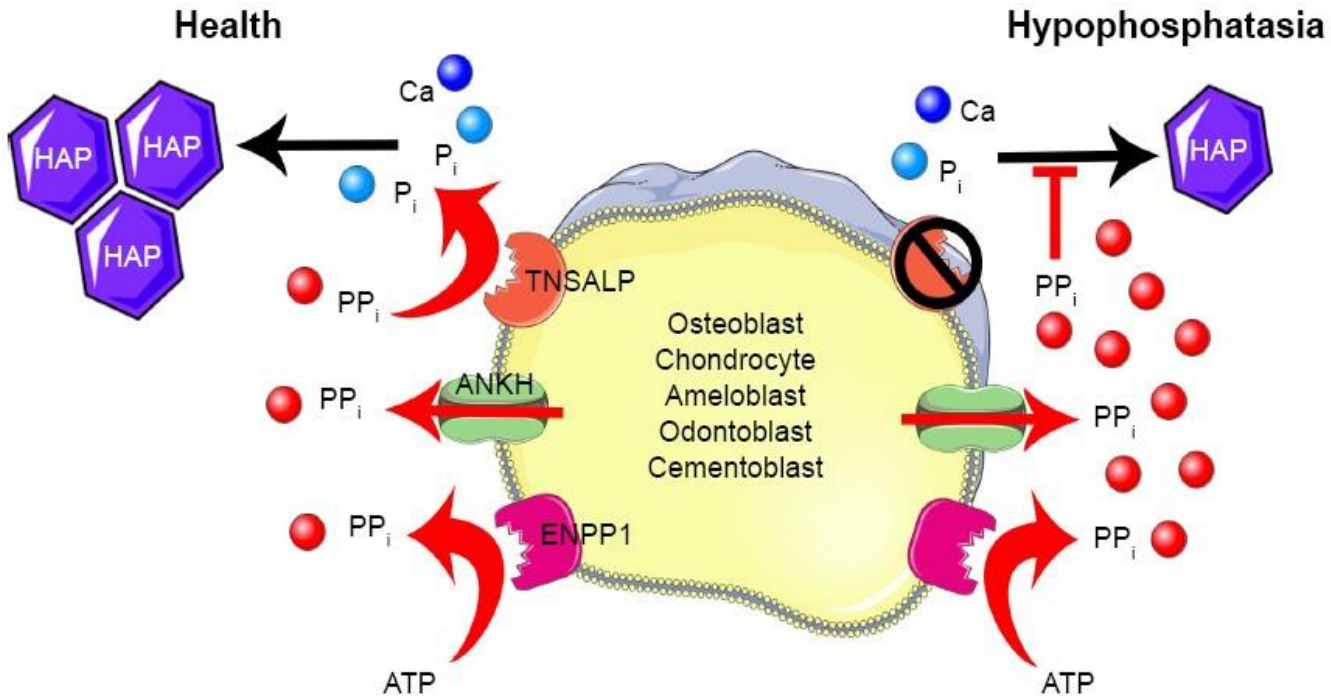
I am a full-time employee and hold an equity interest in Rallybio

At the time the presented work was done, I and all contributors were full-time employees of and held equity interests in Alexion Pharmaceuticals

Overview

- Rare/ultra-rare diseases are generally poorly understood and poorly researched
- This extends to both the preclinical and clinical areas
- Almost always there is no precedent for designing studies in the treatment of rare/ultra-rare disease. Irreversible disease morbidity/mortality may constrain design and analytical approaches
- Assessment tools are often unavailable and almost never validated in the rare/ultra-rare disease under study
- One approach to improve the availability of assessment tools is to thoroughly review assessment tools in alternative disease areas with relevant morbidity/functional disability and pre-apply them to natural history cohorts
- This importation and logical application of assessment tools was successfully used in the development of asfotase alfa (Strensiq®) in the treatment of patients with juvenile-onset hypophosphatasia (HPP)

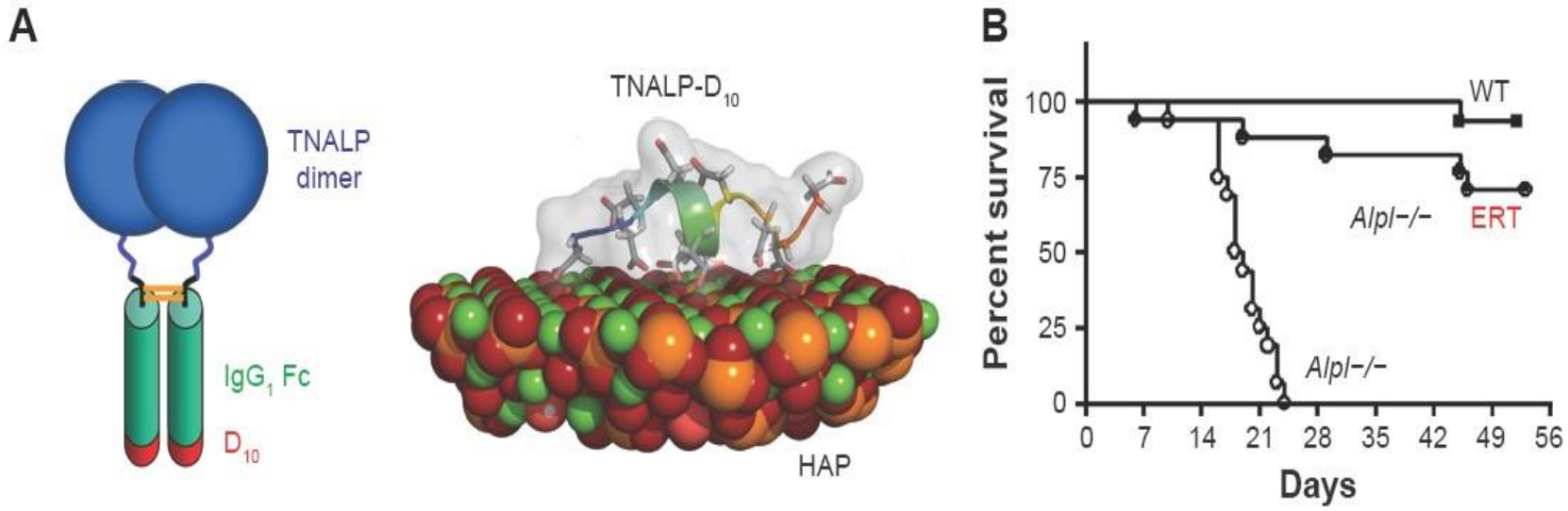
Hypophosphatasia (HPP)



Genotypes	Phenotypes/Onset (Perinatal/Infantile, Juvenile, Adult)

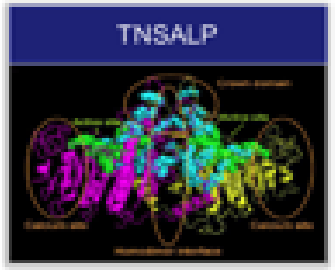
Bowden and Foster, Drug Design, Development and Therapy (2018)

Strensiq®



Bowden and Foster, Drug Design, Development and Therapy (2018)

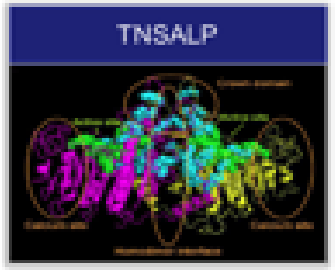
Strensiq® (asfotase alfa) [hypophosphatasia; HPP]

Biology	Pathology	Clinic	QoL / Survival
TNSALP  Substrates (PPi, PLP)	Skeletal System Bone Mineralization (Bone Biopsy; DEXA) Rickets Severity (RGI-C; RSS) Growth	Physical Function Ambulation (6MWT) Development Milestones (BSID-III; BOT-2) Strength (HDD)	Survival/ Respiratory Status Activities of Daily Living/Pain (CHAQ; PODCI; LEFS; BPI-SF)

6MWT = 6 minute walk test; BOT 2 = Bruininks-Oseretsky Test of Motor Proficiency BPI SF = Brief Pain Inventory-Short Form; BSID III = Bayley Scales of Infant and Toddler Development; CHAQ = Child Health Assessment Questionnaire; DEXA = dual energy x ray absorptiometry; HHD = hand-held dynamometry; LEFS = Lower Extremity Functional Scale; PODCI = Pediatric Outcomes Data Collection Instrument; PLP = pyridoxal 5□ phosphate; PPi = inorganic pyrophosphate; RGI C = Radiographic Global Impression of Change; RSS = rickets severity scale

Strensiq® (asfotase alfa) [hypophosphatasia; HPP]

Perinatal/Infantile-onset

Biology	Pathology	Clinic	QoL / Survival
TNSALP  Substrates (PPi, PLP)	Skeletal System Bone Mineralization (Bone Biopsy; DEXA) Rickets Severity (RGI-C; RSS) Growth	Physical Function Ambulation (6MWT) Development Milestones (BSID-III; BOT-2) Strength (HDD)	**Survival/ Respiratory Status** Activities of Daily Living/Pain (CHAQ; PODCI; LEFS; BPI-SF)

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QoL/Survival

Perinatal/Infantile-onset

Ventilatory Support and Patient Outcomes: 20 Historical Control (top) and 14 Asfotase Alfa–Treated (bottom) Patients b

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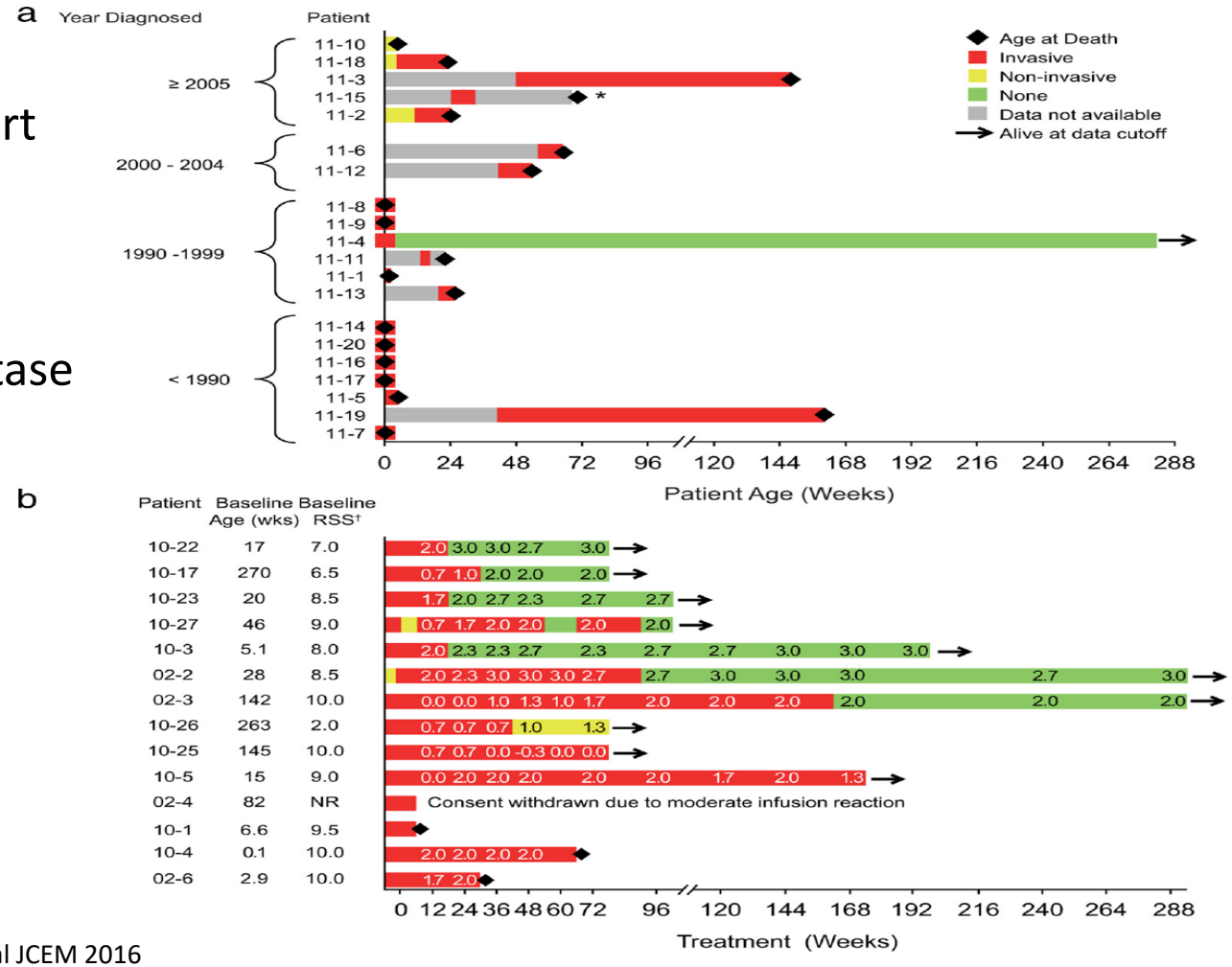
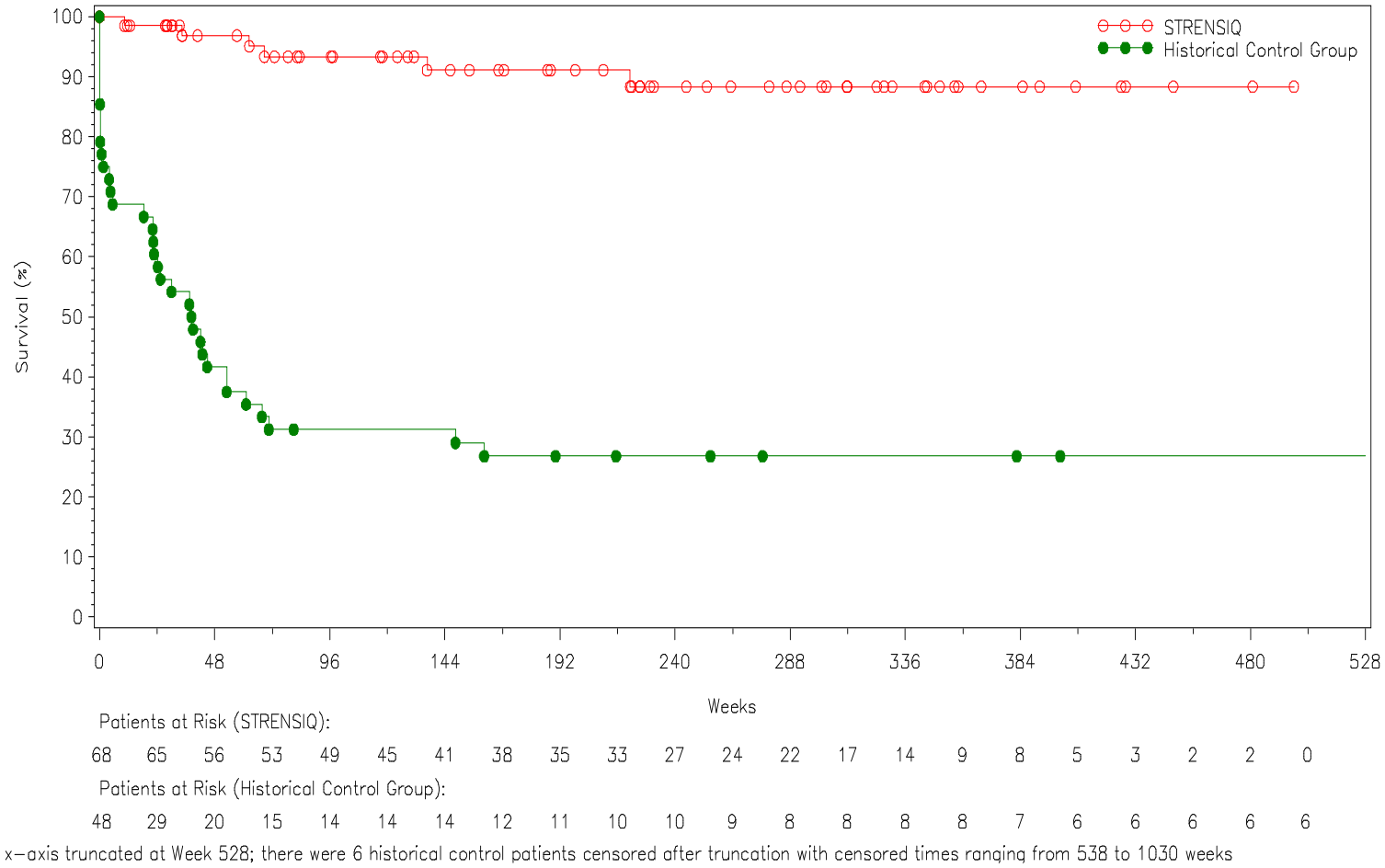


Whyte et al JCEM 2016

QoL/Survival

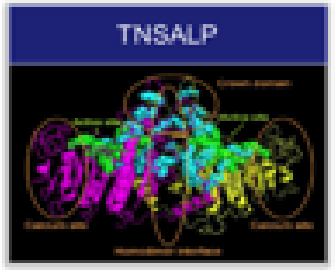
Perinatal/Infantile-onset



STRENSIQ™ (asfotase alfa) injection; US Label; Figure 1: Overall Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP

Strensiq® (asfotase alfa) [hypophosphatasia; HPP]

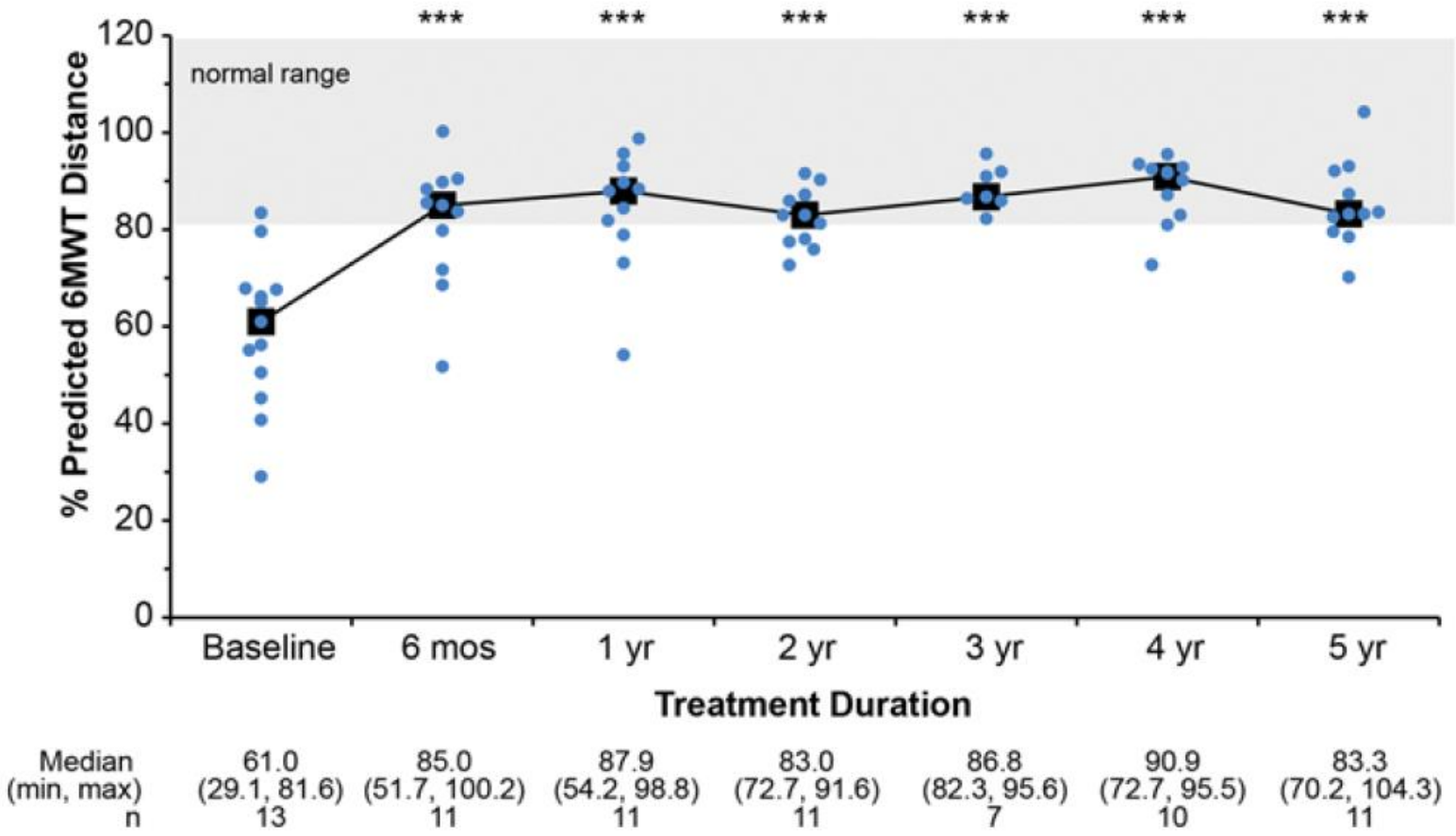
Juvenile-onset

Biology	Pathology	Clinic	QoL / Survival
TNSALP  Substrates (PPi, PLP)	Skeletal System Bone Mineralization (Bone Biopsy; DEXA) Rickets Severity (RGI-C; RSS) Growth	Physical Function **Ambulation (6MWT)** **Development Milestones (BSID-III; BOT-2)** **Strength (HDD)**	Survival/ Respiratory Status **Activities of Daily Living/Pain (CHAQ; PODCI; LEFS; BPI-SF)**

6MWT = 6 minute walk test; BOT 2 = Bruininks-Oseretsky Test of Motor Proficiency BPI SF = Brief Pain Inventory-Short Form; BSID III = Bayley Scales of Infant and Toddler Development; CHAQ = Child Health Assessment Questionnaire; DEXA = dual energy x ray absorptiometry; HHD = hand-held dynamometry; LEFS = Lower Extremity Functional Scale; PODCI = Pediatric Outcomes Data Collection Instrument; PLP = pyridoxal 5□ phosphate; PPi = inorganic pyrophosphate; RGI C = Radiographic Global Impression of Change; RSS = rickets severity scale

Clinic

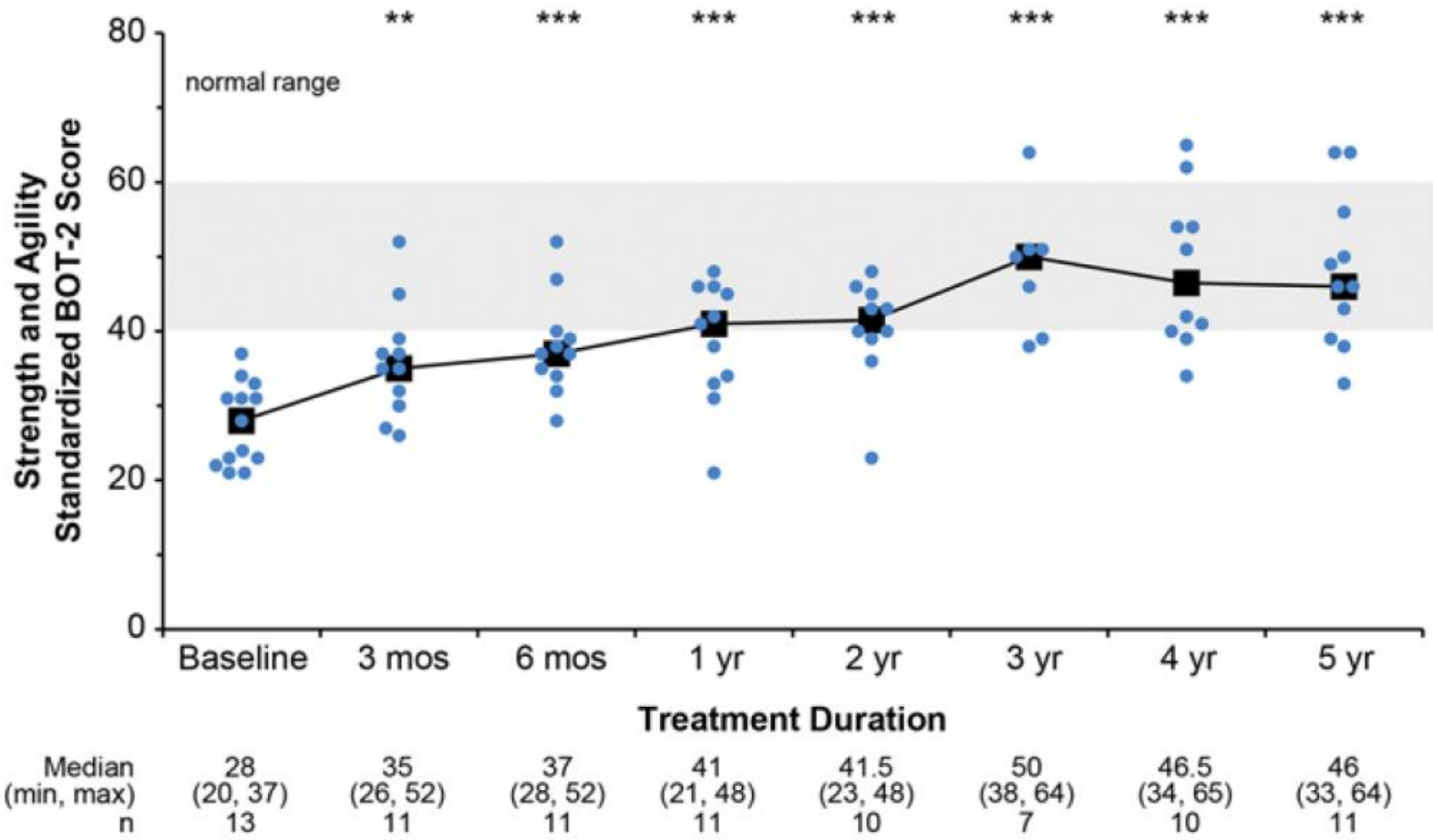
Juvenile-onset



Whyte et al. JCI Insight. 2016

Clinic

Juvenile-onset



Whyte et al. JCI Insight. 2016

Clinic

Juvenile-onset

BOT2: Shuttle Run

Baseline

22.2 sec

6 Months

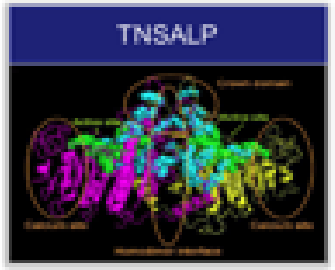
12.3 sec

36 Months

8.6 sec

Strensiq® (asfotase alfa) [hypophosphatasia; HPP]

Juvenile-onset

Biology	Pathology	Clinic	QoL / Survival
TNSALP  Substrates (PPi, PLP)	Skeletal System Bone Mineralization (Bone Biopsy; DEXA) Rickets Severity (RGI-C; RSS) Growth	Physical Function Ambulation (6MWT) **Gait (mPOMA-G)** Development Milestones (BSID-III; BOT-2) Strength (HDD)	Survival/ Respiratory Status Activities of Daily Living/Pain (CHAQ; PODCI; LEFS; BPI-SF)

6MWT = 6 minute walk test; BOT 2 = Bruininks-Oseretsky Test of Motor Proficiency BPI SF = Brief Pain Inventory-Short Form; BSID III = Bayley Scales of Infant and Toddler Development; CHAQ = Child Health Assessment Questionnaire; DEXA = dual energy x ray absorptiometry; HHD = hand-held dynamometry; LEFS = Lower Extremity Functional Scale; PODCI = Pediatric Outcomes Data Collection Instrument; PLP = pyridoxal 5□ phosphate; PPi = inorganic pyrophosphate; RGI C = Radiographic Global Impression of Change; RSS = rickets severity scale

Clinic

Juvenile-onset

Performance-Oriented Assessment of Mobility Problems in Elderly Patients

Mary E. Tinetti, MD

Tinetti ME. JAGS 1986; 34: 119-126

Clinic

Juvenile-onset

Development and validation of a modified performance-oriented mobility assessment tool for assessing mobility in children with hypophosphatasia

Dawn Phillips[a,1,*], Donna Griffin[b], Tracy Przybylski[b], Erica Morrison[b], Amy L. Reeves[b], Marc Vallee[c], Kenji P. Fujita[d] and Katherine L. Madson[b,1]

[a]*Division of Physical Therapy, University of North Carolina, Chapel Hill, NC, USA*
[b]*Shriners Hospitals for Children, St. Louis, MO, USA*
[c]*Biostatistics, Alexion Pharmaceuticals, Inc., Boston, MA, USA*
[d]*Clinical Development, Alexion Pharmaceuticals, Inc., Boston, MA, USA*

Phillips et al. JPRM 2018; 11: 187-192

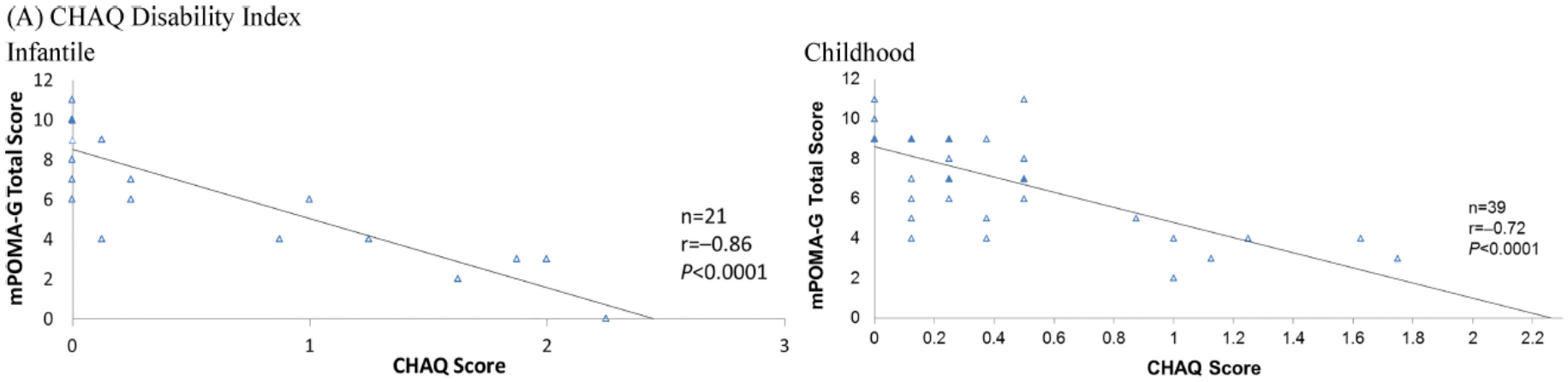
mPOMA-G Review and Adaptation

- An expert panel of physicians, physical therapists, and statisticians evaluated the suitability of the POMAG for assessing gait in children with HPP using observational, non-instrumented video footage
- Most POMA-G components were relevant and could be used
- Several modifications were recommended to adapt it for use in children with HPP resulting in the modified POMA-G (mPOMA-G)
- Modifications included:
  (1) removing the rating of initiation of gait;
  (2) expanding the assessment of step length and step continuity;
  (3) removing the rating of path;
  (4) adding new items within observations for step length and height;
  (5) clarifying descriptions of specific items to increase sensitivity and consistency among raters; and
  (6) Creating a scoring key that provides detailed instructions and illustrations

Phillips et al. JPRM 2018; 11: 187-192

mPOMA-G Validation

- Concurrent validation of mPOMA-G scores was made to other outcome measures assessing functional impairments
- Pearson correlation coefficients demonstrated strong concurrent validity between mPOMA-G scores and
  - Childhood Health Assessment Questionnaire (CHAQ) Disability Index,
  - Pediatric Outcomes Data Collection Instrument (PODCI), and
  - 6-Minute Walk Test.



Phillips et al. JPRM 2018; 11: 187-192

mPOMA-G Application

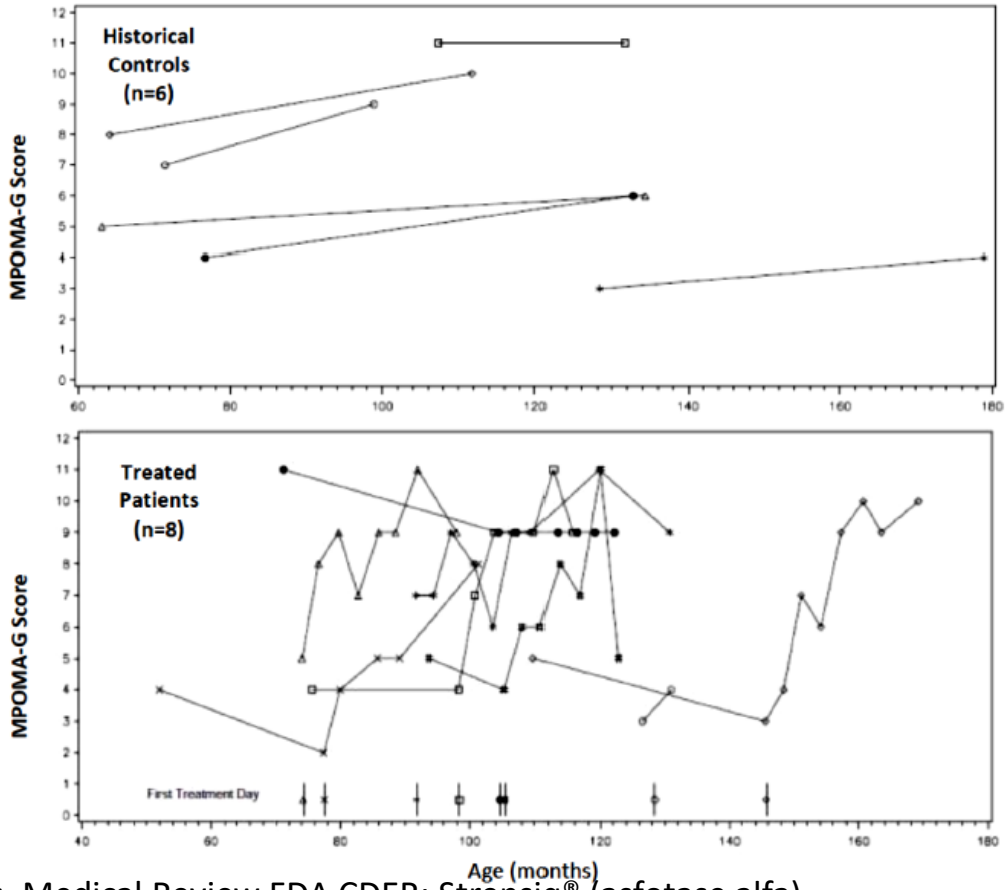
- Conducted in accordance with GCP and after IRB review and approval. Parents or legal guardians of the patients provided written informed consent and patients provided written assent. Visible faces in videos were permanently blurred, and all videos (n = 64) were assigned a new masking code and randomized before each scoring
- 3 trained physical therapists applied the mPOMAG to score videos of 14 children with HPP while walking.
- Patients (age range: 5–15 years) were enrolled in an open-label asfotase alfa clinical study (NCT00952484) with extension (NCT01203826) or a natural history study (NCT02235493)
- Videos of children in the treated group (n = 8) were taken before and after treatment; videos of children in the natural history group (n =6) were taken at routine follow-up visits

Phillips et al. JPRM 2018; 11: 187-192

mPOMA-G Application

The median (range) rate of change per year was 2.51/year (0.0, 4.6) in asfotase alfa-treated patients compared with 0.33/year (0.0, 0.9) for untreated historical controls (p=0.0303, Wilcoxon rank-sum test)

Figure 7: MPOMA-G Results for Historical Controls vs. Treated Patients



C. Epps, Medical Review FDA CDER; Strensiq® (asfotase alfa)

Forward Recommendation

- In the development of rare/ultra-rare disease, build in a forward review of assessment tools in alternative disease areas with relevant morbidity/functional disability
- Consider its application in the development program and review/modify the clinimetric characteristics when applied to the specific disease under study
- Conduct rater training and assessment tool validation using established scales
- Apply to relevant natural history and study drug datasets

Henrik Zetterberg

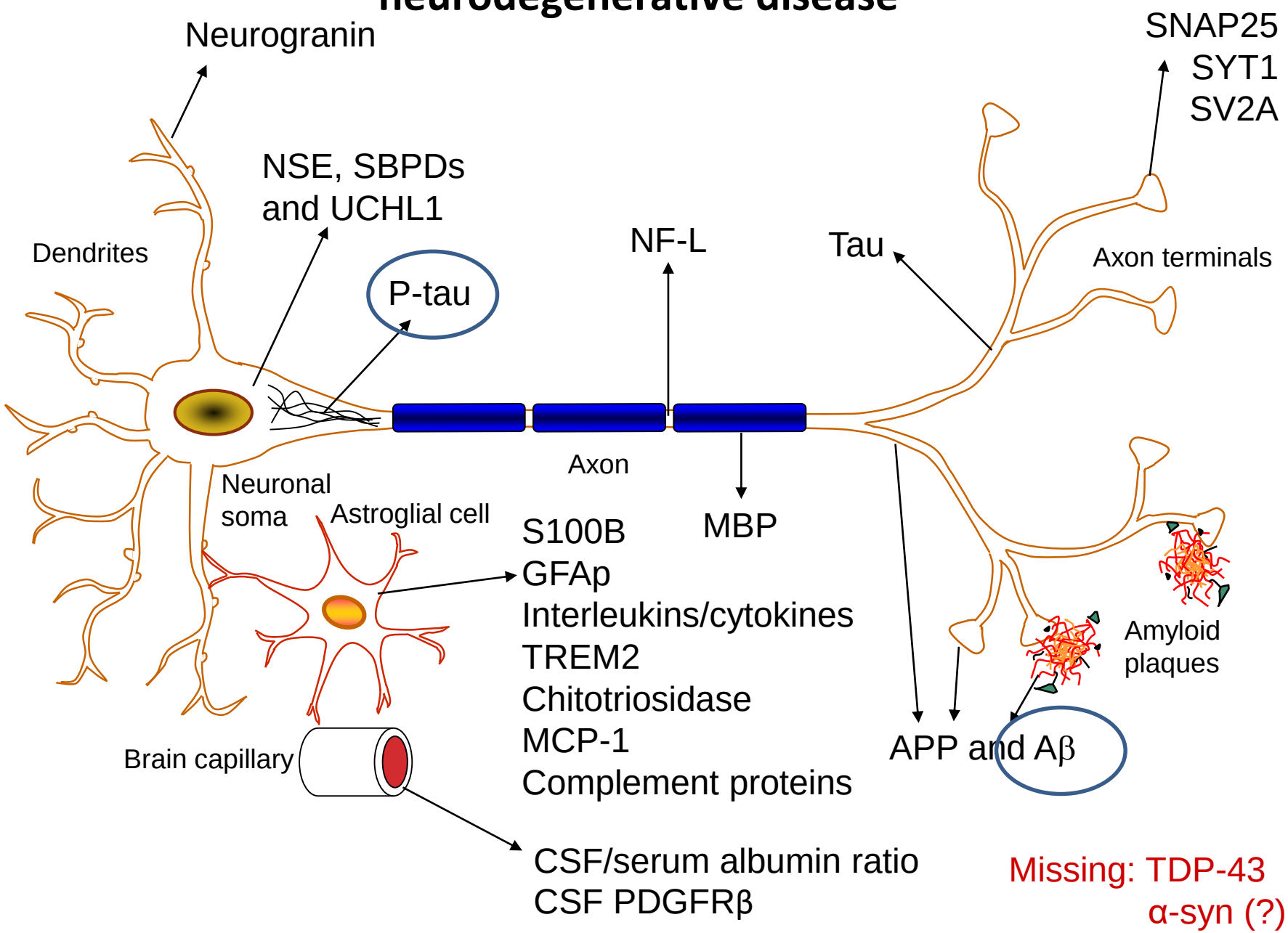
Professor of Neurochemistry

University of Gothenburg and University College London

Development and validation of cerebrospinal fluid and blood biomarkers for neurodegenerative diseases

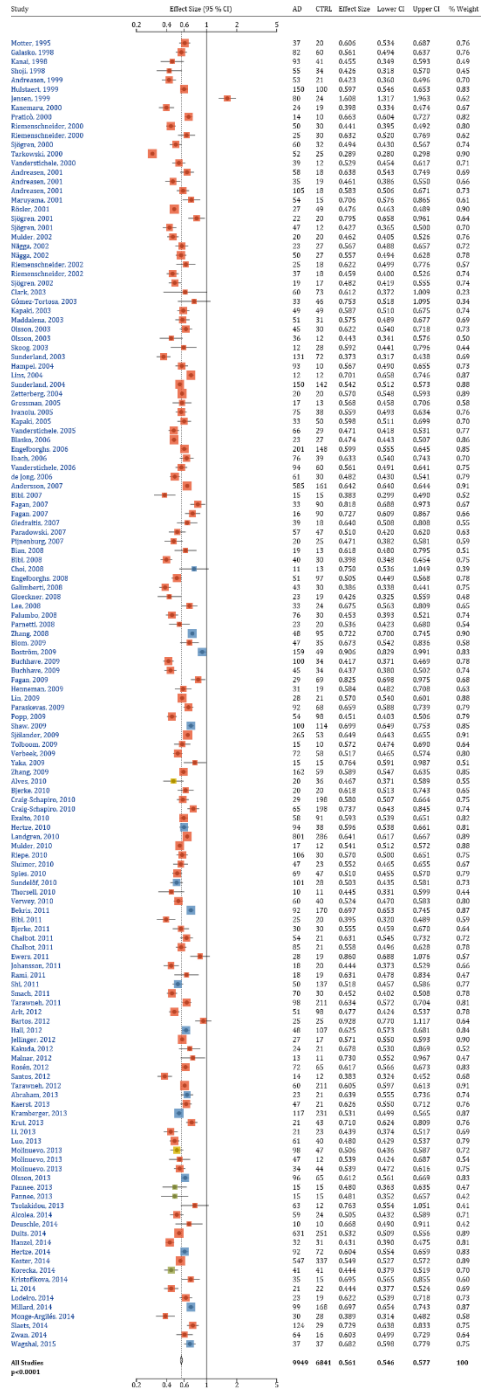
Henrik Zetterberg, MD, PhD
Department of Psychiatry and Neurochemistry,
University of Gothenburg, Sweden;
Institute of Neurology and UK Dementia Research Institute, UCL, UK

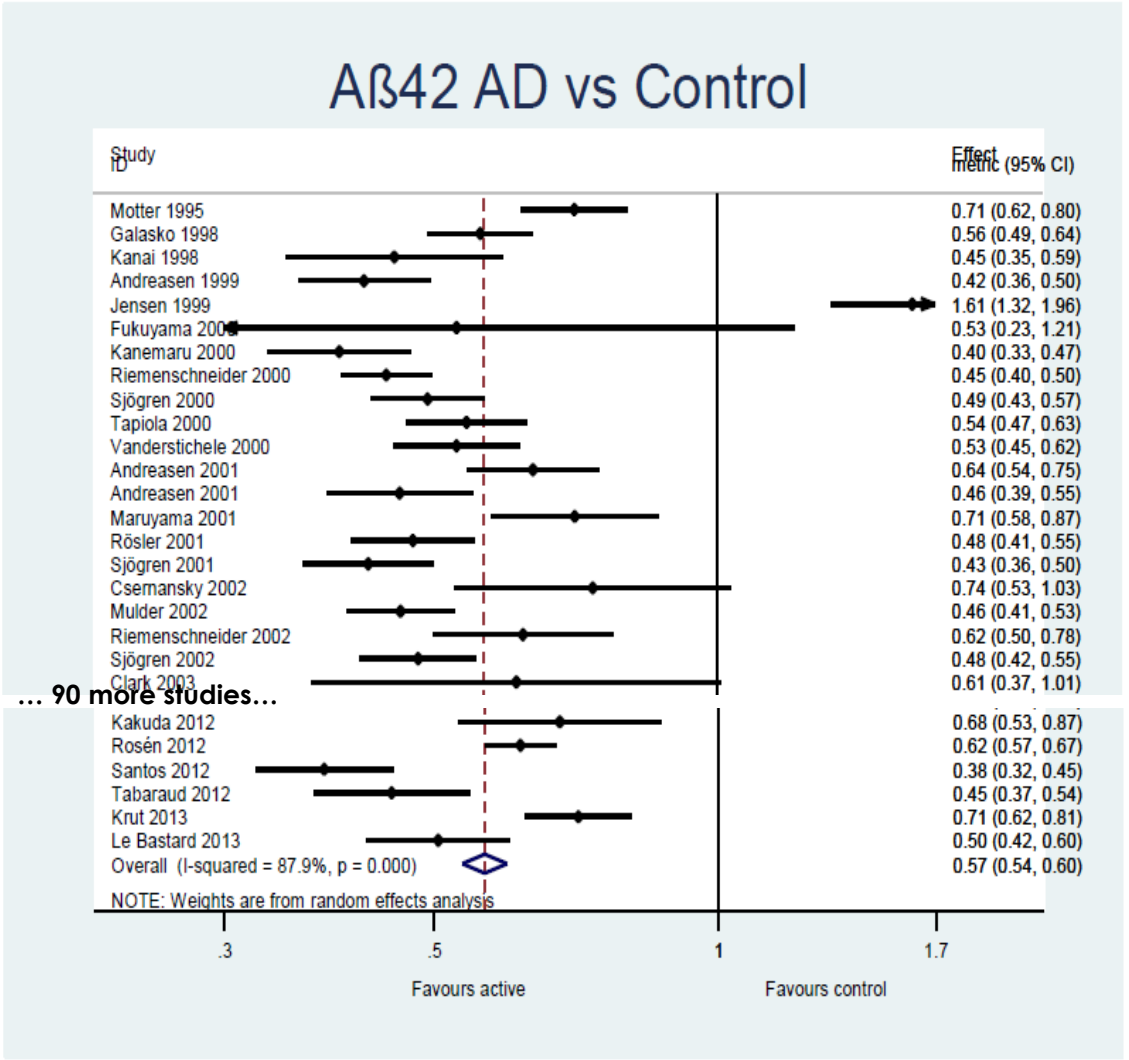
Fluid biomarker candidates of potential relevance to neurodegenerative disease



A = amyloid pathology

CSF Aβ42 is decreased in AD



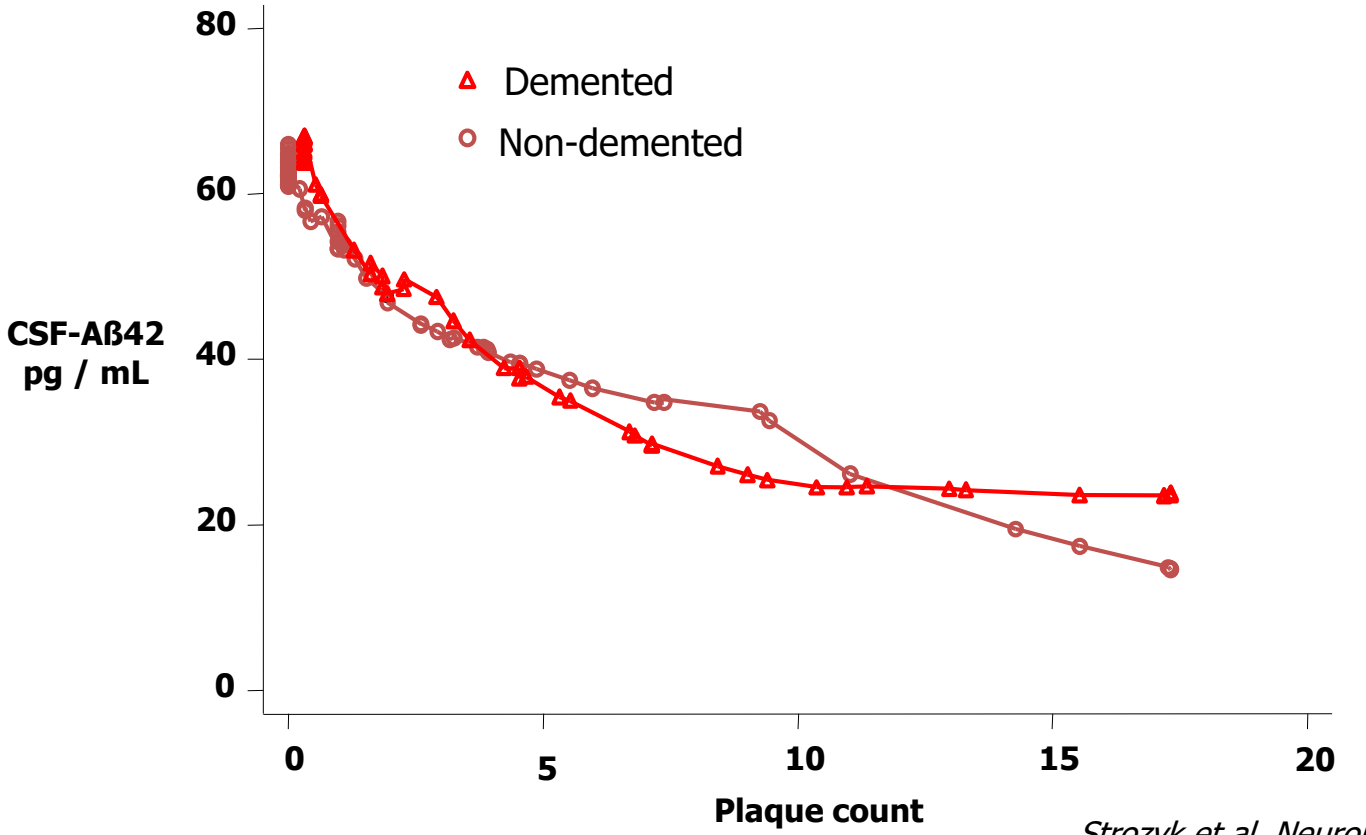


AlzBiomarker Database

CSF Aβ42 is a marker of amyloid plaque pathology

Study design:

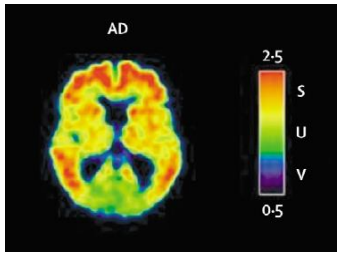
155 autopsy cases
Plaque counts – neocortex and hippocampus
Post-mortem CSF samples



Strozyk et al, Neurology 2003;60:652-656.

➔ CSF Aβ42 correlates with amyloid cortical amyloid plaque load

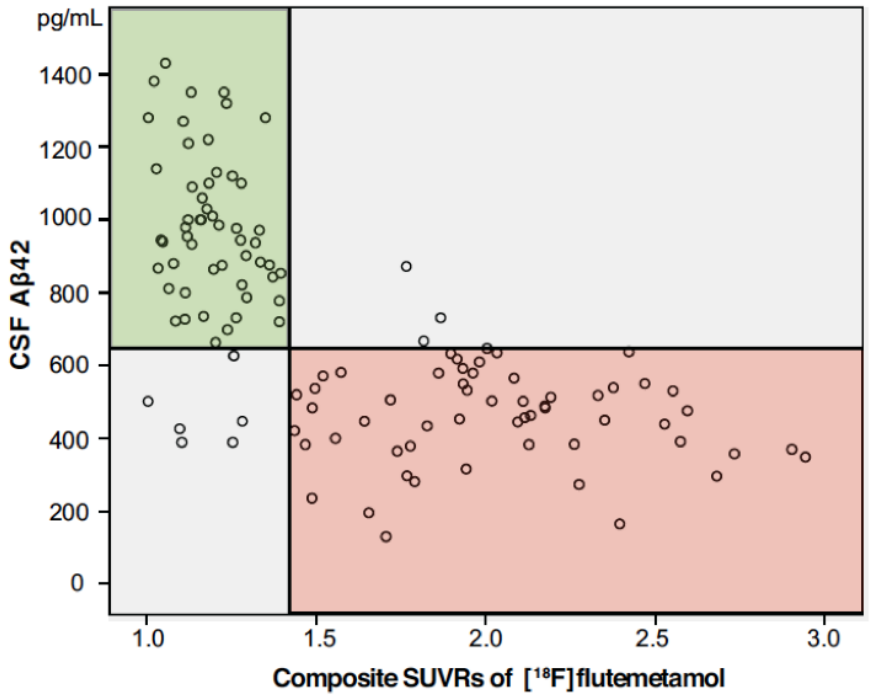
CSF Aβ42 concentration correlates with amyloid PET



Study design: 118 patients with cognitive complaints examined for both CSF biomarkers - as part of clinical routine – 2 years and amyloid ^{18}F-flutemetamol PET

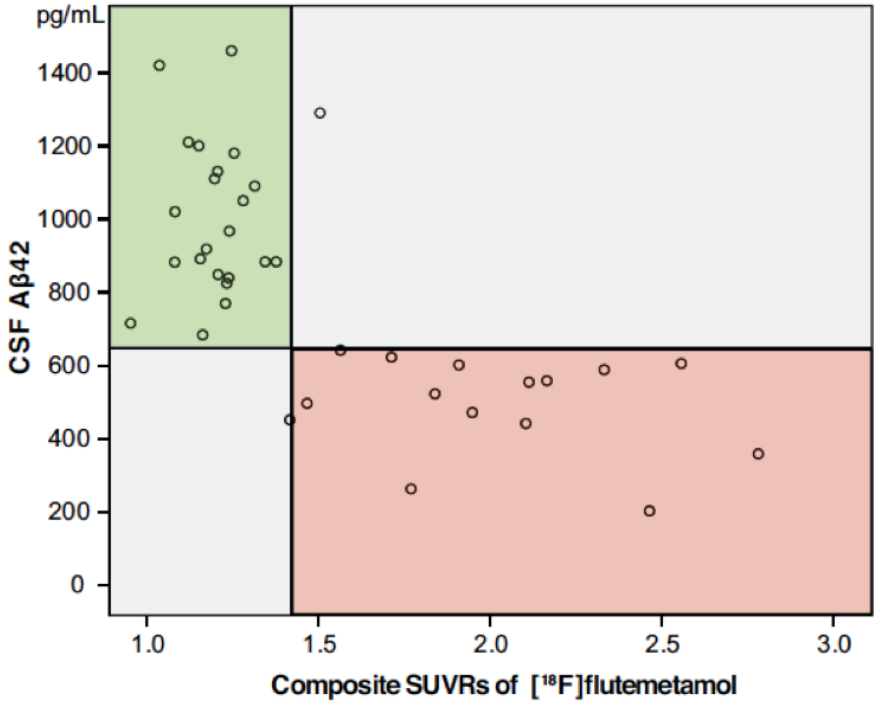
Cut-offs: CSF Aβ42 < 647 pg/mL
^{18}F-flutemetamol PET > 1.42

Original cohort n= 118



Positive PET+CSF or Negative PET+CSF 92 %

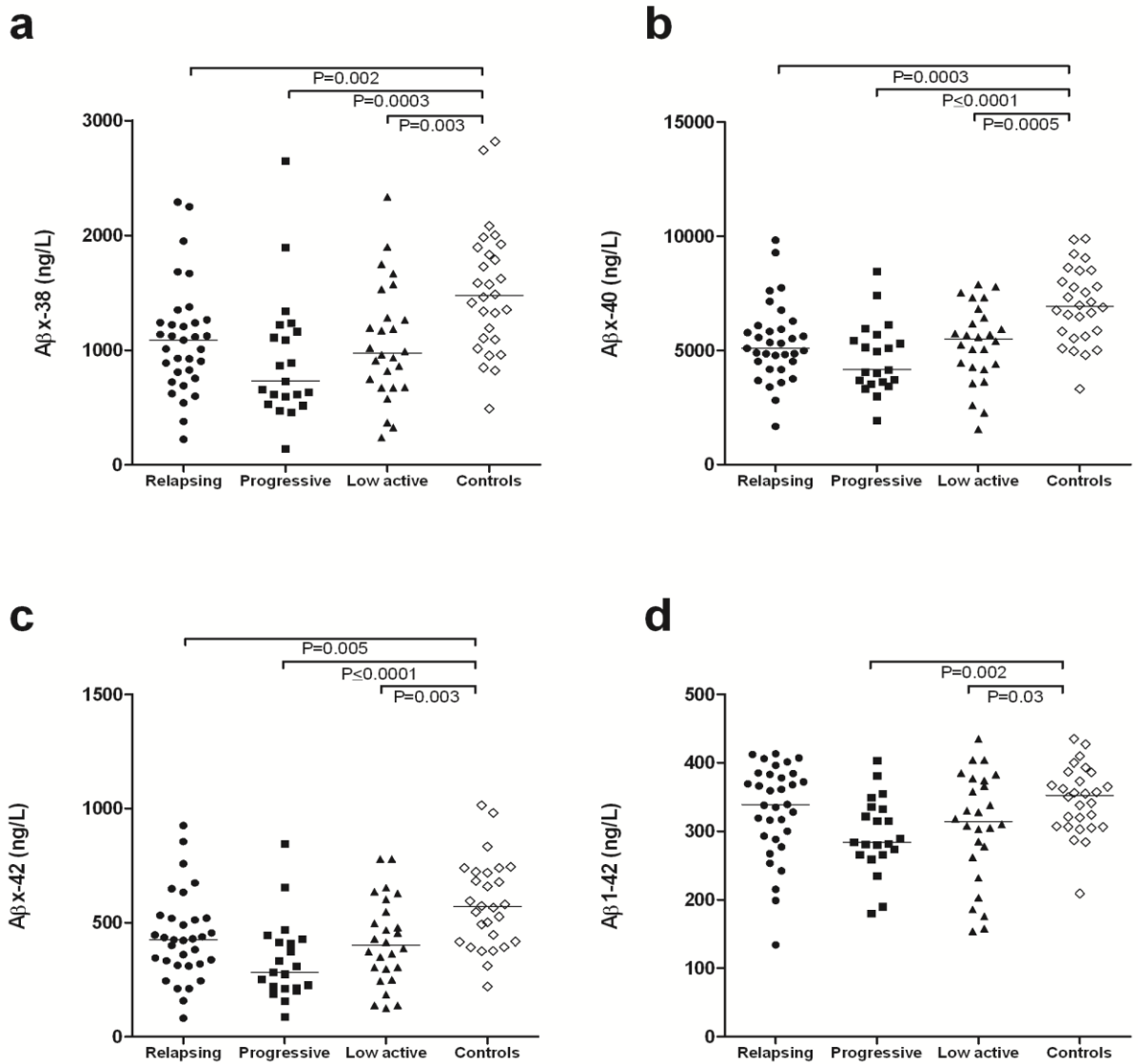
Validation cohort n= 38



Positive PET+CSF or Negative PET+CSF 97 %

Palmquist S, et al, JAMA Neurol 2014

CSF Aβ42 concentration may be decreased in neuroinflammatory conditions



Augutis et al., Multiple Sclerosis 2013

CSF Aβ42 concentration may be decreased in normal pressure hydrocephalus

Table 2 LCSF biomarkers in patients with iNPH and HI[a]

	iNPH (n = 28)	HI (n = 20)	iNPH/HI ratio
NFL	1,260 (840-2,290) ↑	825 (653-1,243)	1.53[b]
MBP	1.5 (1.1-1.9) ↔	1.3 (1.0-1.5)	1.12 NS
Aβ38	637 (438-894) ↓	1,641 (1,231-2,173)	0.39[c]
Aβ40	5,067 (3,634-6,573) ↓	10,083 (7,626-12,794)	0.50[c]
Aβ42	221 (156-325) ↓	498 (391-669)	0.44[c]
sAPPα	505 (338-739) ↓	1,110 (727-1,244)	0.46[c]
sAPPβ	176 (110-258) ↓	414 (250-545)	0.43[c]
t-tau	39 (34-50) ↓	84 (64-107)	0.47[c]
p-tau	39 (33-50) ↓	59 (47-75)	0.67[d]
IL-8	34 (26-38) ↔	31 (26-40)	1.10 NS
IL-10	0.66 (0-0.9) ↔	0.67 (0-0.8)	0.99 NS
MCP1	746 (602-874) ↑	628 (564-686)	1.19[b]
Albumin CSF	287 (188-408) ↔	232 (203-280)	1.24 NS
Albumin ratio	6.8 (5.0-10) ↔	5.6 (4.5-6.4)	1.22 NS

Abbreviations: Aβ = amyloid β; HI = healthy elderly individuals; IL = interleukin; iNPH = idiopathic normal-pressure hydrocephalus; LCSF = lumbar CSF; MBP = myelin basic protein; MCP1 = monocyte chemoattractant protein 1; NFL = neurofilament light protein; NS = nonsignificant; p-tau = phosphorylated tau; sAPP = soluble amyloid precursor protein; t-tau = total tau.

[a] Arrows indicate levels in iNPH in comparison with HI. Values are given as median (Q1–Q3 range).

[b] $p \leq 0.05$.

[c] $p \leq 0.001$.

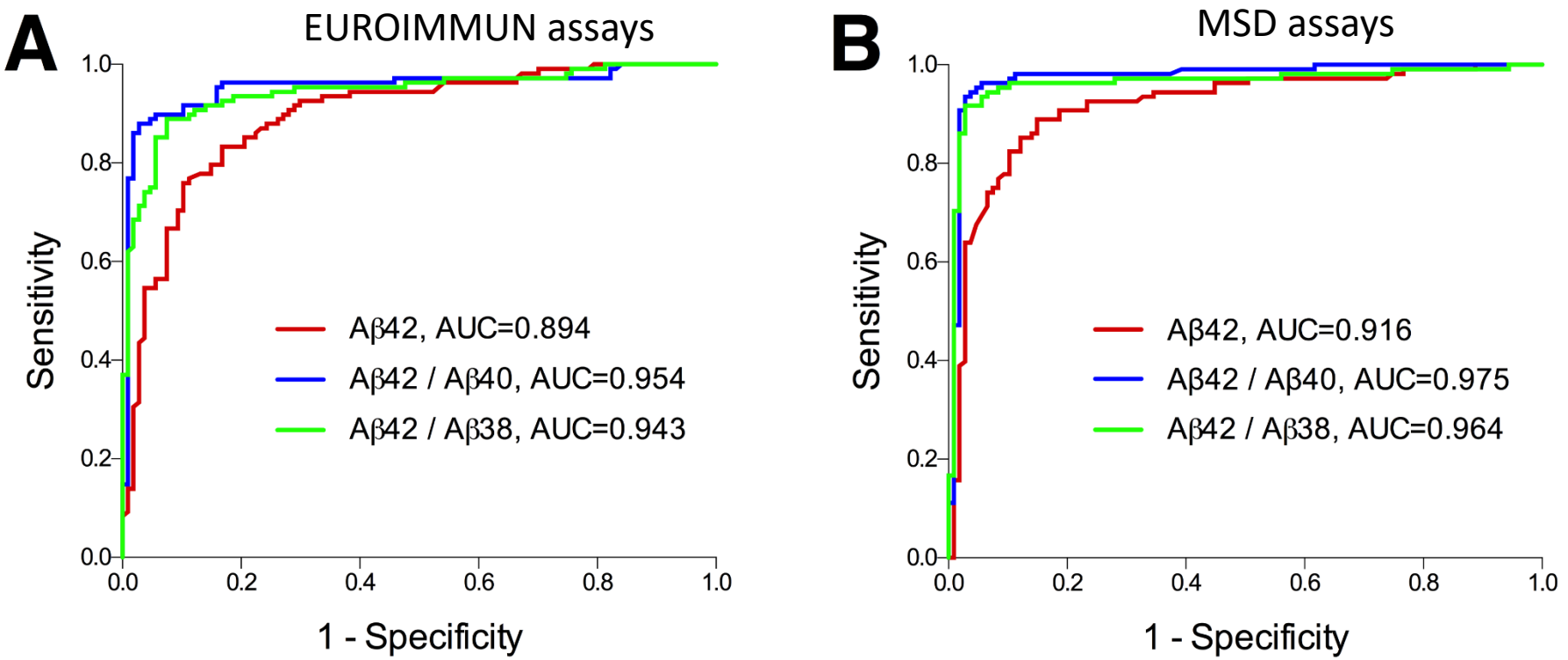
[d] $p \leq 0.01$.

Jeppsson et al., Neurology 2013

…and there may be constitutively low Aβ producers who are close to the Aβ42 cutpoint for positivity

The CSF Aβ42/Aβ40 ratio corrects for this

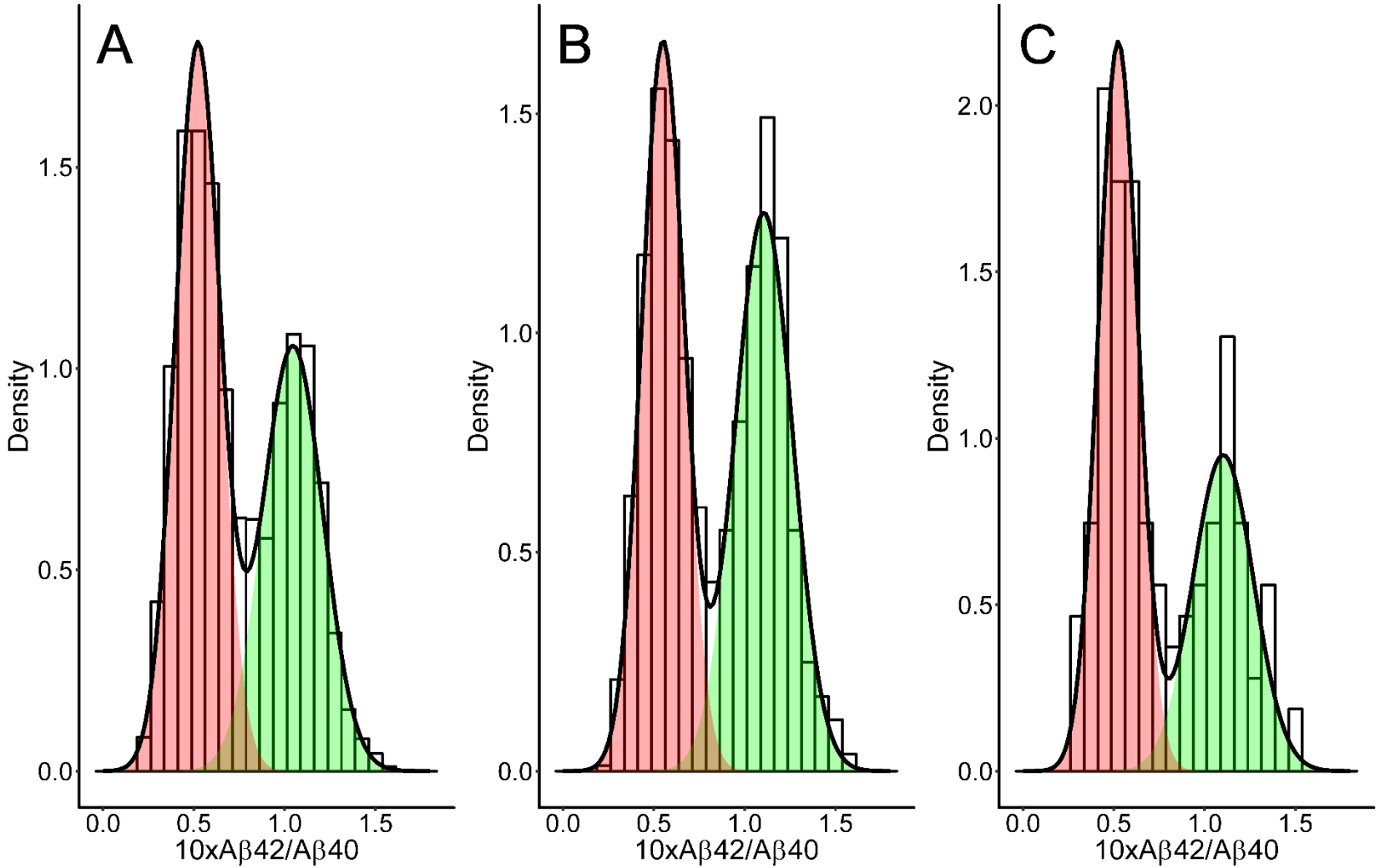
CSF Aβ42/40 (or Aβ38) and PET Aβ



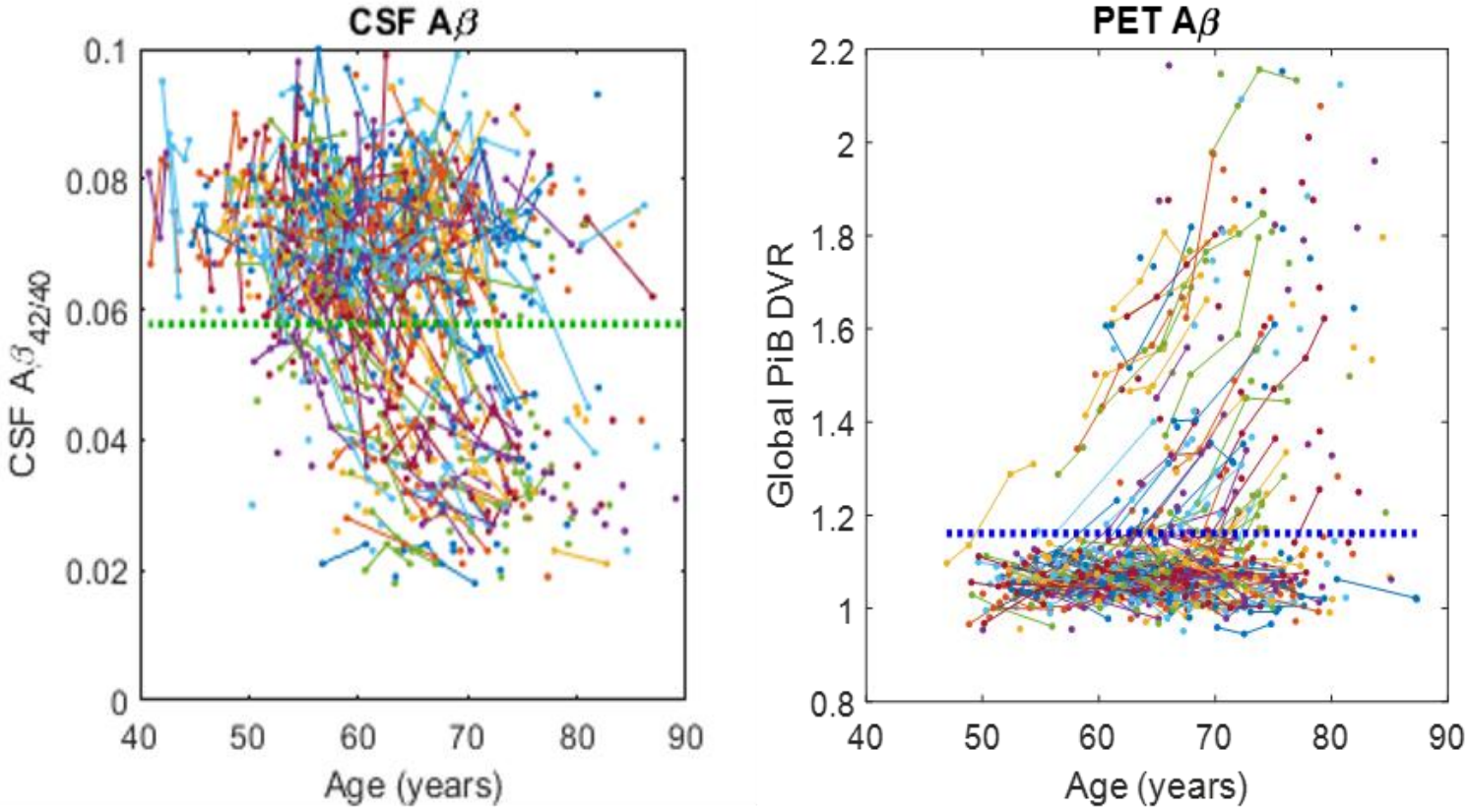
Cohort: Swedish BioFINDER
215 SCD/MCI (108 PET^{+} and 107 PET-)
PET: flutemetamol

Janelidze *et al.*, Ann Clin Transl Neurol. 2016

The CSF Aβ42/Aβ40 ratio in clinical practice

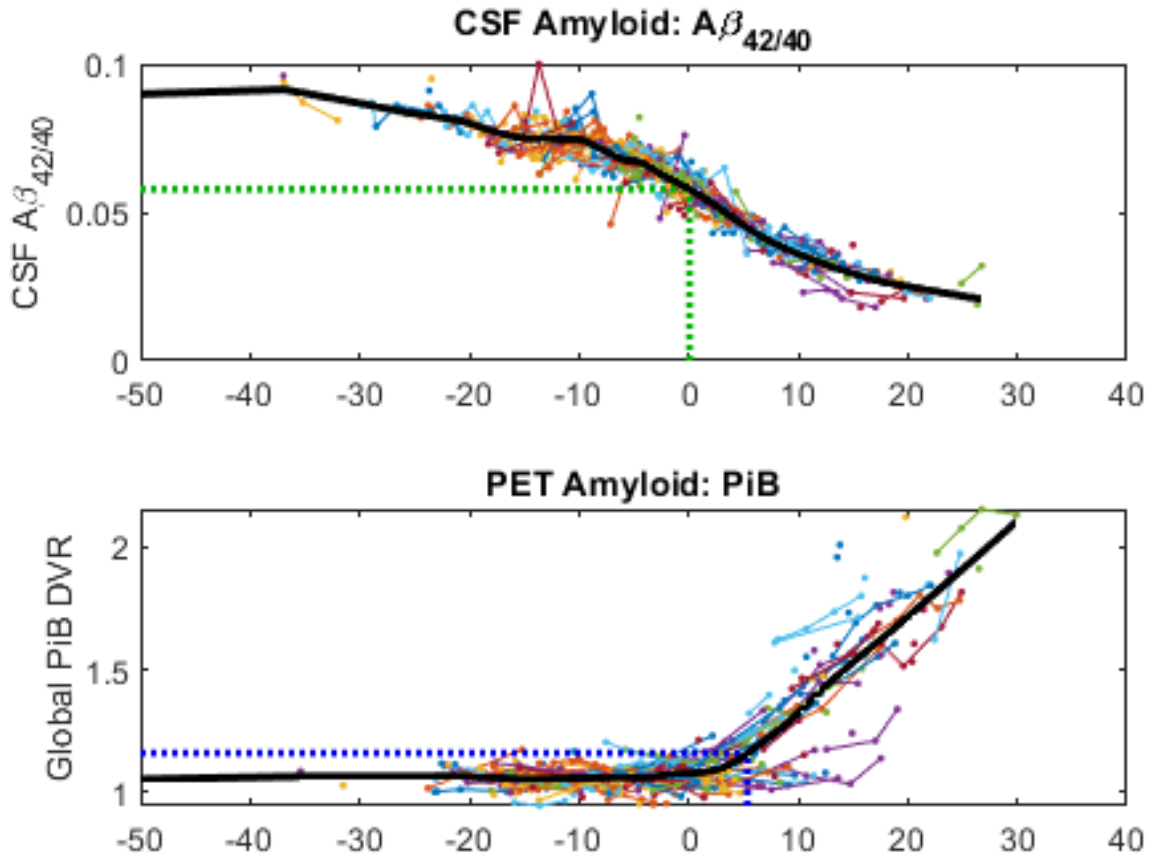


CSF Aβ42/Aβ40 ratio – longitudinal data



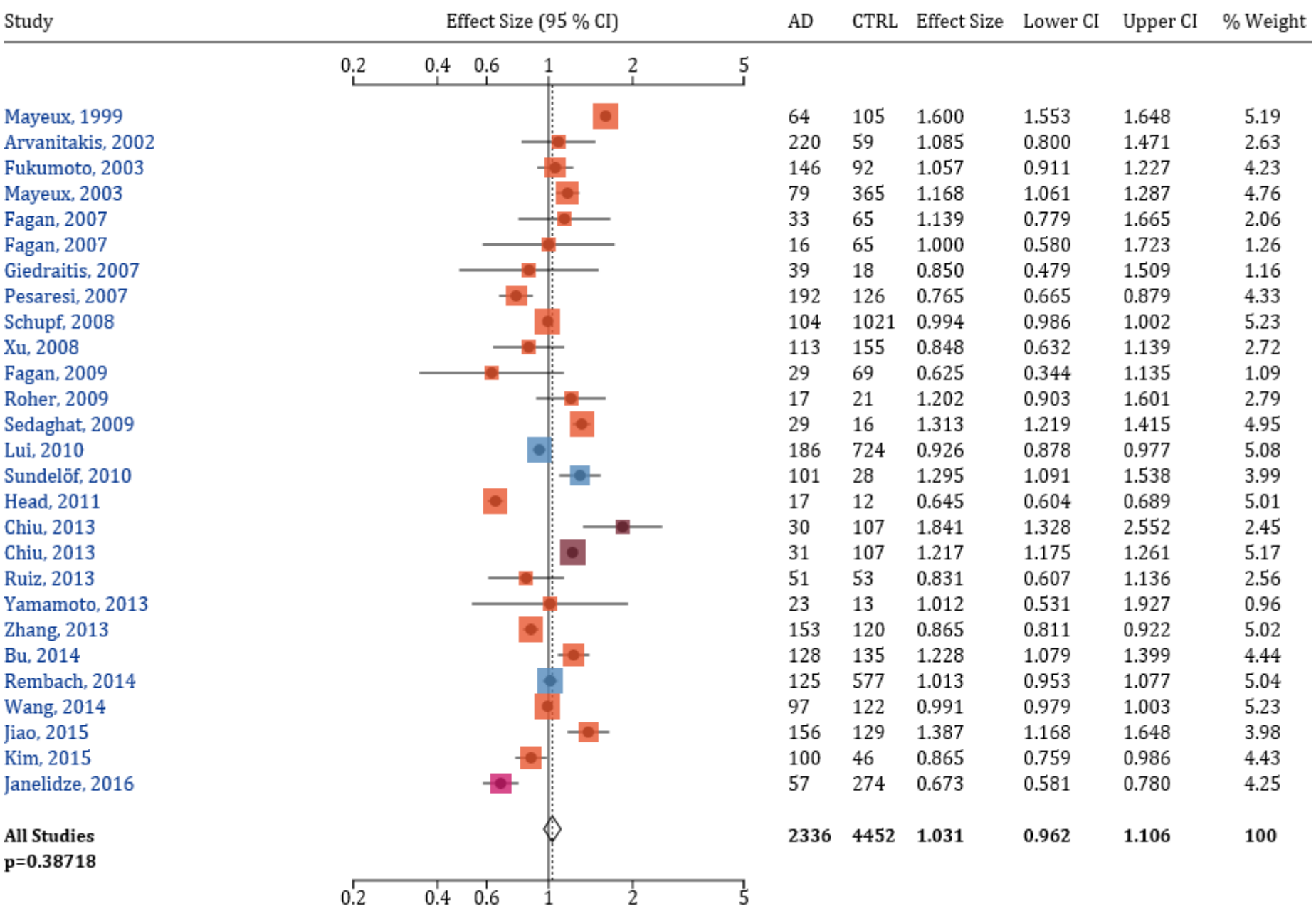
Betthauser T et al., AAIC 2021
Neuroimaging: Multimodal Biomarkers
July 27, 2021

CSF Aβ42/Aβ40 ratio – longitudinal data

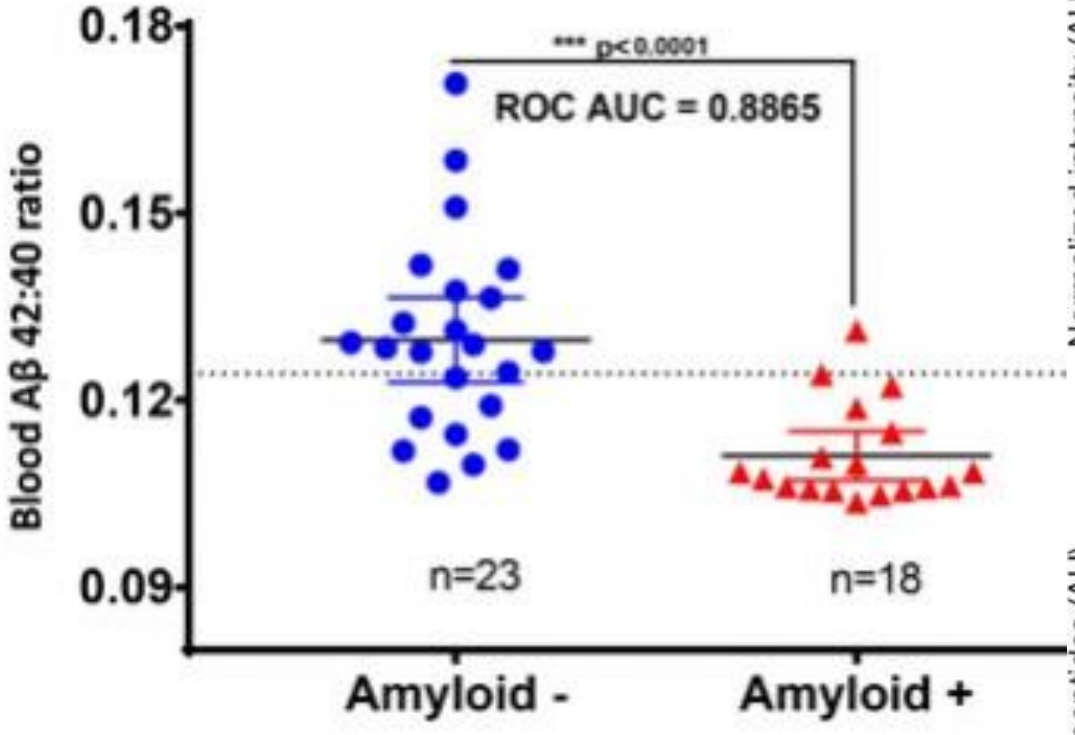


Betthauser T et al., AAIC 2021
Neuroimaging: Multimodal Biomarkers
July 27, 2021

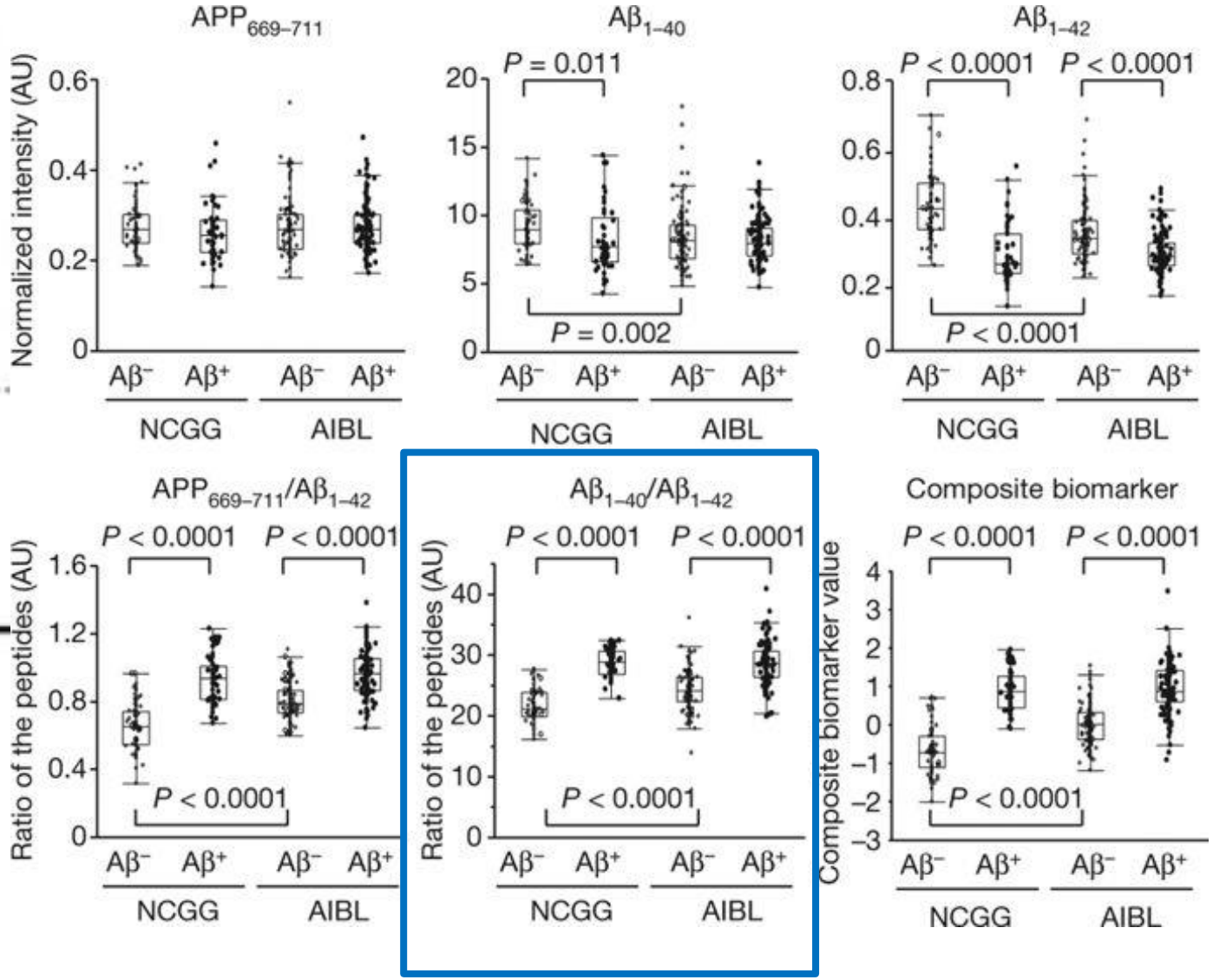
How about plasma Aβ?



Highly sensitive and precise mass spec methods work



Ovod et al. A&D, 2017



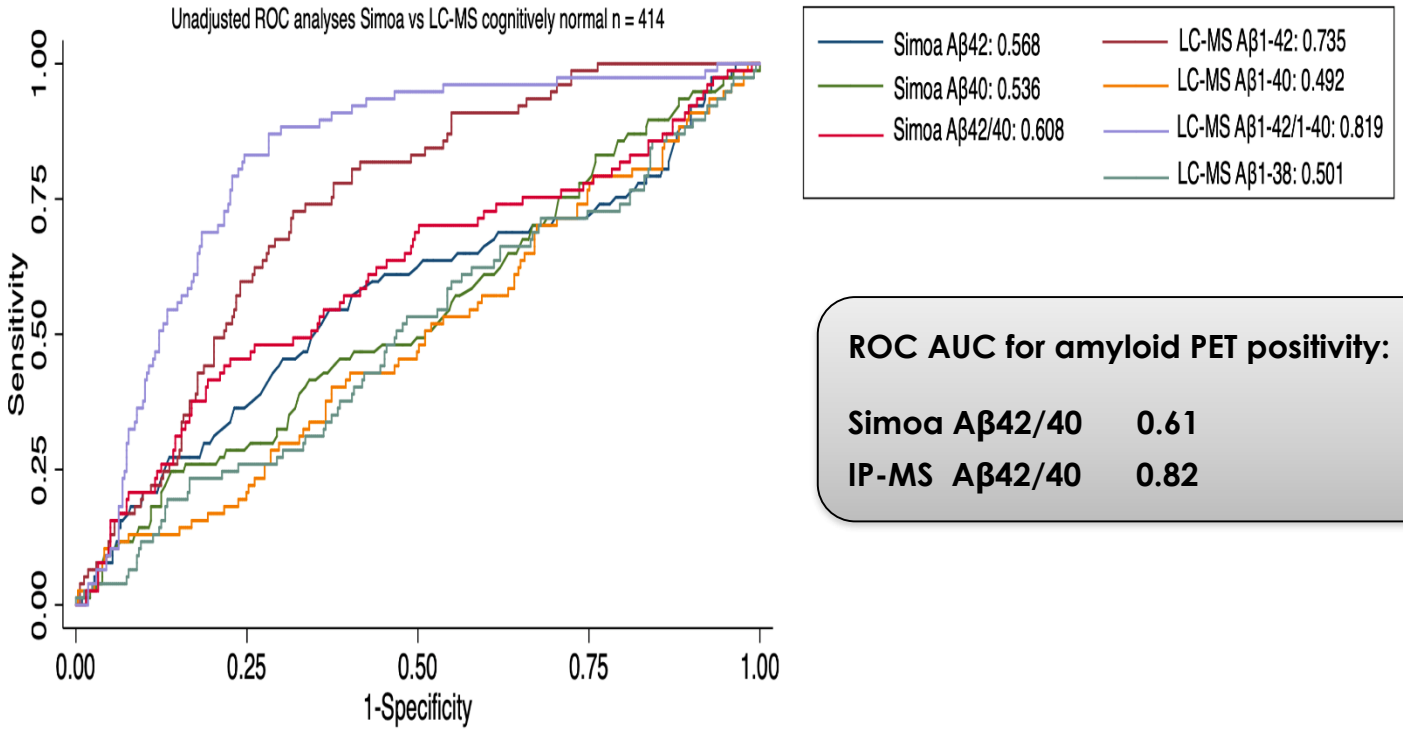
Nakamura et al., Nature, 2018

Plasma Aβ in the Insight46 cohort

Study design: Insight46 - epidemiological study people born 1946 (n= 414 cognitively unimpaired)

APOE genotype, neuropsych testing, amyloid PET

Plasma Aβ42, Aβ42/40 using immunoassay (Simoa) and IP LC-MS/MS



ROC AUC for amyloid PET positivity:

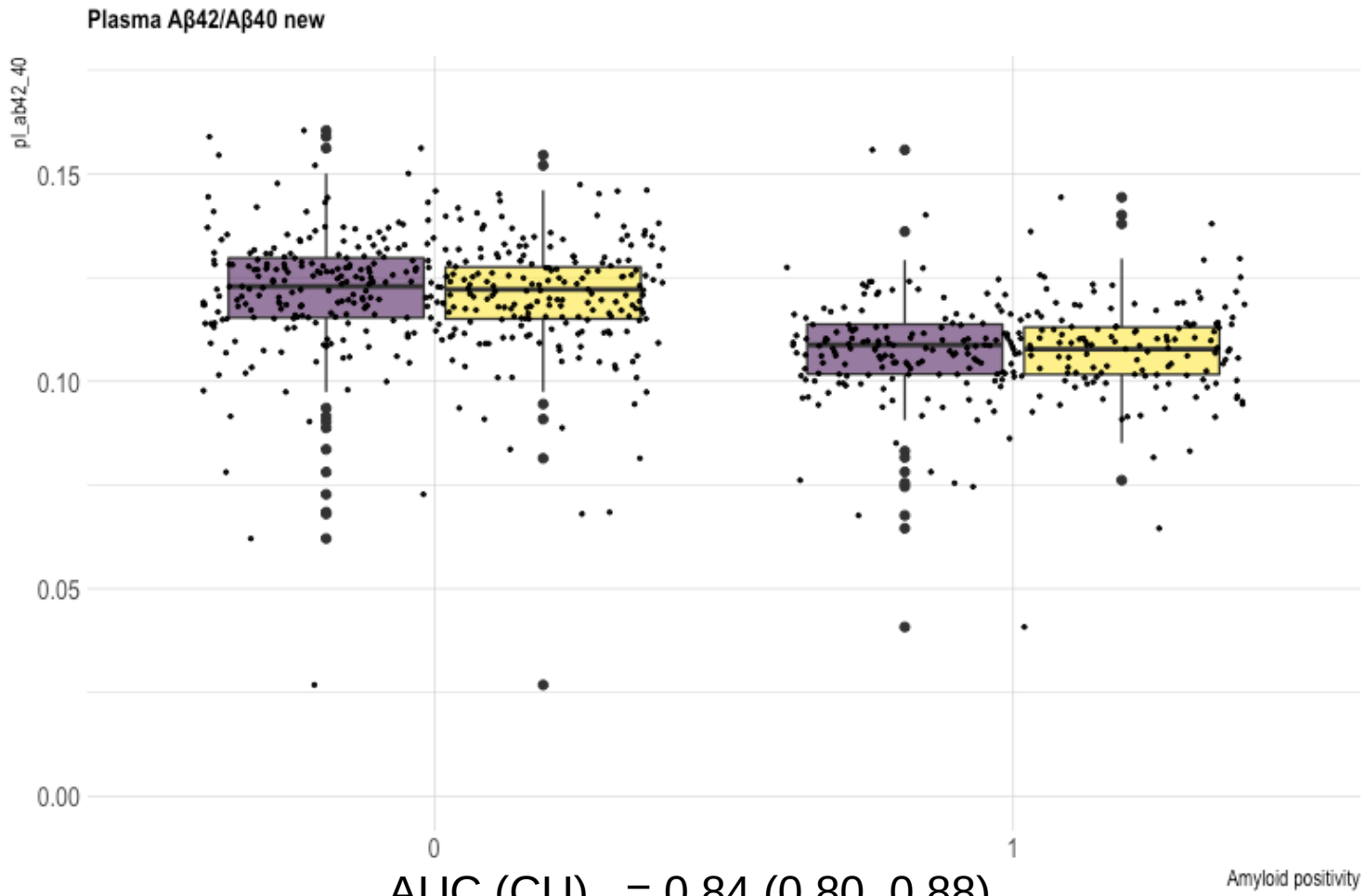
Simoa Aβ42/40	0.61
IP-MS Aβ42/40	0.82

➔ Plasma Aβ42 and Aβ40/42 ratio by IP-MS/MS show high concordance with brain amyloidosis

Keshavan A *et al.*, Brain 2021

Plasma Aβ42/Aβ40 ratio using a fully automated Cobas assay

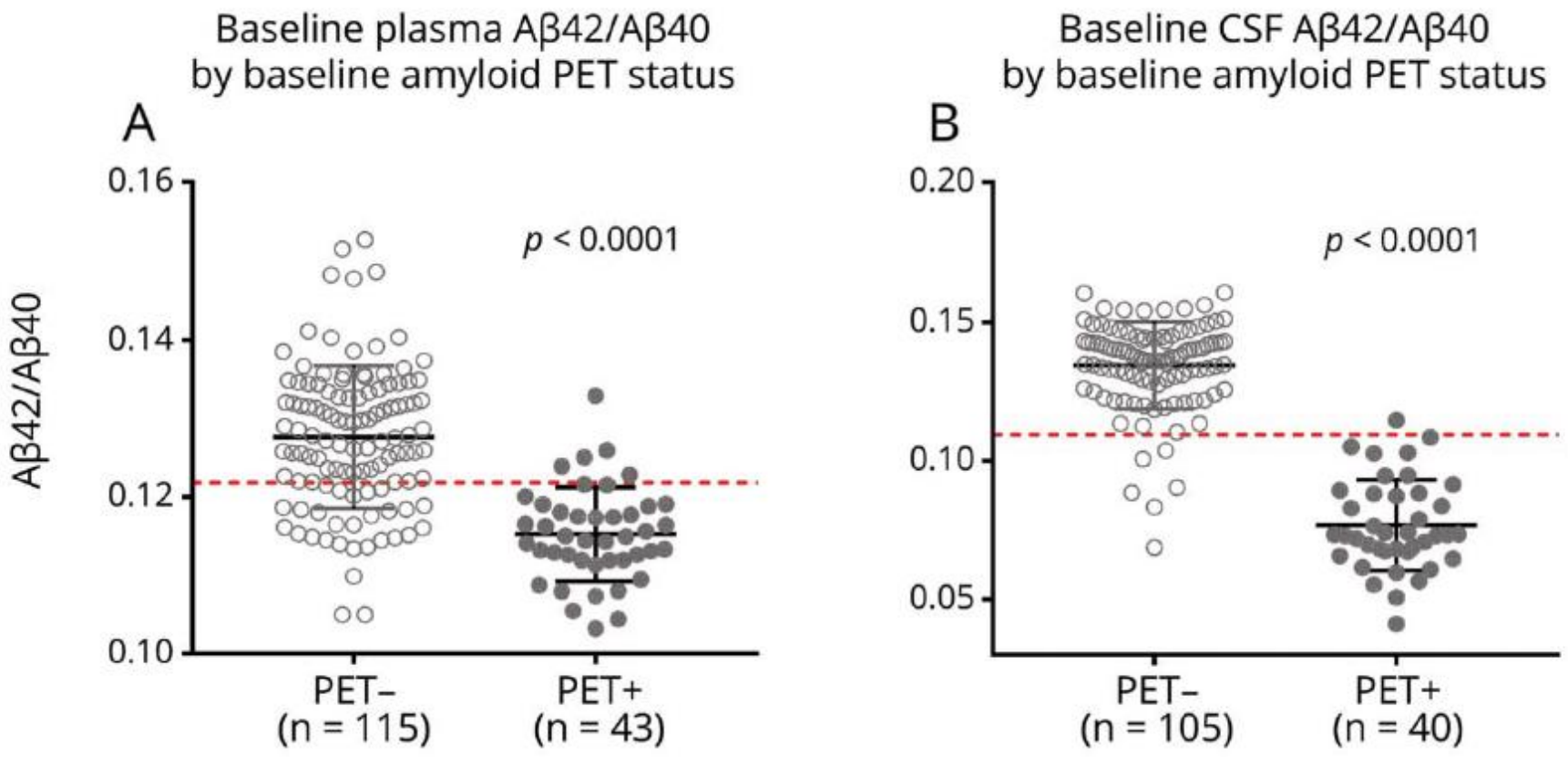
- Purple = CU
- Yellow = MCI



AUC (CU) = 0.84 (0.80, 0.88)
AUC (MCI) = 0.79 (0.72, 0.85)

Palmqvist *et al.*, unpublished

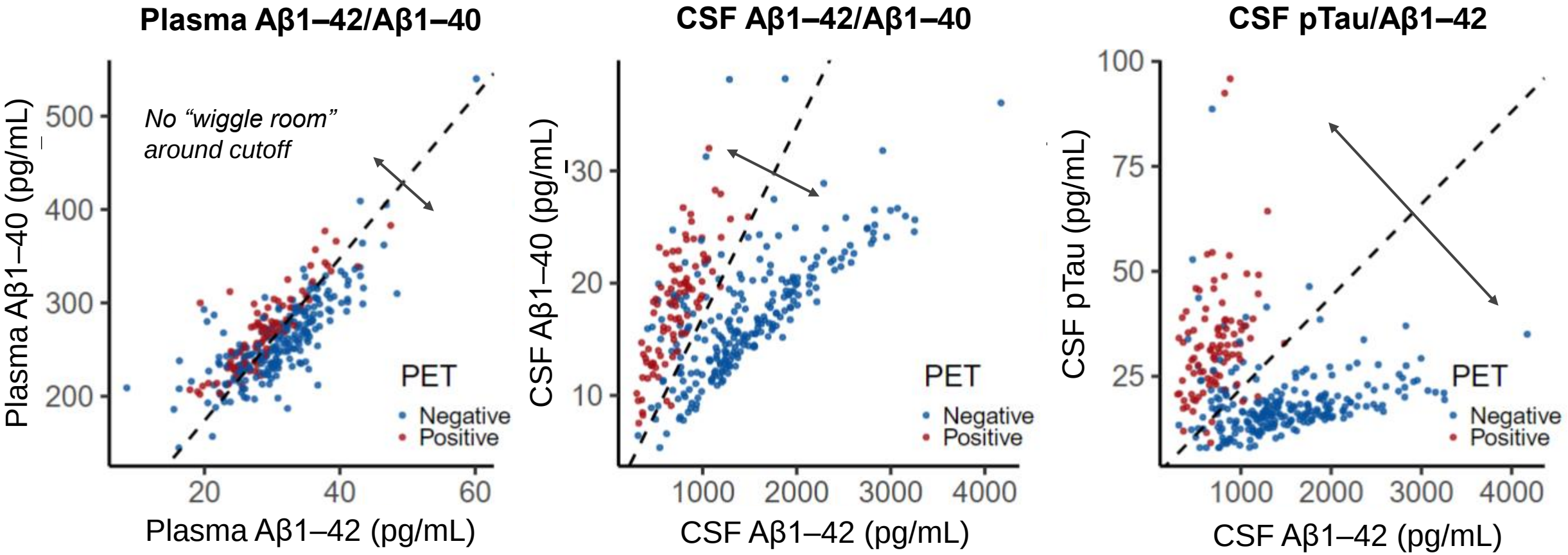
The challenge



The fold reduction in CSF Aβ ratio is much greater than in plasma because of peripheral Aβ

Schindler et al., Neurology, 2019

The challenge, continued…



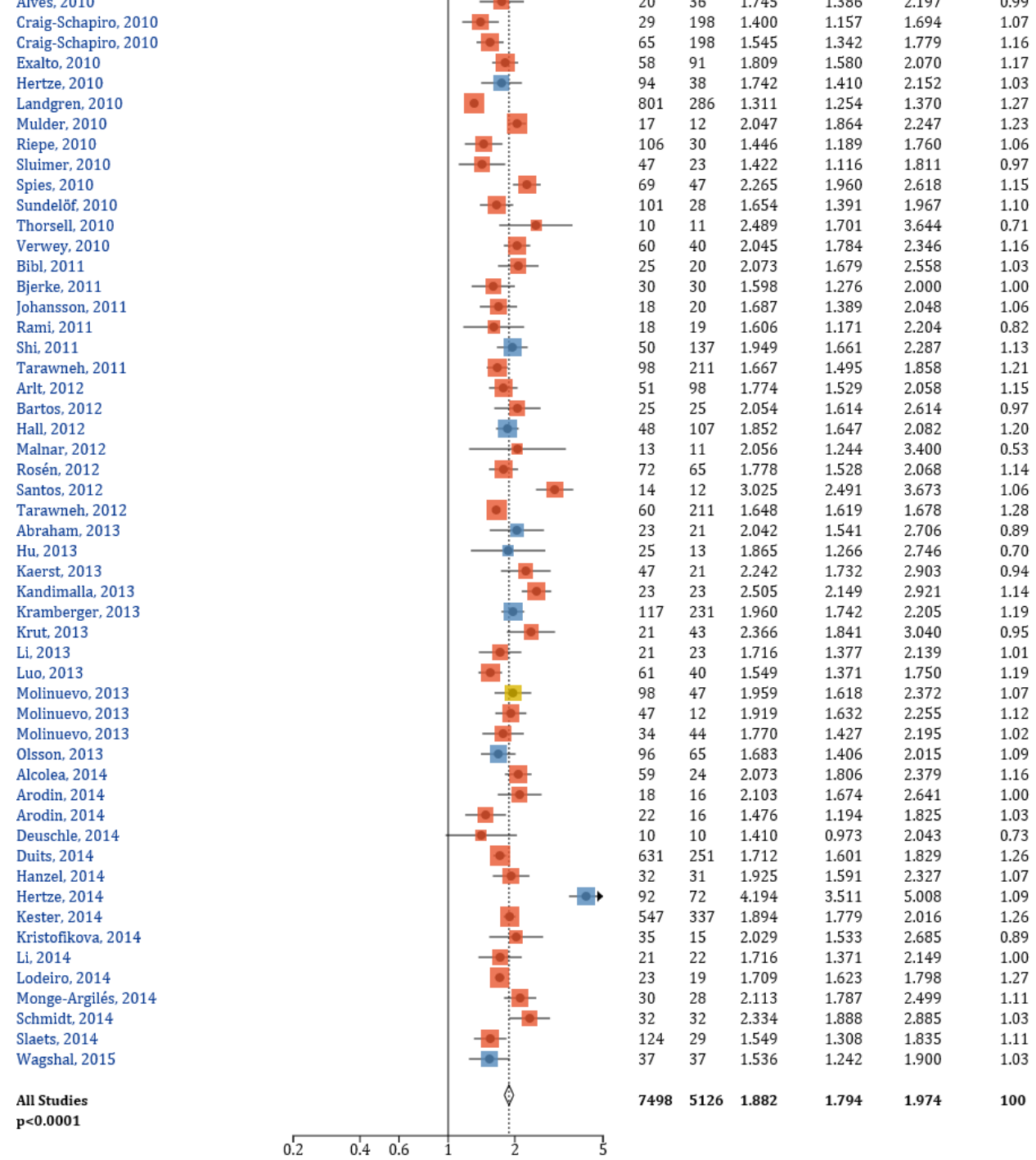
Rabe C *et al*., under review

Diagnosing amyloid pathology with a blood test: are we there yet?

Group level enrichment/screening: Yes

Individual diagnostics: No, or maybe, but with great caution

T = tau pathology



Alves, 2010	20	36	1.745	1.386	2.197	0.99
Craig-Schapiro, 2010	29	198	1.400	1.157	1.694	1.07
Craig-Schapiro, 2010	65	198	1.545	1.342	1.779	1.16
Exalto, 2010	58	91	1.809	1.580	2.070	1.17
Hertze, 2010	94	38	1.742	1.410	2.152	1.03
Landgren, 2010	801	286	1.311	1.254	1.370	1.27
Mulder, 2010	17	12	2.047	1.864	2.247	1.23
Riepe, 2010	106	30	1.446	1.189	1.760	1.06
Sluimer, 2010	47	23	1.422	1.116	1.811	0.97
Spies, 2010	69	47	2.265	1.960	2.618	1.15
Sundelöf, 2010	101	28	1.654	1.391	1.967	1.10
Thorsell, 2010	10	11	2.489	1.701	3.644	0.71
Verwey, 2010	60	40	2.045	1.784	2.346	1.16
Bibl, 2011	25	20	2.073	1.679	2.558	1.03
Bjerke, 2011	30	30	1.598	1.276	2.000	1.00
Johansson, 2011	18	20	1.687	1.389	2.048	1.06
Rami, 2011	18	19	1.606	1.171	2.204	0.82
Shi, 2011	50	137	1.949	1.661	2.287	1.13
Tarawneh, 2011	98	211	1.667	1.495	1.858	1.21
Arlt, 2012	51	98	1.774	1.529	2.058	1.15
Bartos, 2012	25	25	2.054	1.614	2.614	0.97
Hall, 2012	48	107	1.852	1.647	2.082	1.20
Malnar, 2012	13	11	2.056	1.244	3.400	0.53
Rosén, 2012	72	65	1.778	1.528	2.068	1.14
Santos, 2012	14	12	3.025	2.491	3.673	1.06
Tarawneh, 2012	60	211	1.648	1.619	1.678	1.28
Abraham, 2013	23	21	2.042	1.541	2.706	0.89
Hu, 2013	25	13	1.865	1.266	2.746	0.70
Kaerst, 2013	47	21	2.242	1.732	2.903	0.94
Kandimalla, 2013	23	23	2.505	2.149	2.921	1.14
Kramberger, 2013	117	231	1.960	1.742	2.205	1.19
Krut, 2013	21	43	2.366	1.841	3.040	0.95
Li, 2013	21	23	1.716	1.377	2.139	1.01
Luo, 2013	61	40	1.549	1.371	1.750	1.19
Molinuevo, 2013	98	47	1.959	1.618	2.372	1.07
Molinuevo, 2013	47	12	1.919	1.632	2.255	1.12
Molinuevo, 2013	34	44	1.770	1.427	2.195	1.02
Olsson, 2013	96	65	1.683	1.406	2.015	1.09
Alcolea, 2014	59	24	2.073	1.806	2.379	1.16
Arodin, 2014	18	16	2.103	1.674	2.641	1.00
Arodin, 2014	22	16	1.476	1.194	1.825	1.03
Deuschle, 2014	10	10	1.410	0.973	2.043	0.73
Duits, 2014	631	251	1.712	1.601	1.829	1.26
Hanzel, 2014	32	31	1.925	1.591	2.327	1.07
Hertze, 2014	92	72	4.194	3.511	5.008	1.09
Kester, 2014	547	337	1.894	1.779	2.016	1.26
Kristofikova, 2014	35	15	2.029	1.533	2.685	0.89
Li, 2014	21	22	1.716	1.371	2.149	1.00
Lodeiro, 2014	23	19	1.709	1.623	1.798	1.27
Monge-Argilés, 2014	30	28	2.113	1.787	2.499	1.11
Schmidt, 2014	32	32	2.334	1.888	2.885	1.03
Slaets, 2014	124	29	1.549	1.308	1.835	1.11
Wagshal, 2015	37	37	1.536	1.242	1.900	1.03
All Studies	**7498**	**5126**	**1.882**	**1.794**	**1.974**	**100**

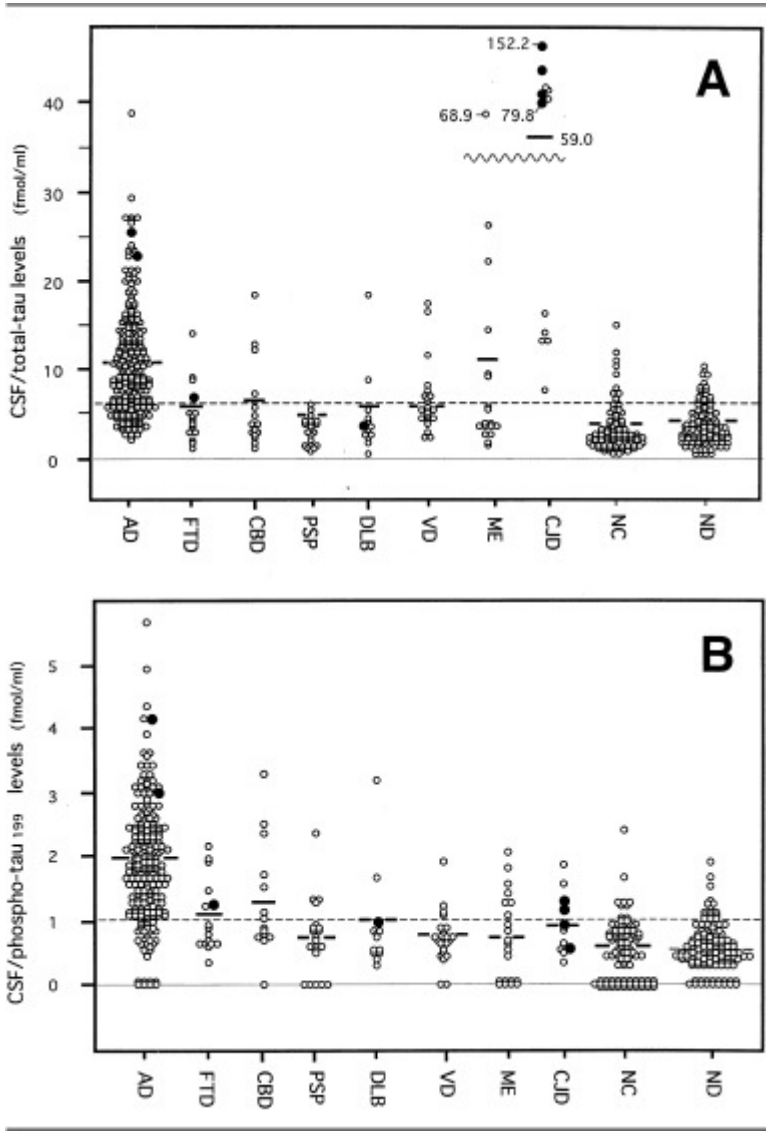
p<0.0001

0.2 0.4 0.6 1 2 5

CSF P-tau is increased in AD

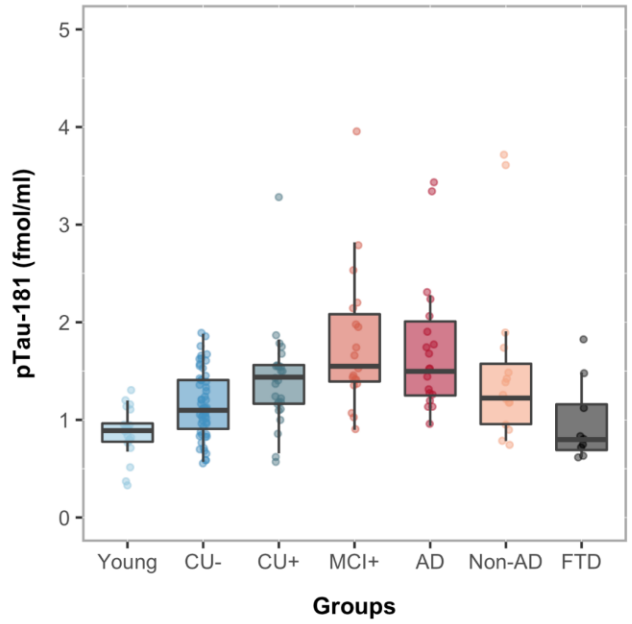
AlzBiomarker Database

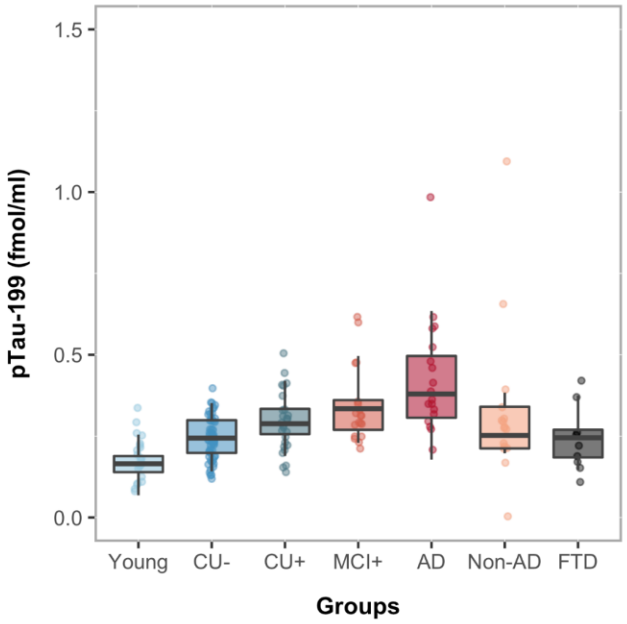
CSF P-tau increase only in AD, not in (most) other neurodegenerative diseases

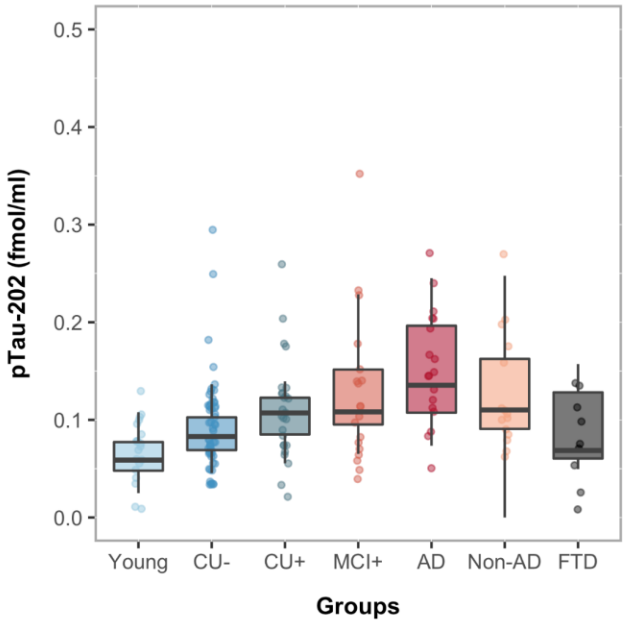


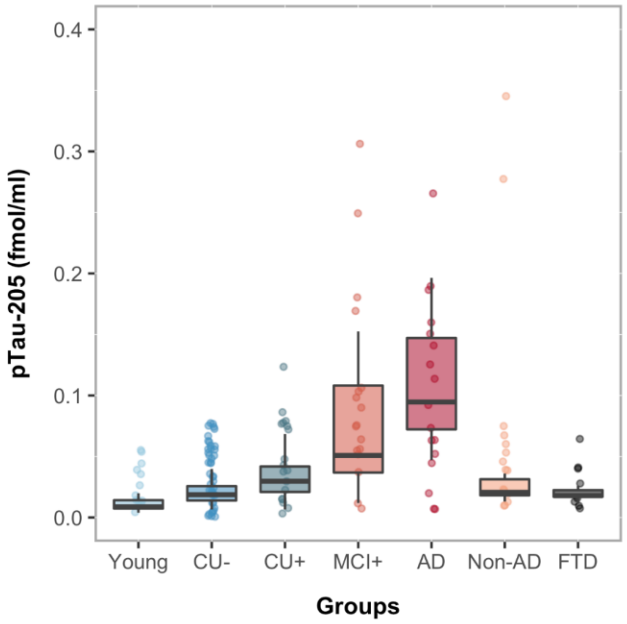
Itoh *et al*., Ann Neurol 2001

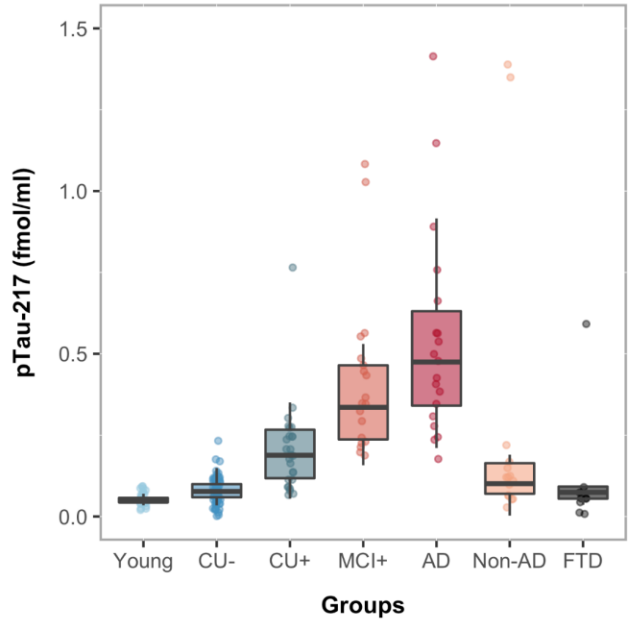
Differential detection of AD measuring different phospho-forms of tau in CSF

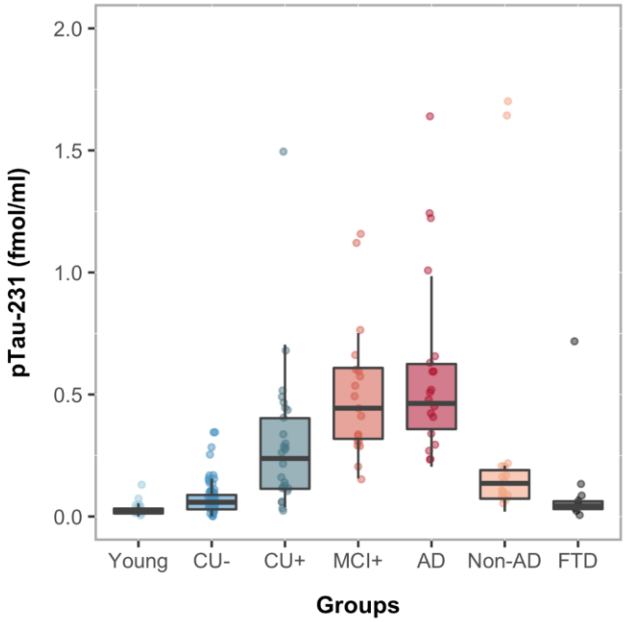


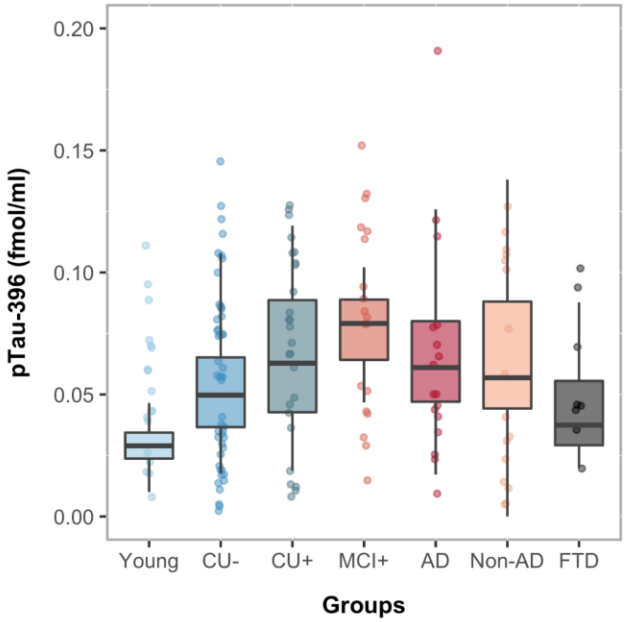


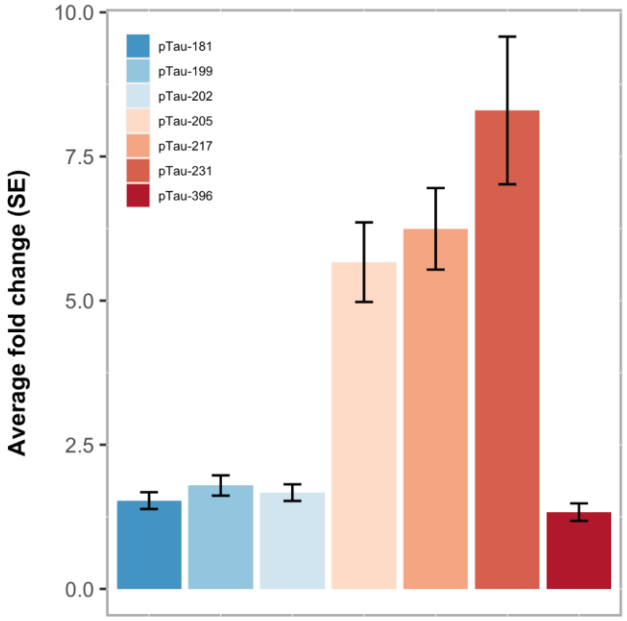






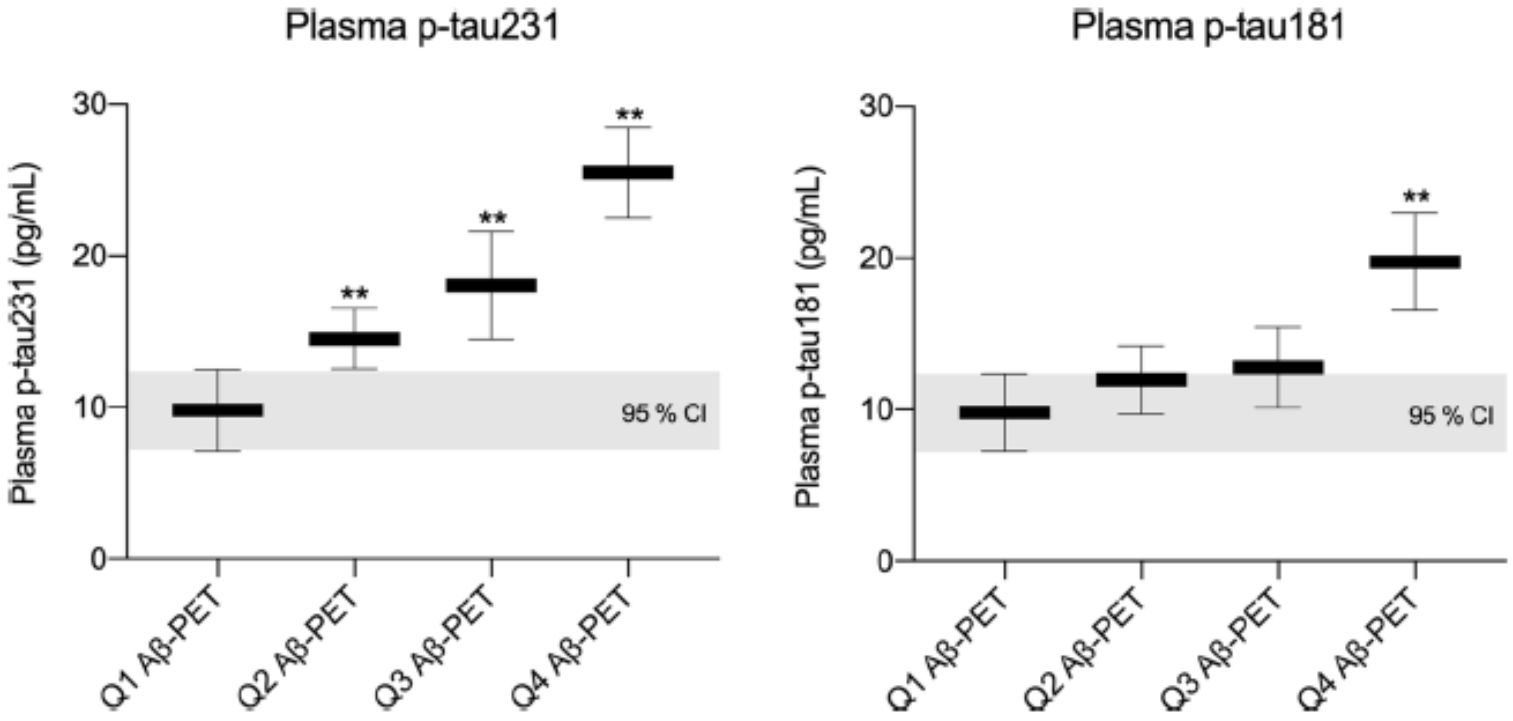






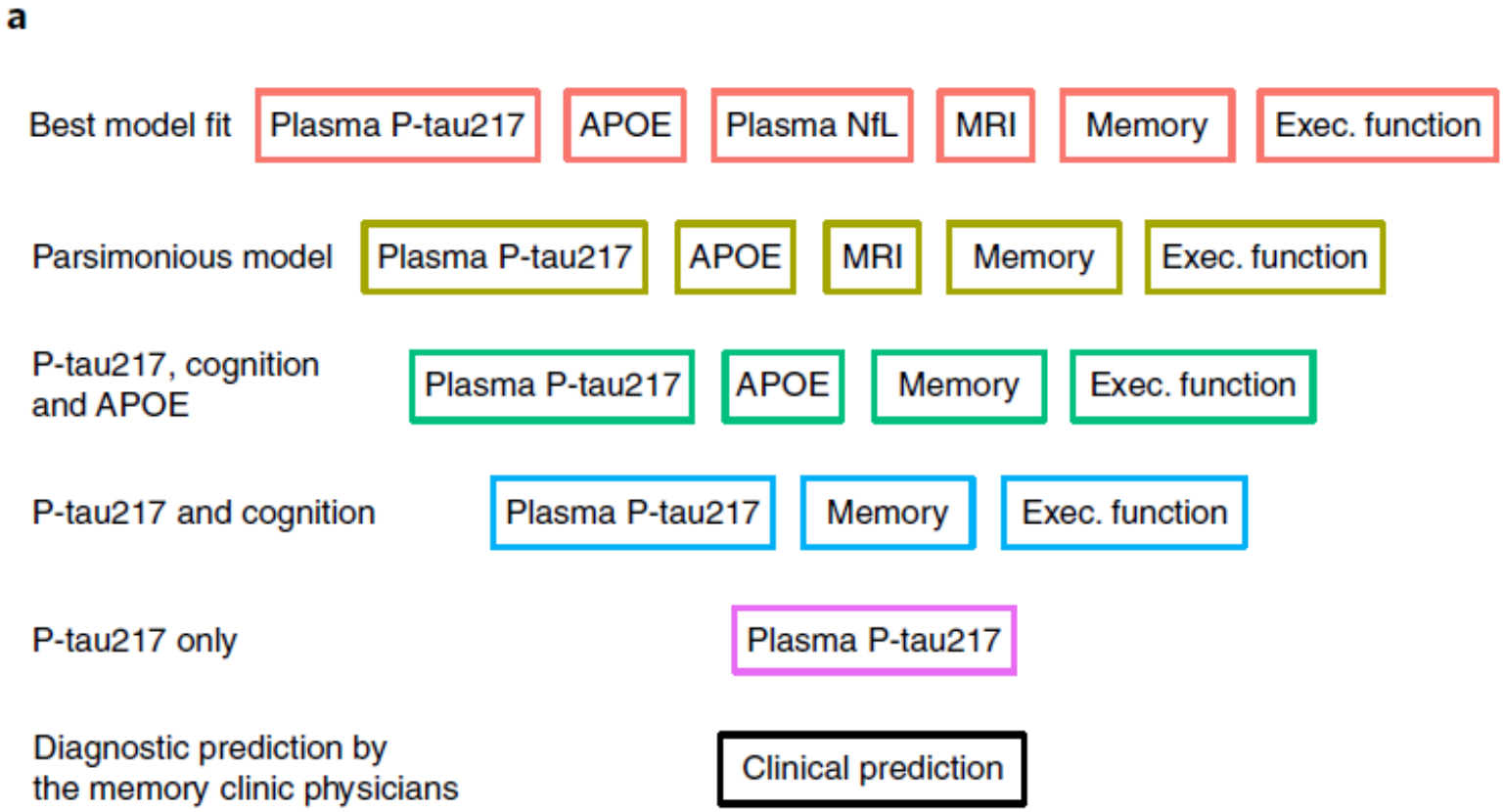
Benedet, Gobom *et al.*, unpublished

Different phospho-forms of tau can be measured in plasma



Ashton *et al*., Acta Neuropathol. 2021

Plasma tests as clinical tools to predict AD-type dementia in patients with subjective or mild cognitive impairment

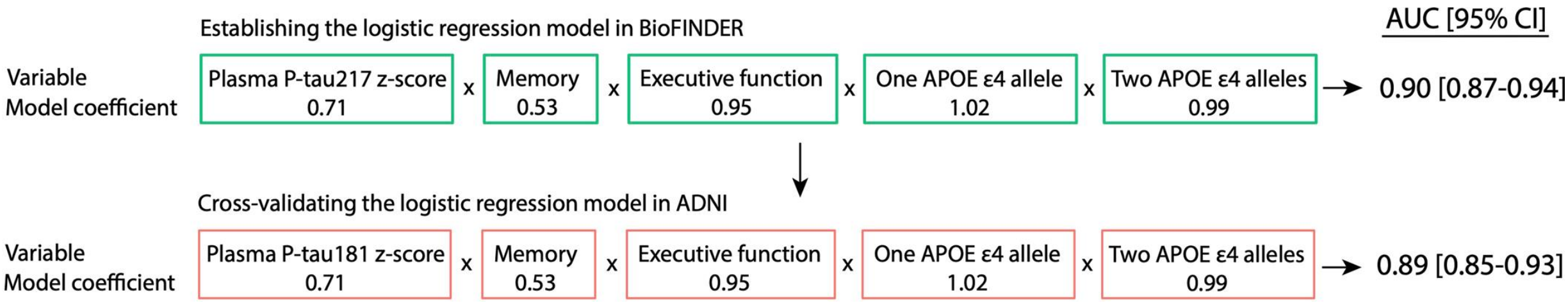


	AUC (95% CI)	AIC
Best model fit	0.92 (0.89–0.95)**	159
Parsimonious model	0.92 (0.88–0.95)**	161
P-tau217, cognition and APOE	0.90 (0.86–0.94)**	166
P-tau217 and cognition	0.89 (0.84–0.93)**	171
P-tau217 only	0.81 (0.75–0.87)*	207
Diagnostic prediction by the memory clinic physicians	0.72 (0.65–0.78)	228

*$P < 0.05$; **$P < 0.001$ vs the clinical prediction

Palmqvist *et al*., Nature Med. 2021

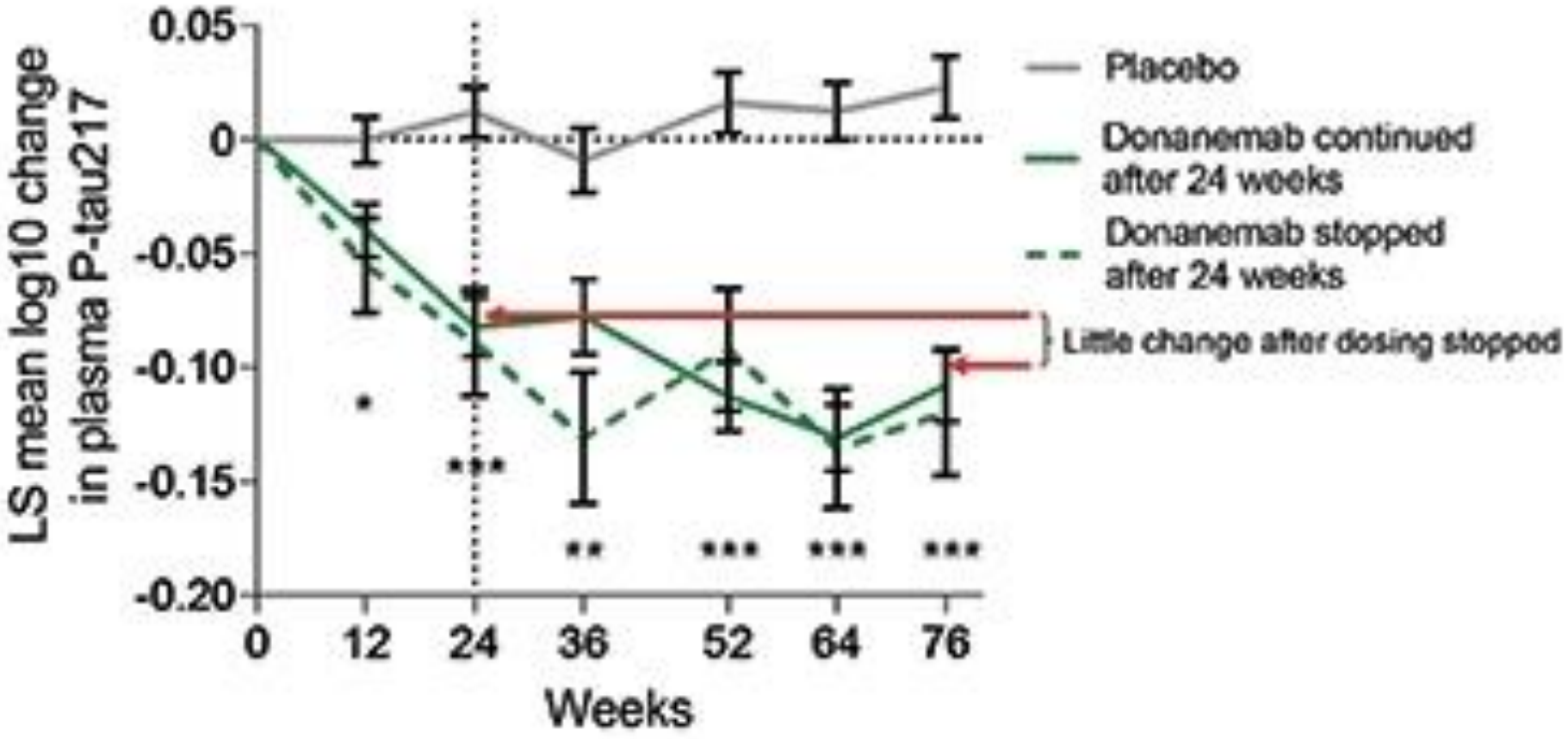
Establishing a cross-validated model



http://predictAD.app

Palmqvist *et al*., Nature Med. 2021

Donanemab lowers plasma P-tau217



Eli Lilly, unpublished

Aducanumab lowers plasma P-tau181

TABLE 1. REDUCTIONS IN PHOSPHORYLATED TAU-181 WITH ADUCANUMAB TREATMENT VS PLACEBO			
	Aducanumab[a]	Placebo	*P* Value
EMERGE (NCT02484547)	-13%	+8%	$P<0.001$
ENGAGE (NCT02477800)	-16%	+9%	$P<0.001$
[a] Values are with the higher of 2 doses used in the EMERGE and ENGAGE trials.			

Hansson O *et al*., unpublished

Diagnosing AD-type tau pathophysiology with a blood test: are we there yet?

Group level enrichment/screening: Yes

Individual diagnostics: Yes, at least we are getting there

Thanks!!

henrik.zetterberg@gu.se
h.zetterberg@ucl.ac.uk

Lesley Inker

Professor of Medicine

Tufts University School of Medicine

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

GFR Decline as a Surrogate Endpoint for Progression of CKD

Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoint

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

May 25 2022

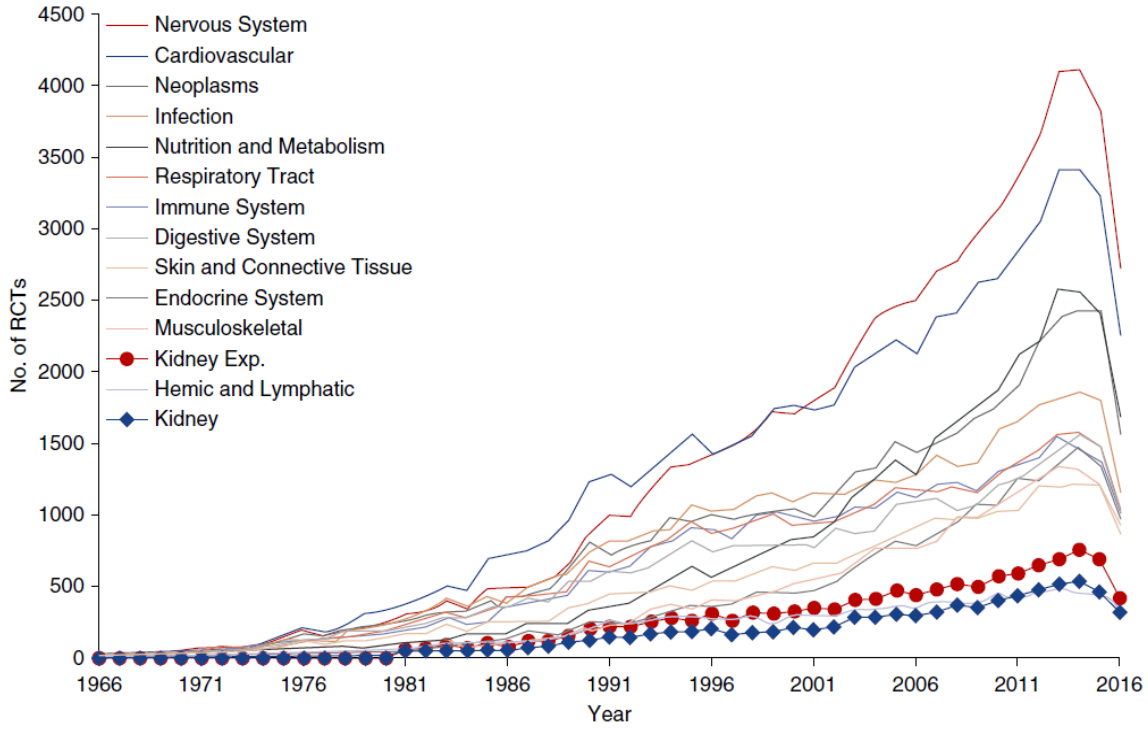
Lesley A Inker MD, MS
Co-Director, Chronic Kidney Disease-Epidemiology Collaboration
Tufts Medical Center &Tufts University School of Medicine, Boston MA

Background

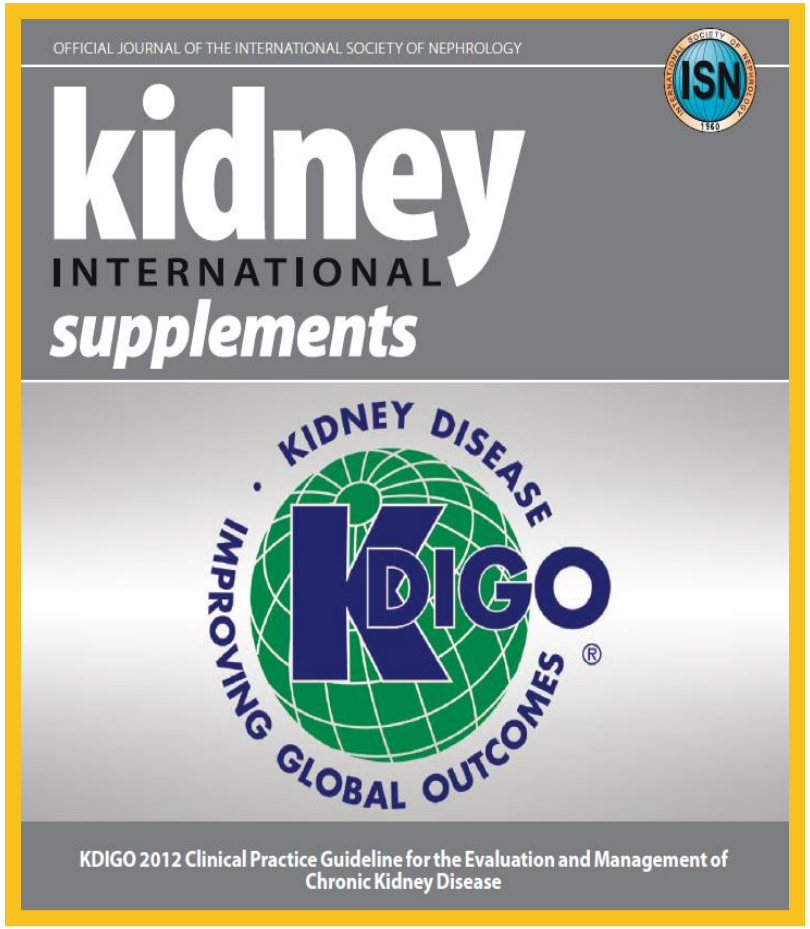
- Kidney disease is slowly progressive
- Clinical trials to evaluate treatments to prevent or slow the progression to kidney failure require long duration of follow-up, leading to expensive and complex trials, or highly selected subset of participants
- Doubting of serum creatinine (57% decline in GFR) is accepted by regulators but still occurs late in disease course
- These challenges have likely contributed to the paucity of therapies to treat CKD

Number of RCT in kidney related domains compared to other medical fields

Kriakos et al JASN 2019.



GFR slope and albuminuria are the two central biomarkers in CKD



Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

CKD-EPI Investigations of Surrogate Endpoints for Trials in CKD Progression

NIH U01 CKD-EPI includes evaluation of urine protein as surrogate

NKF-FDA Workshop May 2008 on UP

NKF-FDA Workshop December 2012 Lesser Decline in GFR

NKF-FDA-EMA Workshop March 2018 GFR Slope and UACR

CKD-EPI CT Funding in partnership with NKF and sponsors

Data identification, acquisition and cleaning; analyses; method development

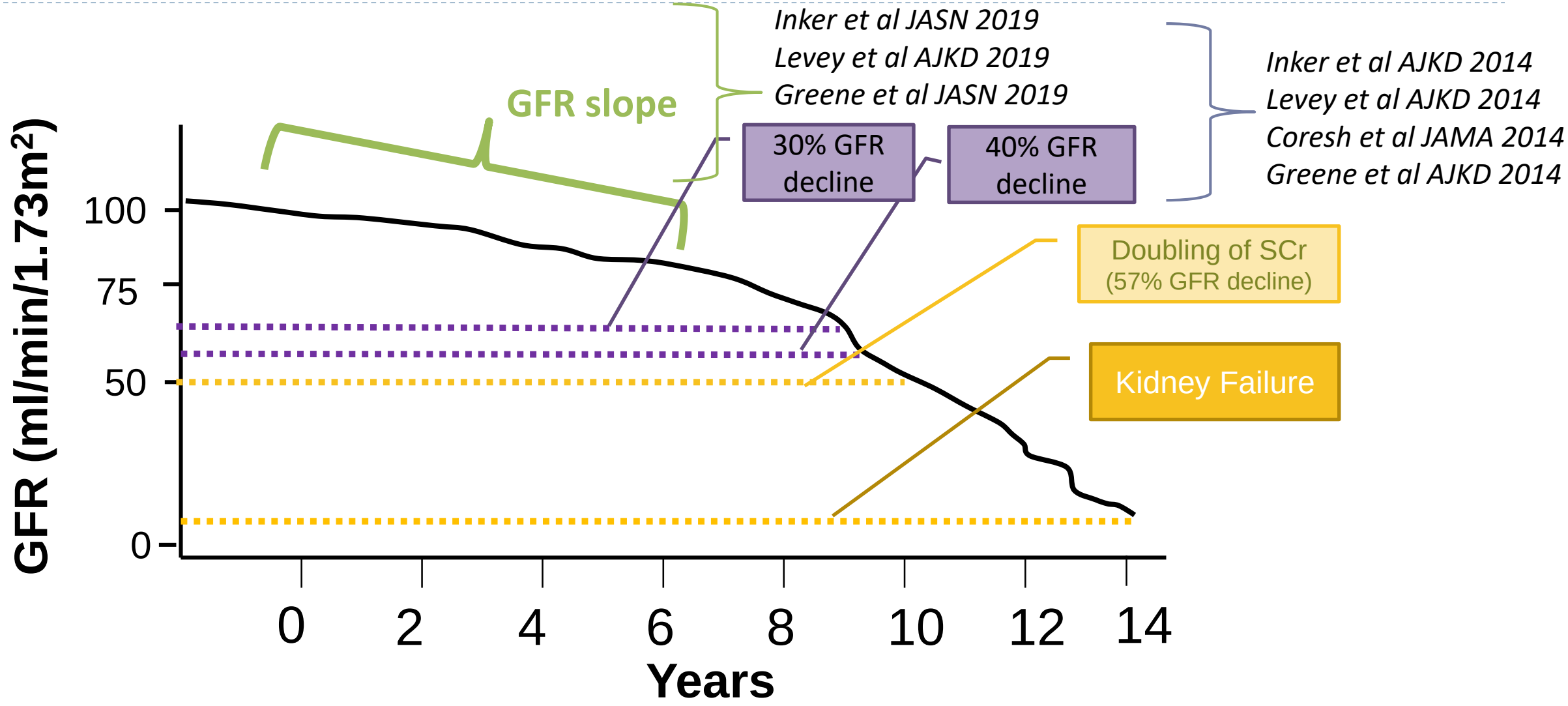
Updated literature search; refined methods

Continual literature updates; Enhanced method development

2003 2008 2012 2016 2018 2020 2022

UP, urine protein; GFR, glomerular filtration rate; UACR urine albumin to creatinine ratio; NKF, National Kidney Foundation

Use of GFR slope as surrogate endpoint



Use of GFR slope as surrogate endpoint

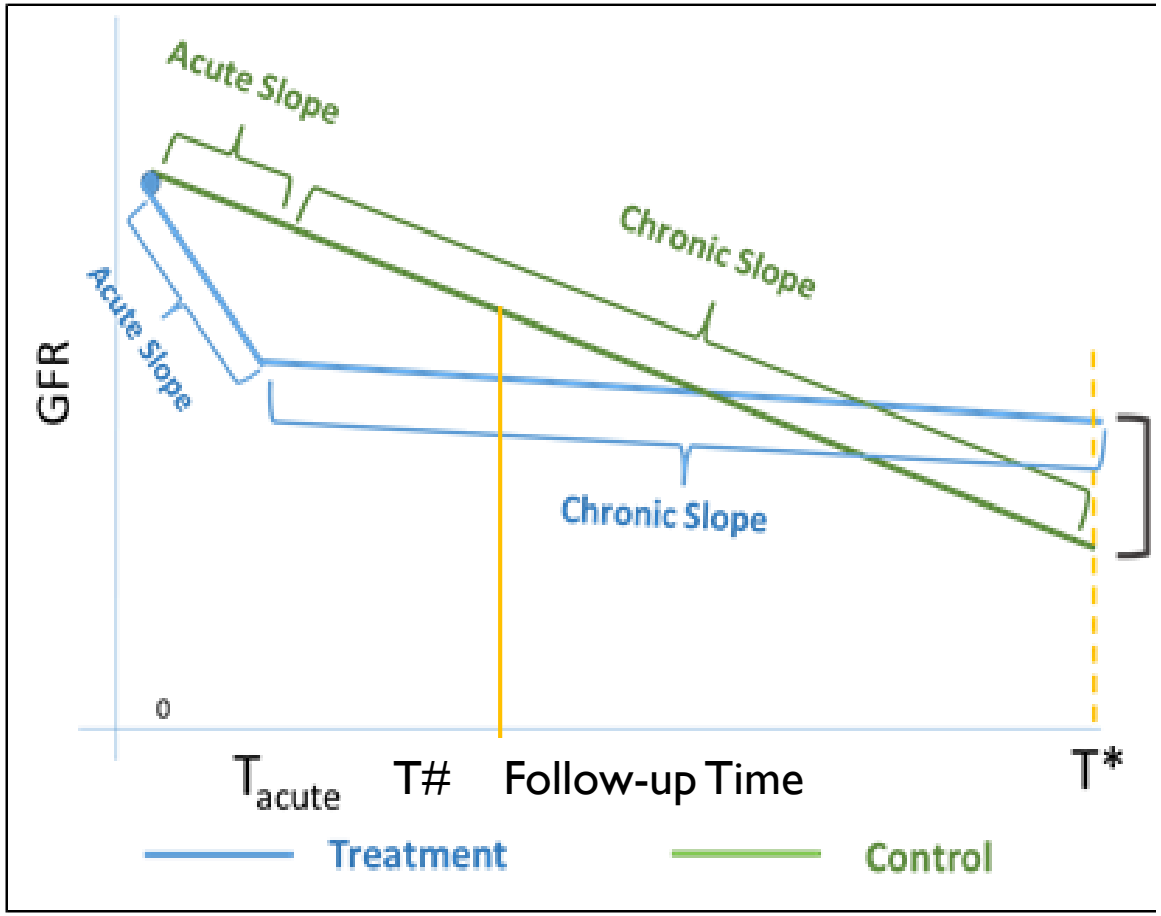
Advantages

- Regardless of cause
  - Decreased GFR defines CKD
  - Level of GFR indicates severity
  - GFR decline is the definition of progression, for all causes
- Compared to time to event
  - Increased power
  - Includes fast and slow progressors
  - Includes patients who have GFR decline that might lead to endpoint even after the end of the trial

Limitations/complications

- eGFR can reflect GFR as well as non GFR determinants
- Nonlinearity
- Heterogeneity
- Informative censoring
- Acute effects

Challenge of acute effects in GFR slope



GFR= N X SNGFR

Control arm
Declining N (number of nephrons)
Stable SNGFR (single-nephron GFR)

Treatment arm
short-term - ↓SNGFR, no change in N
long-term - stable SNGFR, slower decline in N

T, Time
SNGFR, single nephron GFR

Chaudhari and Inker, Current Opinion in Nephrology 2020

Models for computation of GFR Slope

- **Goal:** Provide a set of models that accommodate the range of circumstances expected in trials of CKD progression
- **Linearity:** In general, reasonable assumption that moderate deviations from linearity in the chronic phase do not effect overall slope estimates in trials that are relatively short in duration
- **2-slope model** to allow for acute treatment effect on GFR that differs from chronic slope

Vonesh E, Tighiouart H, Ying J et al Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. Stats in Medicine 2019

GFR slope model parameters

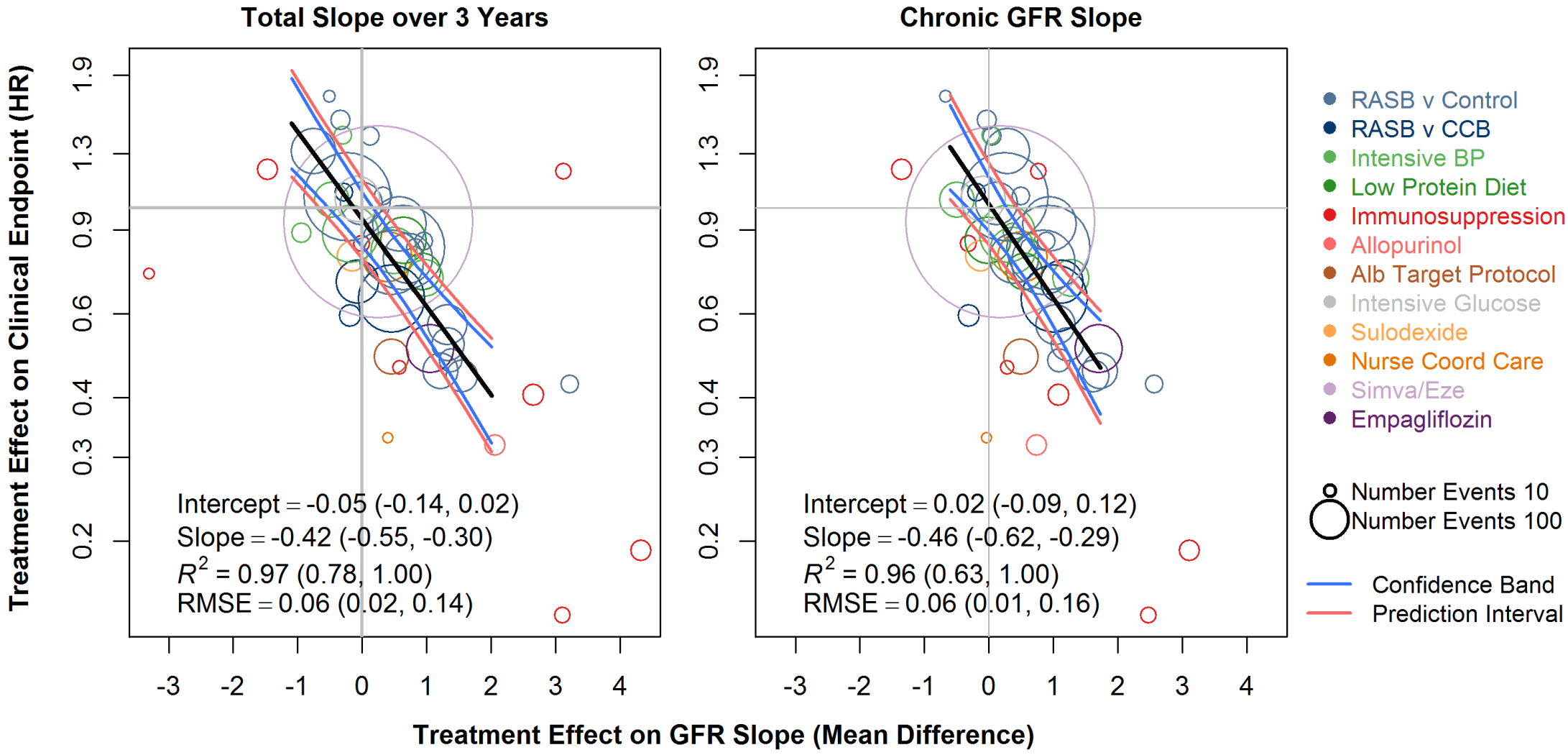
- **Informative censoring:** For studies with > 15 ESRD/Death events, used shared parameter models with Weibull survival times
- **Heterogeneity**
  - **Between subject:** Random slopes and intercepts
  - **Within subject:** Power of the means model to allow greater variability at higher GFR
  - **Treatment effect:** Allowed different slope variance in each group to accommodate non-uniform treatment effects
- **Model Selection**
  - Automated algorithm used to select first the most complicated model (shared parameter and all of heterogeneity components), followed by models that did not have one or more of the parameters

Vonesh E, Tighiouart H, Ying J et al Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. Stats in Medicine 2019

Trial Level Analyses: evaluate the association between treatment effects on GFR slope to that of the clinical endpoint across range of RCT's

- Individual patient meta-regression
  - Consistent definitions
  - Correlation between errors in the estimated treatment effects
- Within study analyses:
  - Estimated treatment effects on GFR slope: GFRslopeTreatment - GFR SlopeControl
  - Estimated treatment effects on the clinical endpoints – Cox models, expressed as HR
- Bayesian meta-regression to obtain
  - Estimate of regression line as summarized by slope, intercept, RMSE and R^2
  - Prediction intervals for HR on the clinical endpoints for future trial over a range of the treatment effect on the mean difference in GFR slopes

Trial-level analyses for the association of treatment effects on 3 year-total slope and chronic slope vs treatment effects on the clinical endpoint



Inker L, Heerspink H, Tighioart H et al GFR Slope as a Surrogate End Point for CKD Progression JASN 2019

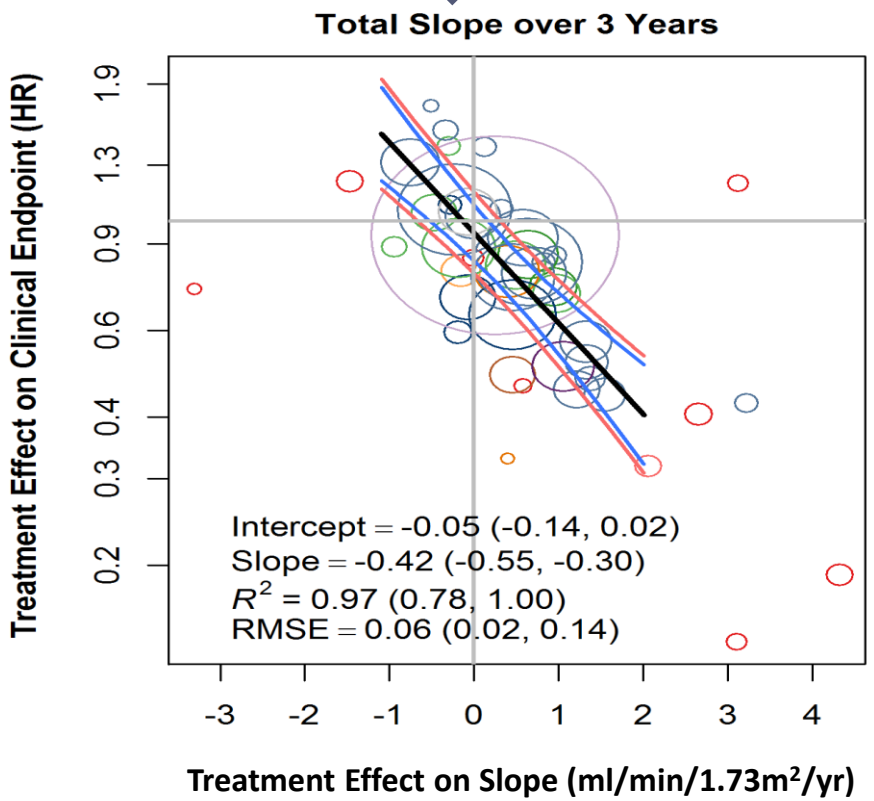
Applying Trial Level Analyses to a New RCT

Trial Level Analysis in Previous RCTs

- Characterizes "causal association" between ITT-based estimates of treatment effects on surrogate & clinical endpoints

Application in New RCT

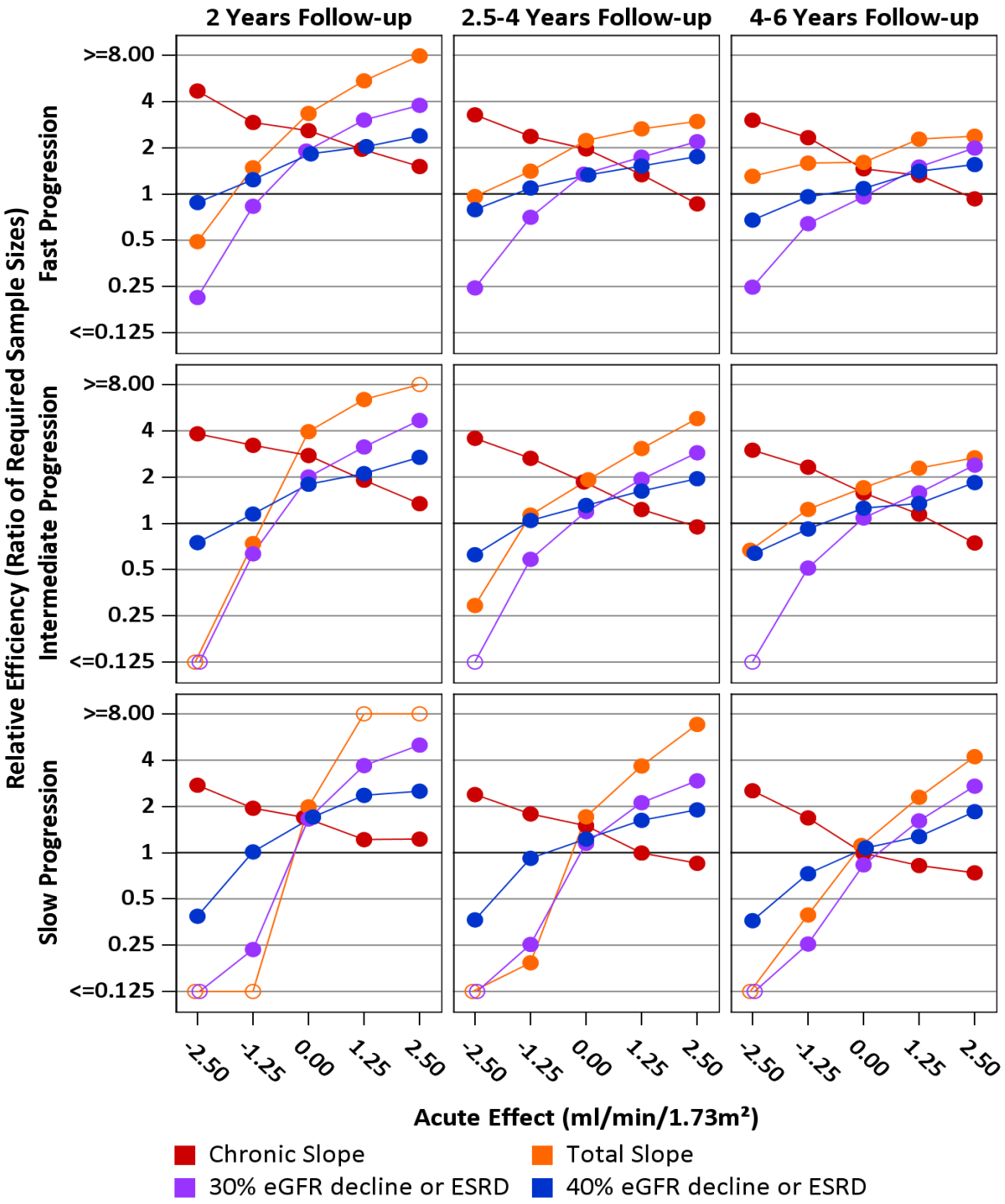
- Convert estimated treatment effect on surrogate(s) to probability of clinical benefit for newly tested intervention



Converting Treatment Effect on 3-Yr Total Slope to Probability of Clinical Benefit

Estimated Effect on GFR Slope (ml/min/1.73m²/yr)	**Large RCT**		**Moderate RCT**	
	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV
0.5	0.77 (0.59, 0.99)	0.98	0.77 (0.53, 1.11)	0.93
0.75	0.69 (0.52, 0.89)	>0.99	0.69 (0.47, 1.00)	0.98
1.0	0.62 (0.47, 0.80)	>0.99	0.62 (0.42, 0.90)	>0.99
Threshold for effect on GFR slope to confer PPV ≥ 97.5	**0.48**		**0.74**	

Inker L, Heerspink H, Tighioart H et al
GFR Slope as a Surrogate End Point for CKD Progression JASN 2019



- Use of total slope instead of the clinical endpoint allows reduction in follow-up from 4-6 years to 2 years while improving efficiency by 17% to 64% (~sample size savings of 14% to 39%)

- Relative gains in power for slope analysis increase when baseline GFR is higher.

- Acute effect is critical consideration in selection of total vs chronic slope vs endpoint

Greene, Ying et al JASN 2019

Next steps/current work

- Update set of studies to account for well powered studies across more interventions

- Methods work on
  - Acute effects
  - Subgroups/interactions

- Joint models to combine slope with albuminuria as can be used in Phase II studies with shorter follow-up

Summary

- Empirical data supports use of GFR decline as surrogate endpoints in RCTs evaluating therapies in CKD

- When applying these data to the design of a future trial, the most appropriate endpoint for the new trial needs to be considered in the context of the trial phase, specific population, treatment, and design.

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

National Kidney Foundation®

Andy Levey, Tom Greene and Josef Coresh

March 2018 CKD-EPI, CKD-PC, EMA, FDA and NKF Teams

CKD-EPI CT Analytical Team

Co Directors: Tom Greene, Hiddo Heerspink
Tufts: Juhi Chaudhari Hocine Tighiouart Jonathan Miao
Utah: Ben Haaland, Jian Ying, Willem Hardie
Chicago: Ed Vonesh
Groningen: Neils Jong

Nicole Gormley

Acting Division Director

Division of Hematologic Malignancies

US Food and Drug Administration

USE OF SURROGATE ENDPOINTS IN ONCOLOGY

DUKE MARGOLIS WORKSHOP
MAY 25, 2022

Nicole Gormley, MD
Division Director
Division of Hematologic Malignancies II
U.S. Food and Drug Administration

Outline

- Regulatory Considerations for Biomarker Development
- pCR Example
- MRD in Multiple Myeloma
- Future Directions

Potential uses of Biomarkers

- Prognostic Biomarker
- Clinical Uses
  - Screening/Early Detection
  - Monitor for relapse
  - Guide therapeutic decisions
- Regulatory Uses
  - Patient Stratification
  - Patient Selection/Enrichment
  - Risk-based treatment assignment
  - Intermediate Endpoint or Surrogate Endpoint

Biomarker as an Endpoint

- Intermediate clinical endpoint
  - Can be measured earlier than morbidity or mortality, but reasonably likely to predict clinical benefit
- Surrogate endpoint reasonably likely to predict clinical benefit
- Surrogate Endpoint
  - Clinical validation that the marker predicts clinical benefit

Development of Endpoints for Regulatory Use: Validation as a Surrogate

- Prentice Criteria
  - The surrogate must be a correlate of the true clinical endpoint
  - The treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint
- Meta-analytical methods
  - Patient-level data
  - Allow for assessment of Individual Level and Trial Level Surrogacy
    - Individual Surrogacy- Correlation between candidate surrogate and true clinical endpoint on an individual level
    - Trial Level Surrogacy- Correlation between effect of treatment on the candidate surrogate and the effect of treatment on the true clinical endpoint
  - Surrogate Threshold Effect
    - Minimum treatment effect on the surrogate necessary to predict an effect on the true clinical endpoint

Buyse Nat Rev Oncol 2010
Sargent JCO 2015

Evidentiary Criteria

- Meta-analysis Considerations
  - Inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address uncertainties.
  - Inclusion of trials with a range of treatment effects (positive and negative trials) increases the accuracy and precision of trial level surrogacy assessment.
  - When designing a meta-analysis, consideration of MRD timing of assessment, missing data is important.
  - The trial populations and treatments included in the meta-analysis inform future applicability of the surrogate biomarker.

Buyse Biomet J 2016
Sargent Clinical Trials 2013

pCR Example

- Collaborative Trials in Neoadjuvant Breast Cancer
  - Conducted a pooled analysis of mature trials that had both pathologic complete response (pCR) and long-term outcome data
  - Objectives
    - Determine the association between pCR and EFS and OS
    - Determine the definition of pCR which best correlated with long-term outcomes
    - Identify breast cancer subtypes in which pCR best correlated with long-term outcome
    - Determine what magnitude of pCR improvement predicts long-term clinical benefit

Cortazar Ann Surg Oncol 2015

pCR Example

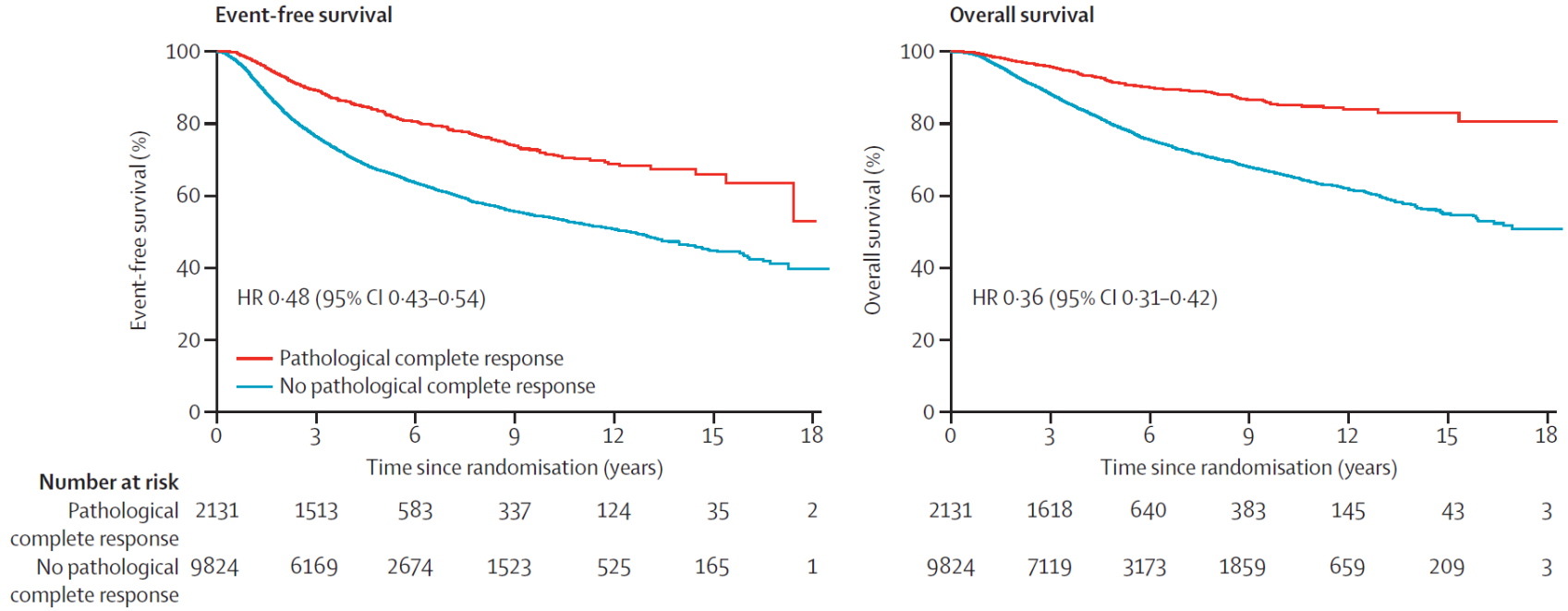
pCR Pooled Analysis Results

pCR definition	Event-free survival HR (95 % CI)	Overall survival HR (95 % CI)
ypT0 ypN0	0.44 (0.39–0.51)	0.36 (0.30–0.44)
ypT0/is ypN0	0.48 (0.43–0.54)	0.36 (0.31–0.42)
ypT0/is	0.60 (0.55–0.66)	0.51 (0.45–0.58)

Cortazar Ann Surg Oncol 2015

pCR Example

- Individual-Level Surrogacy



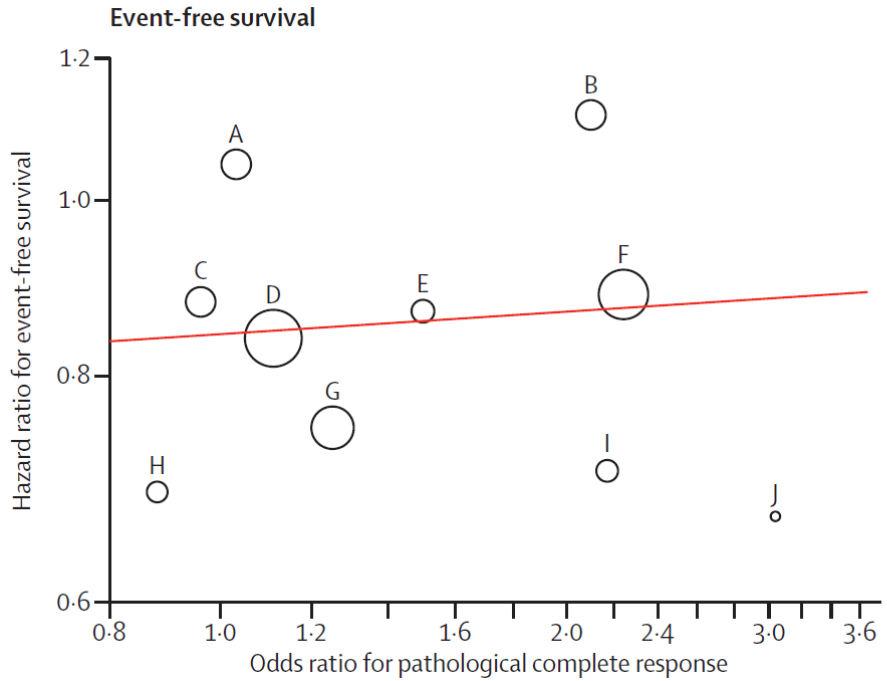
Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

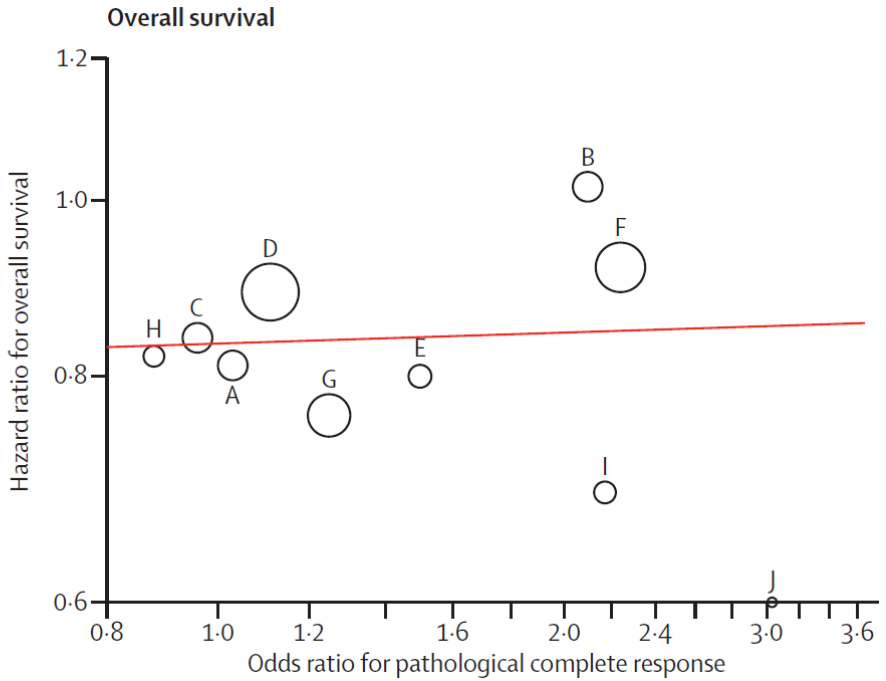
Cortazar Lancet 2014

pCR Example

- Trial-Level Surrogacy



R^2 0.03 (95%CI:0.00,0.25)



R^2 0.24 (95%CI:0.00,0.70)

Cortazar Lancet 2014

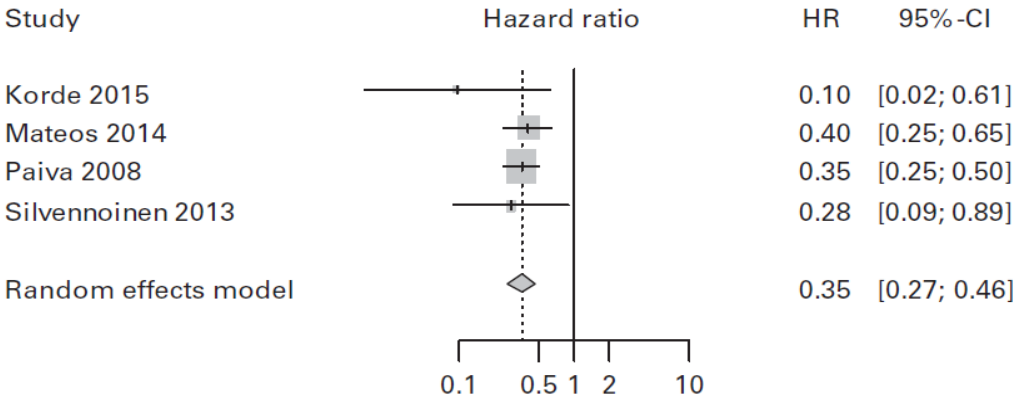
pCR Example

- CTNeoBC Summary
  - No pCR association with long-term outcomes (EFS and OS) at a trial level, only on an individual level
  - A standard definition that includes assessment of the nodes (ypT0ypN0 or ypT0/isypN0) should be used in future trials
  - Magnitude of pCR improvement that predicts long-term clinical benefit could not be established
    - Possibly due to heterogeneity of population, low pCR rates, lack of targeted therapies

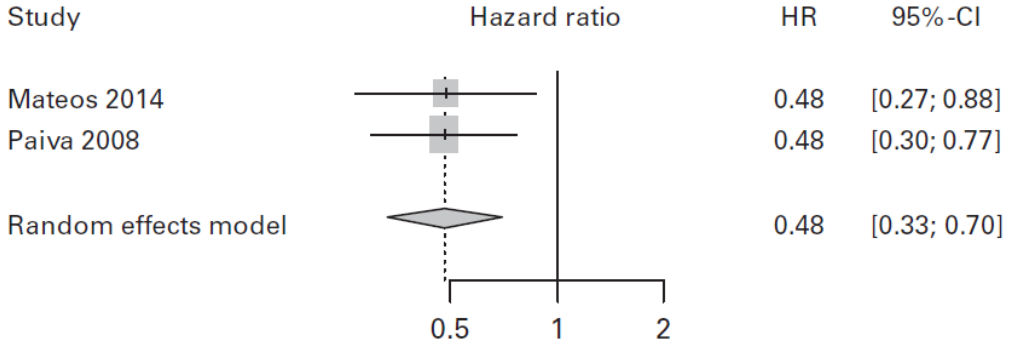
Cortazar Lancet 2014

MRD in MM Meta-analyses

Progression-Free Survival

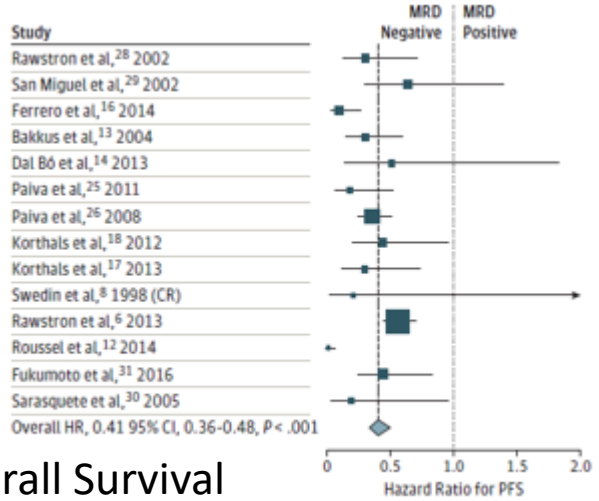


Overall Survival

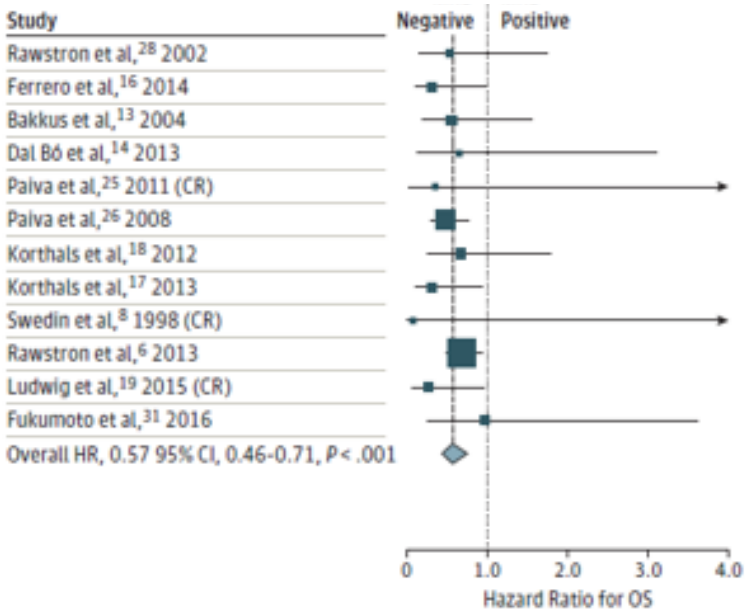


Landgren BMT 2016

Progression-Free Survival



Overall Survival



Munshi Jama Oncol 2016

MRD in MM Meta-analyses

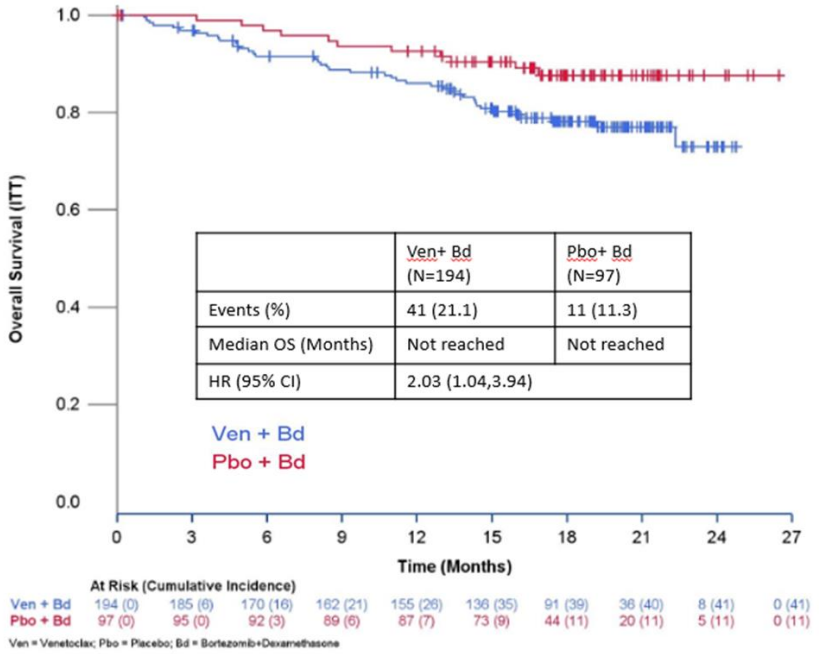
- Remaining Questions
  - Does MRD in MM have trial level surrogacy using individual patient level data?
  - What is the threshold that best correlates with clinical benefit?
  - What is the appropriate timing of assessment?
  - Does Sustained MRD better correlate with long-term outcomes?
  - Should MRD be assessed in those only in CR, VGPR, PR?

Gormley Jama Oncol 2016

BELLINI Trial: A Cautionary Tale

- Phase 3, double-blind, randomized, placebo-controlled trial of bortezomib and dexamethasone with or without venetoclax in patients with relapsed/refractory, multiple myeloma who had received 1-3 prior lines of therapy

	Venetoclax Arm	Placebo Arm
ORR	82.0% (75.8, 87.1)	68.0% (57.8, 77.1)
MRD negativity rate (10^{-5})	13.4% (8.9, 19.0)	1.0% (0.0, 5.6)
Median PFS (mos) (95% CI)	22.4 (15.3, NR)	11.5 (9.6, 15.0)
Hazard Ratio (95% CI)	0.63 (0.44, 0.90)	



https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

BELLINI Trial: A Cautionary Tale

Table. Progression-Free Survival, Overall Survival, and Clinical Response Rates.

	PFS HR (95% CI)	OS HR (95% CI)
All patients (N=291)	0.630 (0.443-0.897)	2.027 (1.042-3.945)
High-risk cytogenetics[a] (N=49)	1.206 (0.577-2.520)	NE
Standard-risk cytogenetics[b] (N=213)	0.544 (0.354-0.837)	1.505 (0.727-3.115)
t(11;14) (N=35)	0.110 (0.022-0.560)	0.343 (0.031-3.842)
BCL-2 high (N=140)	0.502 (0.294-0.856)	1.446 (0.568-3.678)
BCL-2 low (N=37)	1.387 (0.431-4.468)	NE

	All patients		t(11;14)		BCL-2 high	
	Ven (N=194)	**Pbo (N=97)**	**Ven (N=20)**	**Pbo (N=15)**	**Ven (N=93)**	**Pbo (N=47)**
ORR	82%	68%	90%	47%	86%	68%
≥CR	26%	5%	45%	7%	32%	4%
≥VGPR	59%	36%	70%	27%	68%	34%
uMRD	13%	1%	25%	0%	17%	2%

CI, confidence interval; CR, complete response; HR, hazard ratio; NE, not estimable due to no events in placebo; ORR, overall response rate; OS, overall survival; Pbo, placebo; PFS, progression-free survival; uMRD, undetectable minimal residual disease (10^{-5}); VGPR, very good or better partial response.

a. t(4;14), t(14;16), or del(17p)
b. No high-risk cytogenetics

Kumar. EHA Library. 2019 273254; LB2601

BELLINI Trial: A Cautionary Tale

- Concerning OS results
  - Need evaluation of endpoints that can be assessed at Early timepoints *and* Late timepoints that provide definitive evidence of clinical benefit
    - Bellini Trial showed divergent OS and ORR, PFS, MRD results
  - Additional Information is needed on MRD as an endpoint in MM

MRD Today and Future Considerations

- MRD results used to support accelerated approval in ALL
  - Blinatumomab approval in MRD-positive B-cell Precursor ALL
    - Accelerated approval based on MRD response rate and hematological relapse-free survival
- MRD results have been included in Prescribing Information in CLL
  - Venetoclax, Obinutuzumab
- MRD results have been included in the Prescribing Information in MM
  - Daratumumab, Abecma
  - Currently recommended as a secondary endpoint
- Ongoing efforts in various diseases to formally evaluate MRD

Conclusions

- Validated Endpoints are needed for Regular Approval
- pCR and MRD are not validated surrogate endpoints
- Existing uncertainty and remaining questions regarding these endpoints for regulatory purposes
- MRD, pCR and other biomarker assessments in clinical trials should be discussed with the Agency
- FDA is committed to working with the community on the development of biomarkers.

Thanks…

- Laleh Amiri- Kordestani
- Marc Theoret
- Julia Beaver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U.S. FOOD & DRUG
ADMINISTRATION

Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

Moderator:

- Norman Stockbridge, US Food and Drug Administration

Panelists:

- Steve Ryder, Rallybio Inc.
- Henrik Zetterberg, University of Gothenburg
- Lesley Inker, Tufts University
- Nicole Gormley, US Food and Drug Administration
- Aliza Thompson, US Food and Drug Administration
- Jeff Allen, Friends of Cancer Research

Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

Discussion Questions:

1. What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?
2. What characteristics and processes are shared by programs with a strong track record in evaluating candidate surrogates?
3. What more can be done to assist developers in validating candidate surrogates?
4. How can early involvement and communication with regulatory agencies support biomarker validation?

Break

We will be back momentarily.

The next panel will begin at 2:05 p.m. (U.S. Eastern Time)

Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

2:05 pm – 3:30 pm EST

Leslie Gordon

Medical Director and Co-Founder

Progeria Research Foundation

Hutchinson-Gilford Progeria Syndrome Case Study

Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

Translational Science in Drug Development:
Surrogate Endpoints, Biomarkers, and More
May 24, 25, 2022
Duke Margolis Center for Health Policy

Leslie B. Gordon, MD, PhD
The Progeria Research Foundation
Hasbro Children's Hospital & Alpert Medical School of Brown University
Boston Children's Hospital Boston and Harvard Medical School

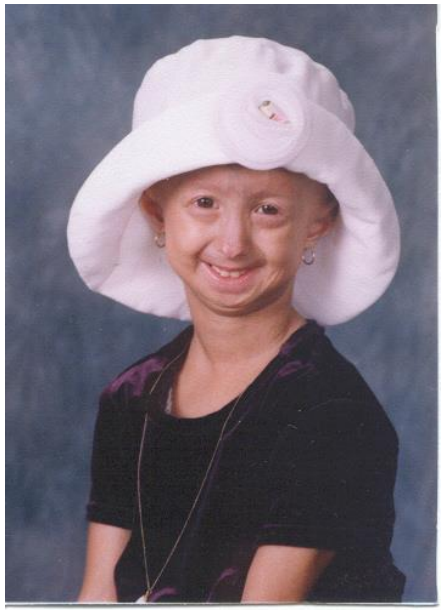
Faculty Disclosures, Leslie B. Gordon, MD, PhD

- Volunteer Medical Director, The Progeria Research Foundation
- In-kind donations: Receive medication for Progeria clinical trials from 3 drug companies (names not included at FDA's request) at no cost
- Sources of Funding for Research: The Progeria Research Foundation; FDA


CUTE
TO THE
RE

Progeria: An Ultrarare Fatal Premature Aging Disease

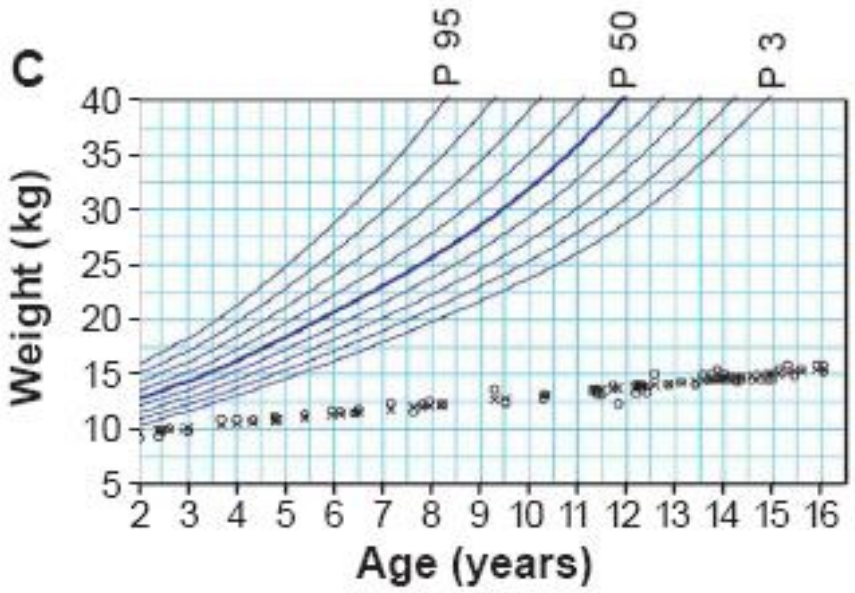


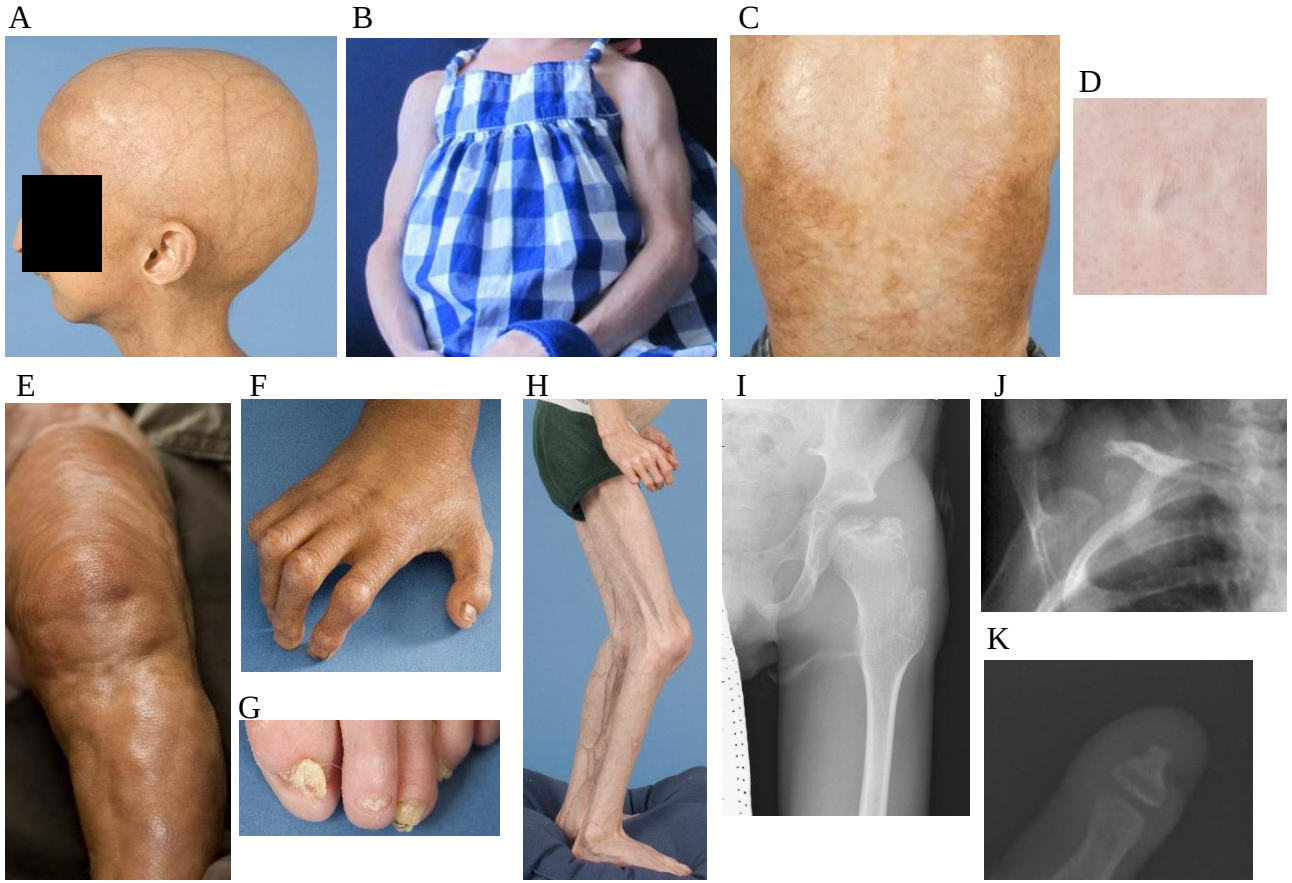



- Segmental “Premature Aging”
- Prevalence 1/20 million
- 19 children in US
- ~400 children worldwide

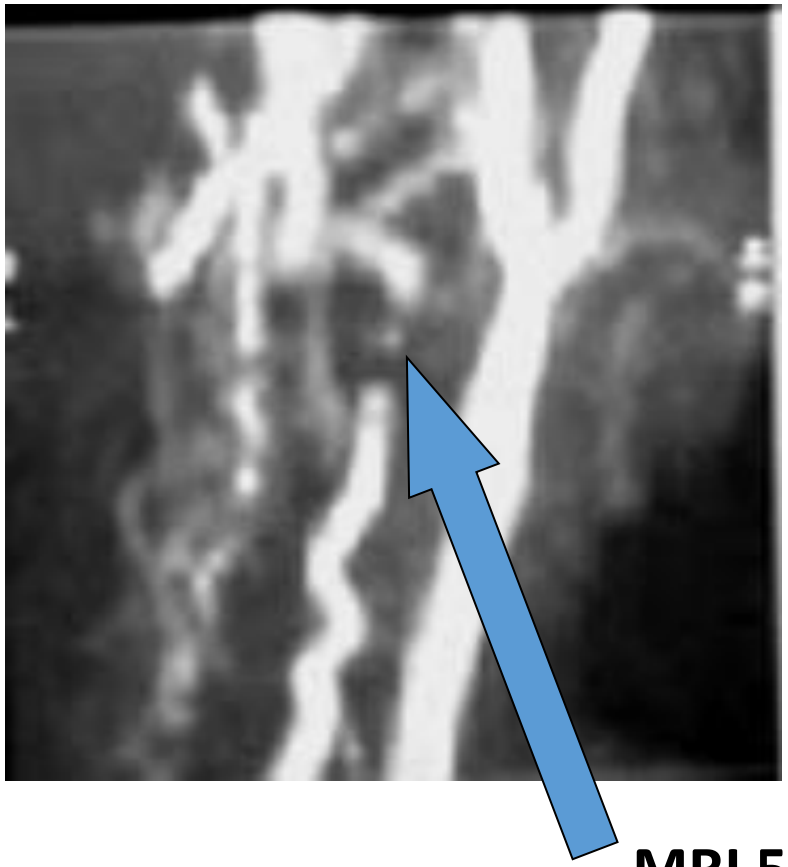
- Autosomal Dominant
- Lifespan Ave 14.5 yrs.
- Death due to premature atherosclerosis

Clinical Signs of HGPS





CV and Neurovascular Disease



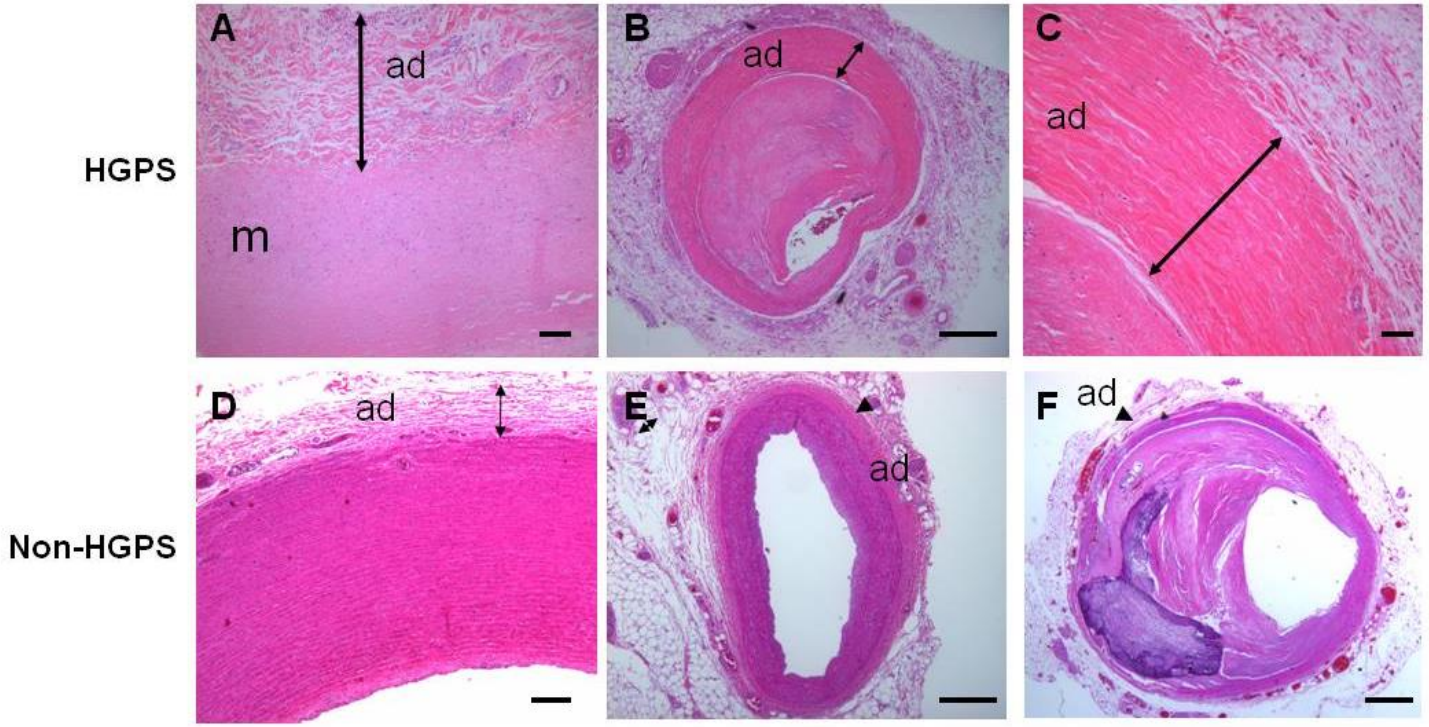
- **Global, Progressive**
- **Heart Failure, Strokes**

MRI 5 year old with carotid obstruction

Gordon et al,. Pediatrics 120(4): 834-841, 2007

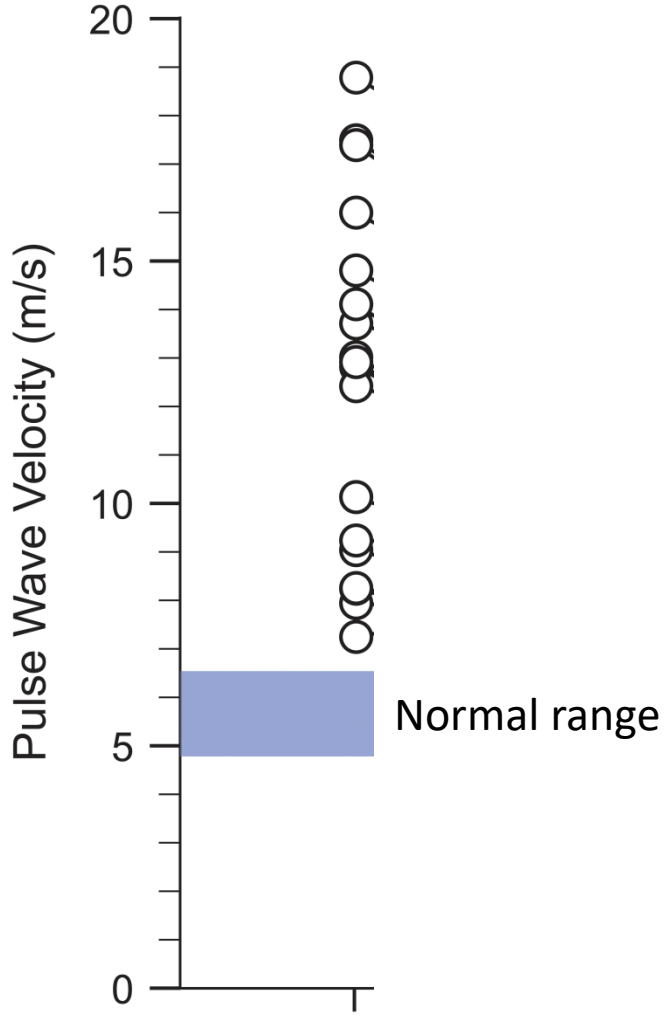
Human HGPS Vascular Disease

- Calcific Plaques
- Thick Fibrotic Adventitia
- Medial Cell Death with Extracellular Matrix Deposition

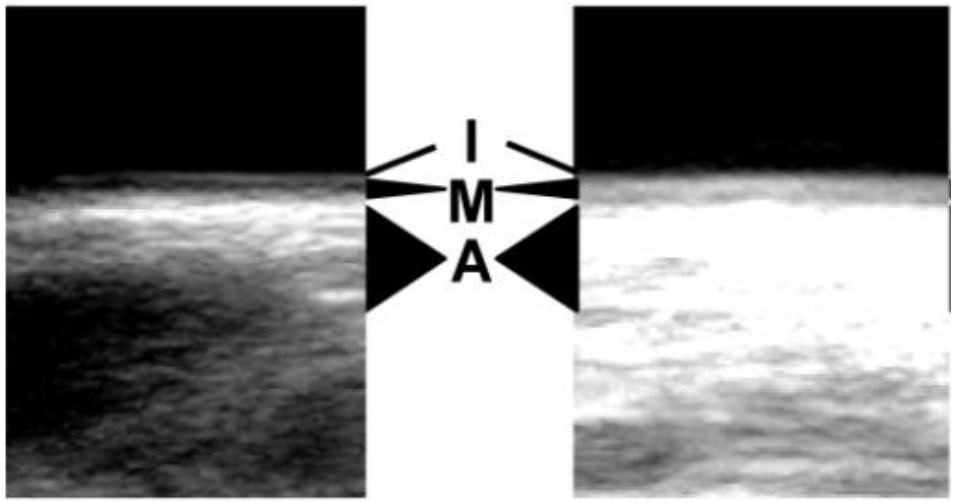


Olive et al, Hypertension, 2010

Assays Demonstrating Extremely Stiff Vessels In HGPS



Avg. PWV 3.5 x normal (40-60 y.o.)



Echodense Carotid Artery Wall

2003 Gene Discovery

letters to nature

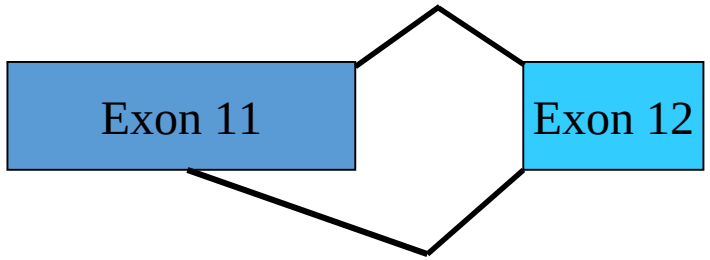
Recurrent *de novo* point mutations in lamin A cause Hutchinson–Gilford progeria syndrome

Maria Eriksson*, W. Ted Brown†, Leslie B. Gordon‡, Michael W. Glynn§, Joel Singer‖, Laura Scott‖, Michael R. Erdos*, Christiane M. Robbins*, Tracy Y. Moses*, Peter Berglund¶, Amalia Dutra*, Evgenia Pak*, Sandra Durkin§, Antonei B. Csoka#, Michael Boehnke‖, Thomas W. Glover§ & Francis S. Collins*

We were catapulted into a new phase…

HGPS is Caused by a Single Base Silent Mutation in the *LMNA* Gene (c.1824 C>T, G608G)

Mutation Optimizes *LMNA* Internal Splice Site



Mutant Splicing

150 bp deletion (50 aa)

“progerin”

Lamin A: Inner Nuclear Membrane Protein

- Lines the inner nuclear membrane-Scaffolding
- Binds chromatin to effect transcription
- Structural and signaling effects
- Expressed by Differentiated Cell Types
- Undergoes post-translational processing that is defective in HGPS due to 50 aa deletion
- Thus, progerin is short, permanently farnesylated and toxic to cells

Biology Leads The Way Towards Treatment Trials

Diagnostic Testing

↕

HGPS Progerin-producing Cells and Mouse Models

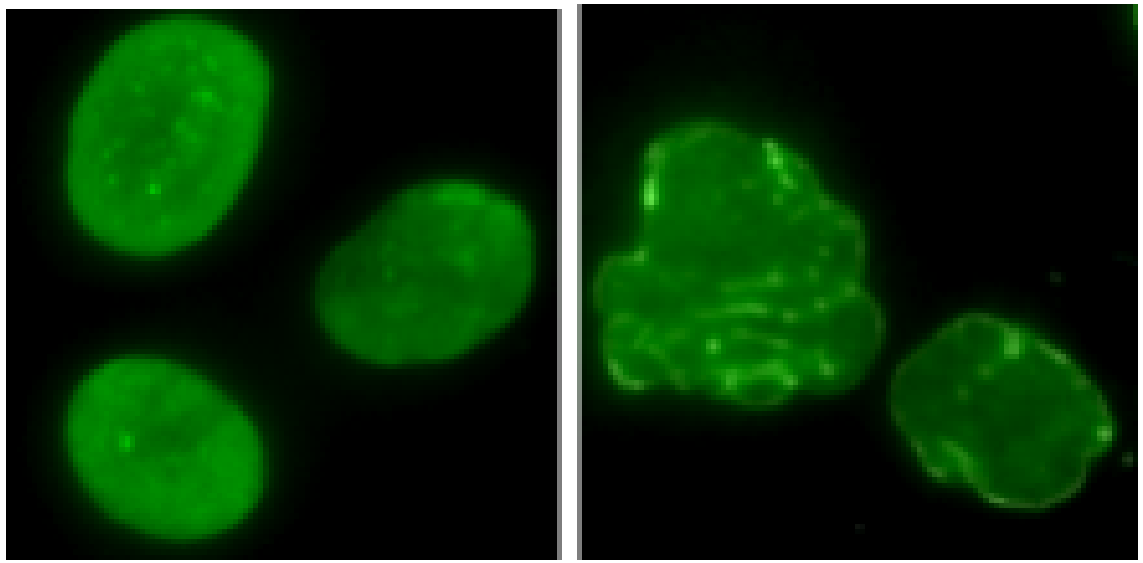
↕

Clinical Studies

↕

Clinical Trials

Progerin Causes Nuclear Blebbing In Cultured Cells
% Blebbed Cells Increases with Passage Number



Normal Fibroblast Nuclei

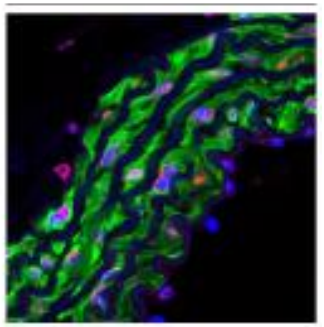
Progeria Fibroblast Nuclei

Human Progerin-Producing Mouse Models Created

- Human BAC Transgenic G608G Mouse Model

(Varga et al (Collins) PNAS 2006)

  - Mice Are Small,
  - Develop CVD but not plaques,
  - Die Early, cause of death unknown
  - Human Progerin Produced

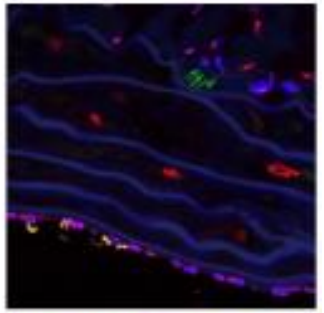


Wild Type Aorta

- Mouse Knock-in G609G Mouse Model

(Osorio et al *(Lopez-Otin) Sci Transl Med 2011)*

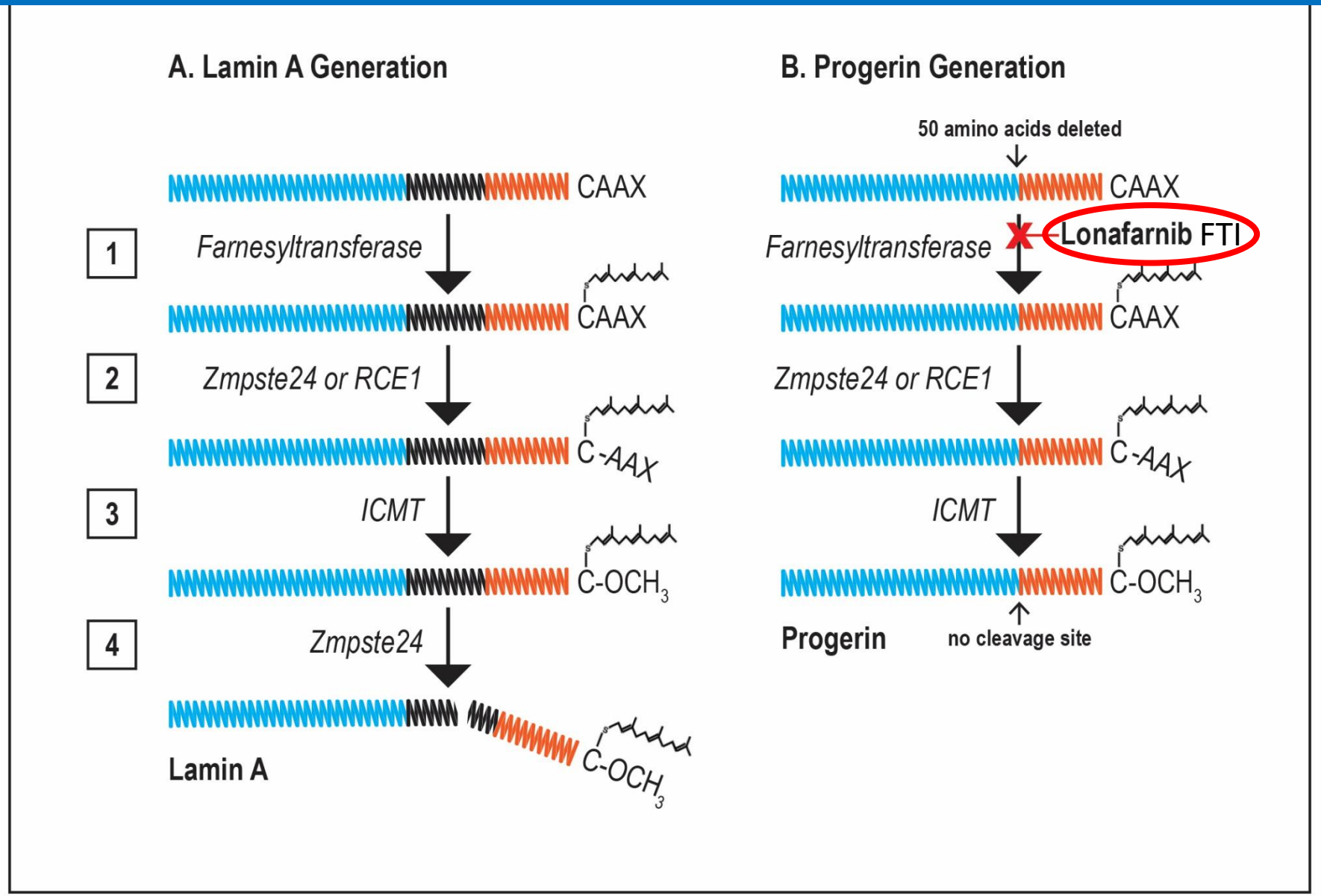
  - Mouse Progerin Produced
  - Mice Are Small
  - Develop CVD but not plaques,
  - Die Early, cause of death unknown



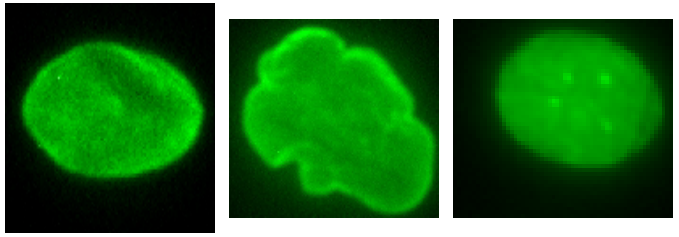
HGPS Aorta

- Additional endothelial-specific and VSMC-specific mouse models have also been developed

Biology Leads Us To Potential Treatment

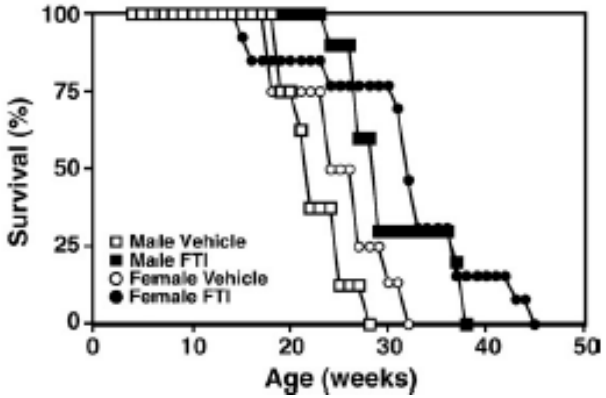


Farnesyltransferase Inhibition as Treatment (not all using the FTI in our trials)



Normal **HGPS** **HGPS with FTI, 72 hrs.**

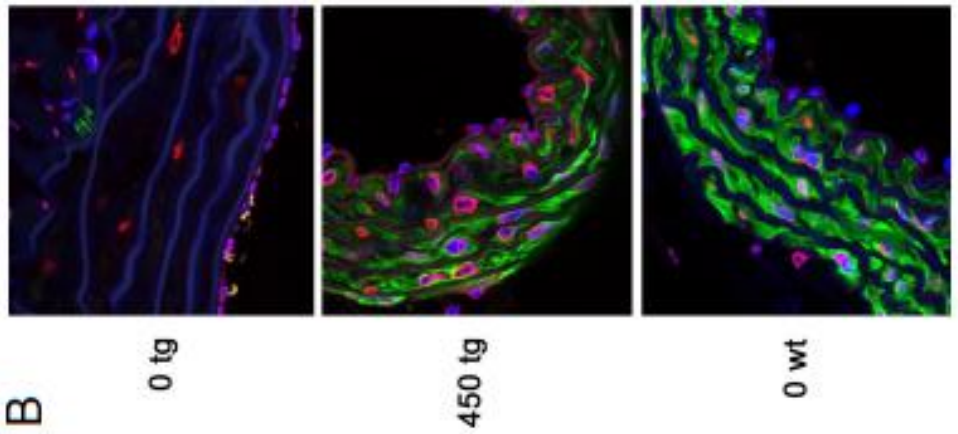
FTI Lonafarnib Normalized human HGPS Fibroblast Nuclear Shape



FTI ABT-100 Improved Disease ***in Zmpste24 Deficient Mouse Model***, Including lifespan

When treated with FTI tipifarnib after birth, Cardiovascular disease did not develop

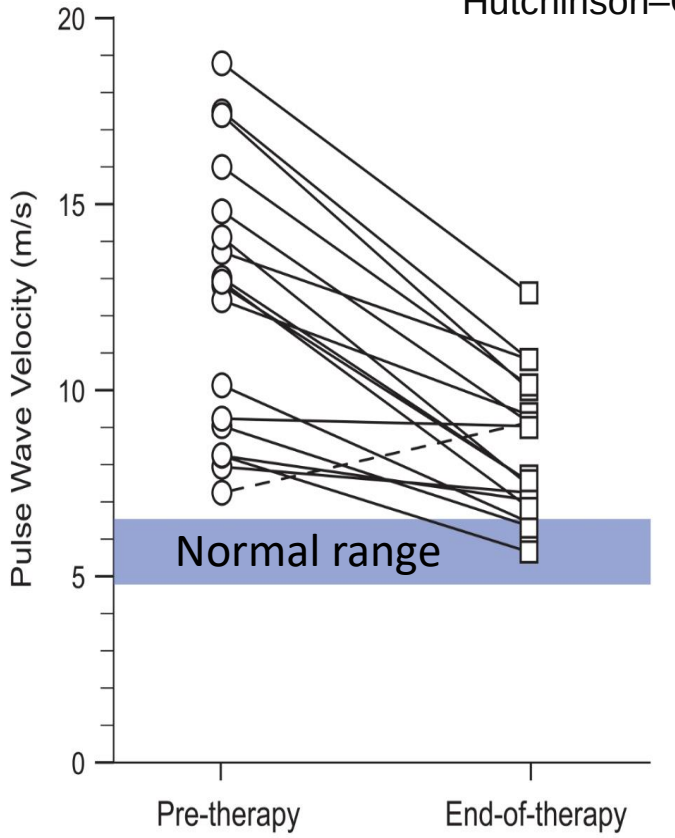
When allowed to develop cardiovascular disease for 9 months, then treated with FTI tipifarnib, Normal vasculature detected



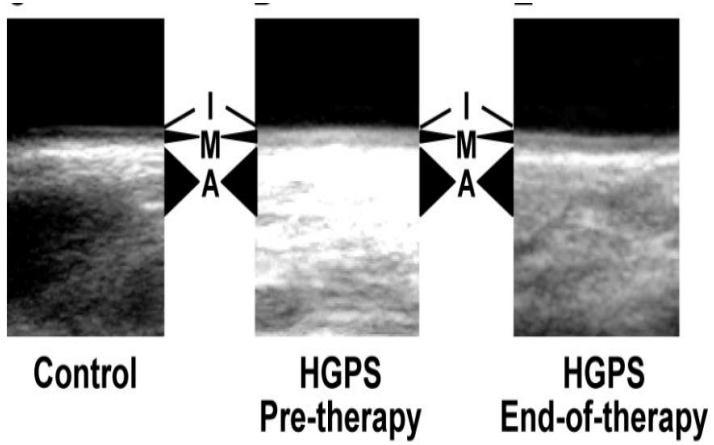
Capell et al 2005; Glynn et al, 2005; Toth et al, 2005; Fong et al, 2006

Improvements With Lonafarnib Treatment in Children: Changes in the Arteries and Extended Survival

PNAS 2012 : Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome



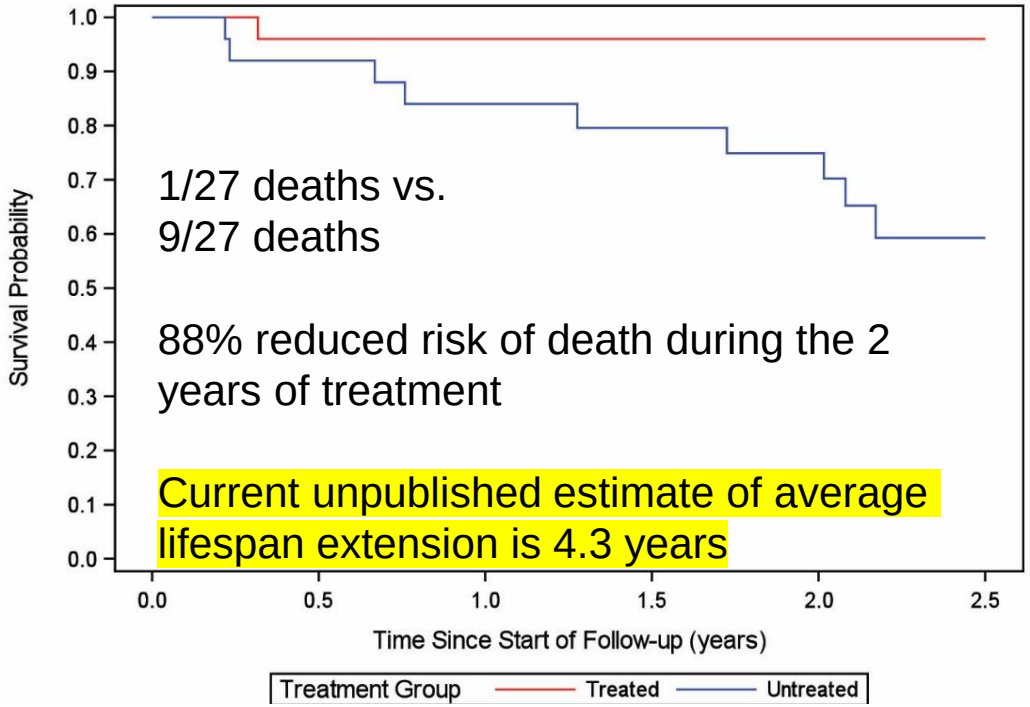
Carotid-Femoral Pulse Wave Velocity



Carotid Artery Echodensity

JAMA | Preliminary Communication 2018

Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome



1/27 deaths vs.
9/27 deaths

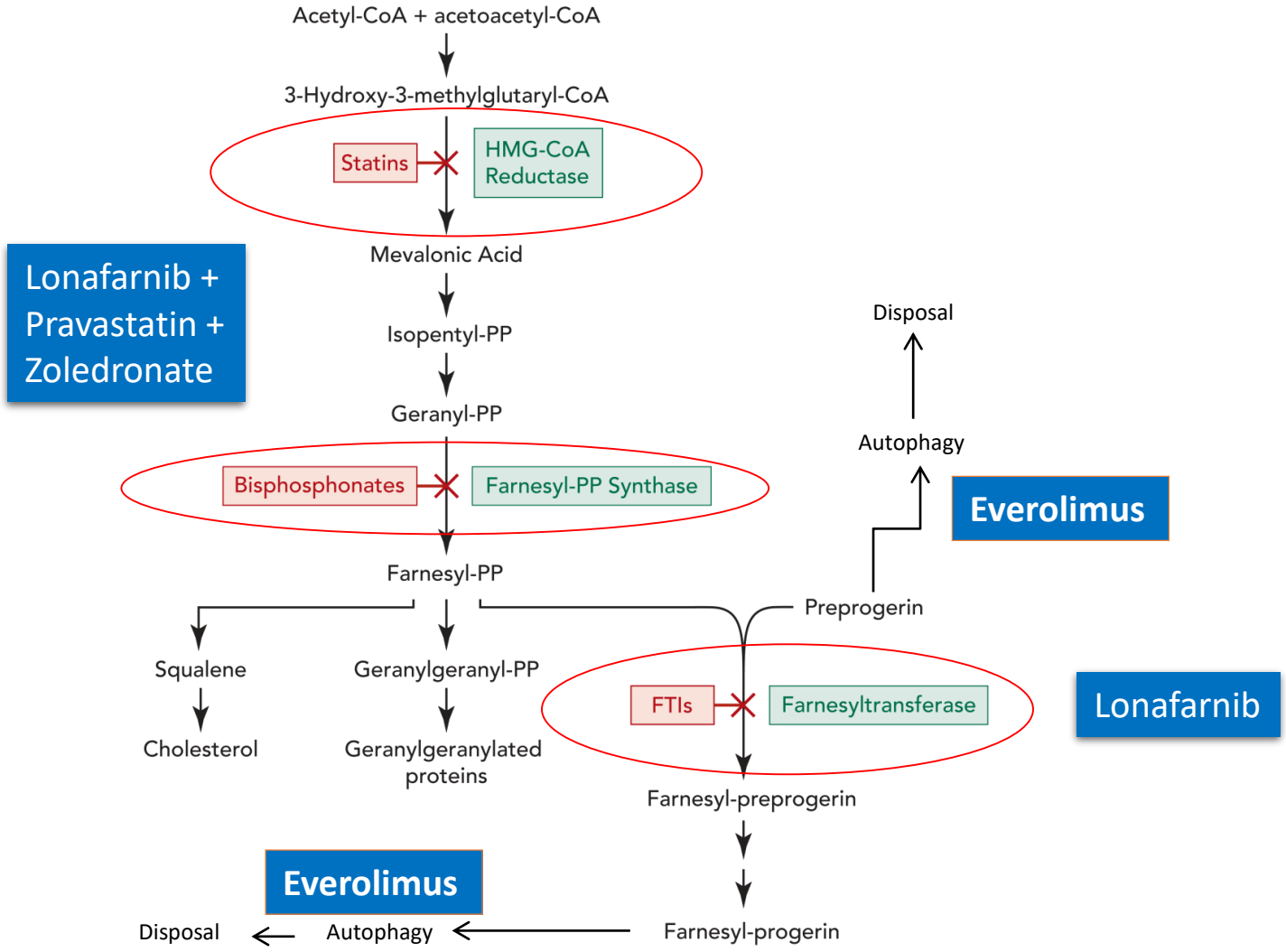
88% reduced risk of death during the 2 years of treatment

Current unpublished estimate of average lifespan extension is 4.3 years

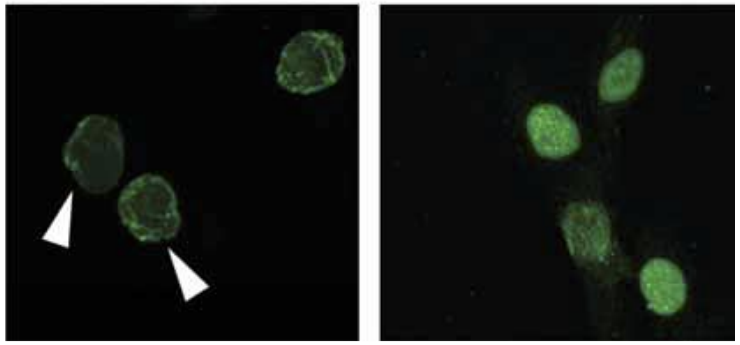
Survival

Lonafarnib (Zokinvy) is our first FDA approved drug for Progeria

Biology Leads Us To Clinical Trials

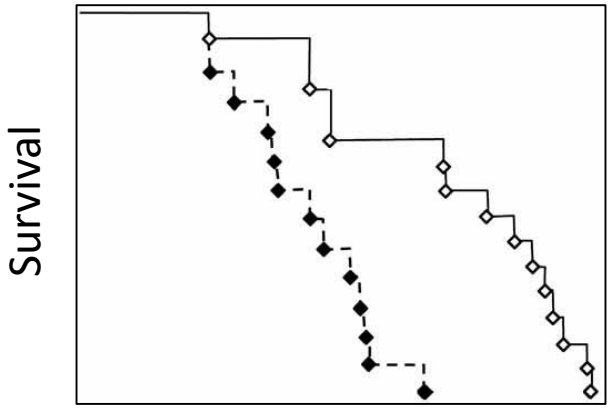


Statin plus Bisphosphonate Farnesyl Formation Inhibition



Untreated Treated

Zmpste24 Mouse Fibroblasts



Zmpste24 Mouse Model

WT Untreated Treated

- Zmpte24 Mutations do result in progeroid disease in humans, but not identical to HGPS and not progerin-producing (abnormal prelamin A causes disease)
- This model is not progerin-producing, no CVD
- Zmpste24 mice have spontaneous fracture and neuro. deficits, unlike HGPS
- Human Clinical Trial of HGPS in Combination with Lonafarnib, Pravastatin and Zoledronic acid Showed No Benefit Over and Above Lonafarnib Monotherapy
- A great animal model, but not optimal for drug development in HGPS

Animal Husbandry: G609G Homozygote:

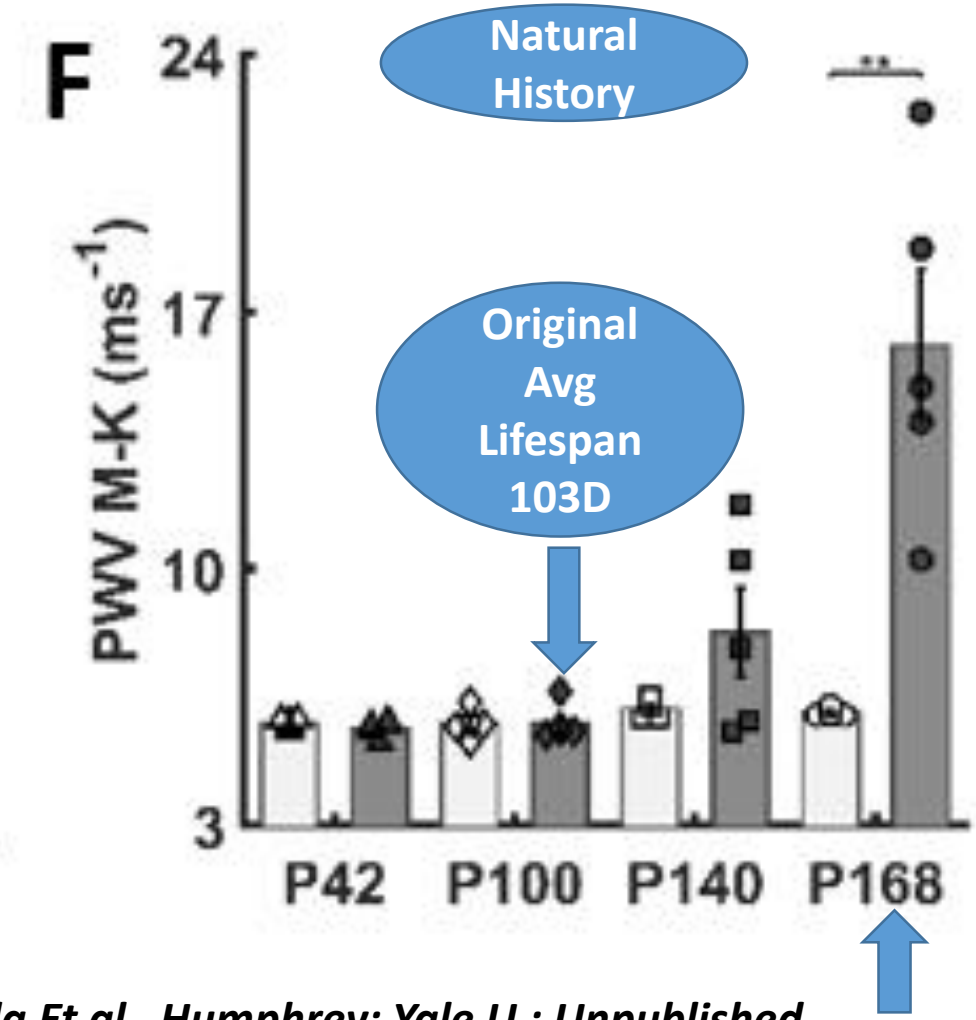
- soft gel-based chow on the floor of cage +
- introduction of a caretaker mouse in each cage

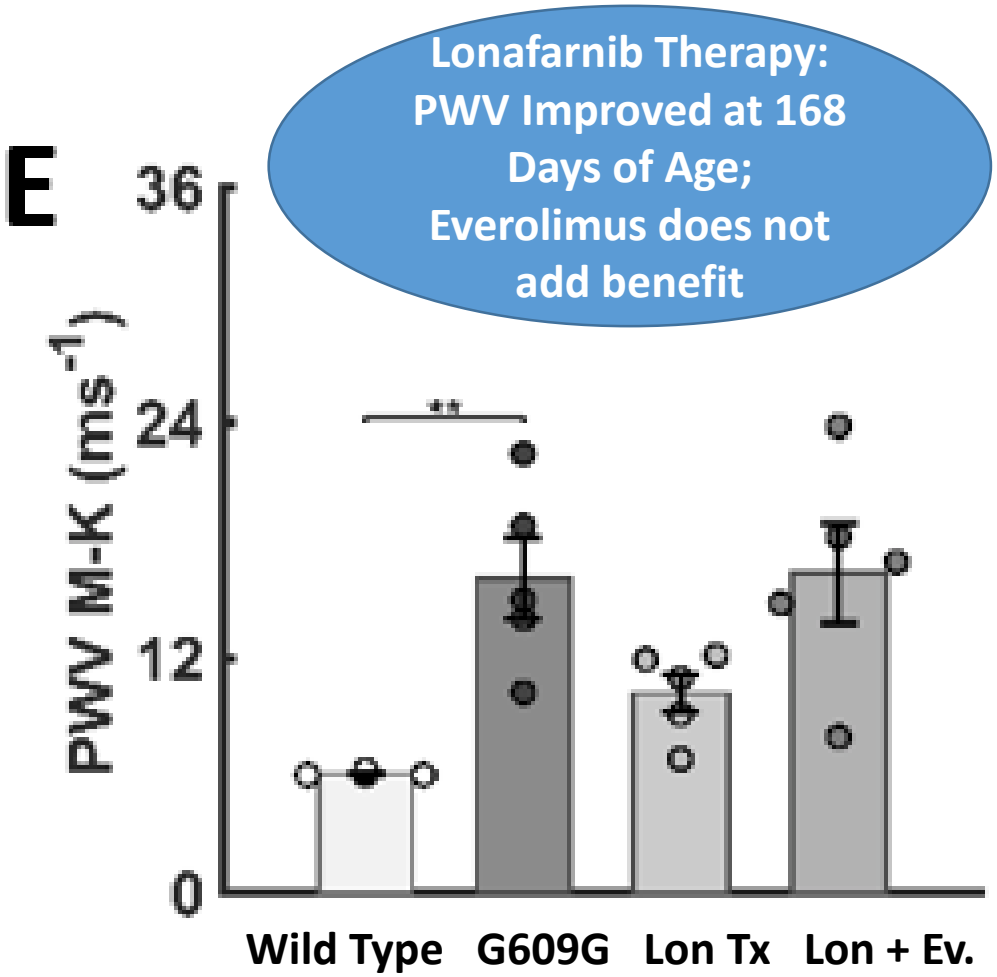
- original 50% survival at 103 days (Osorio et al., 2011)
- new extended the mean lifespan = 168 days

- allowed the cardiovascular phenotype to worsen similar to that observed clinically in patients.

- cardiovascular function progressed to extreme stiffening and diffuse vascular calcification.

Extended Mouse Lifespan Potentiates Overlap with Human Cardiovascular Disease





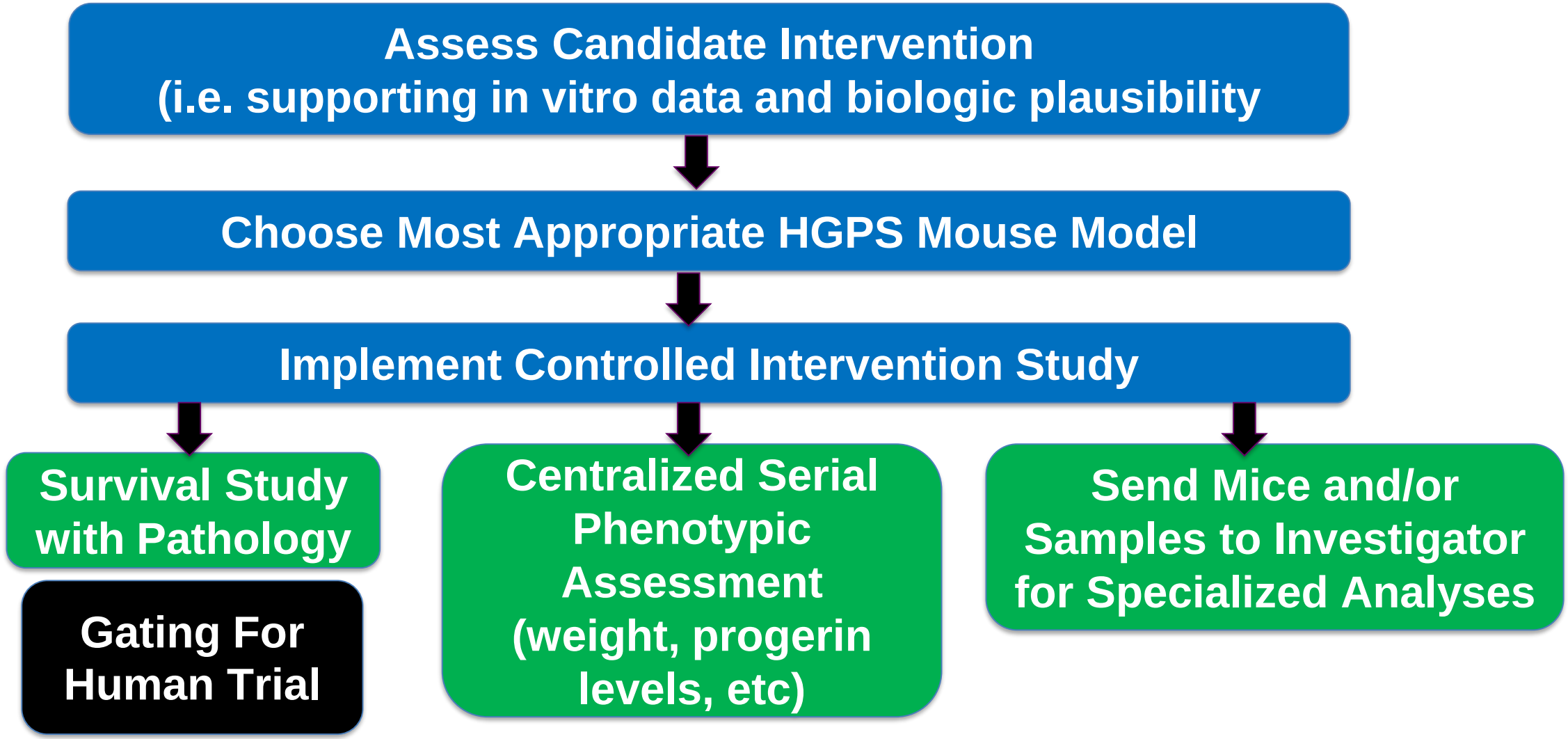
Murtada Et al…Humphrey; Yale U.; Unpublished

Getting The Word Out for Maximal Success

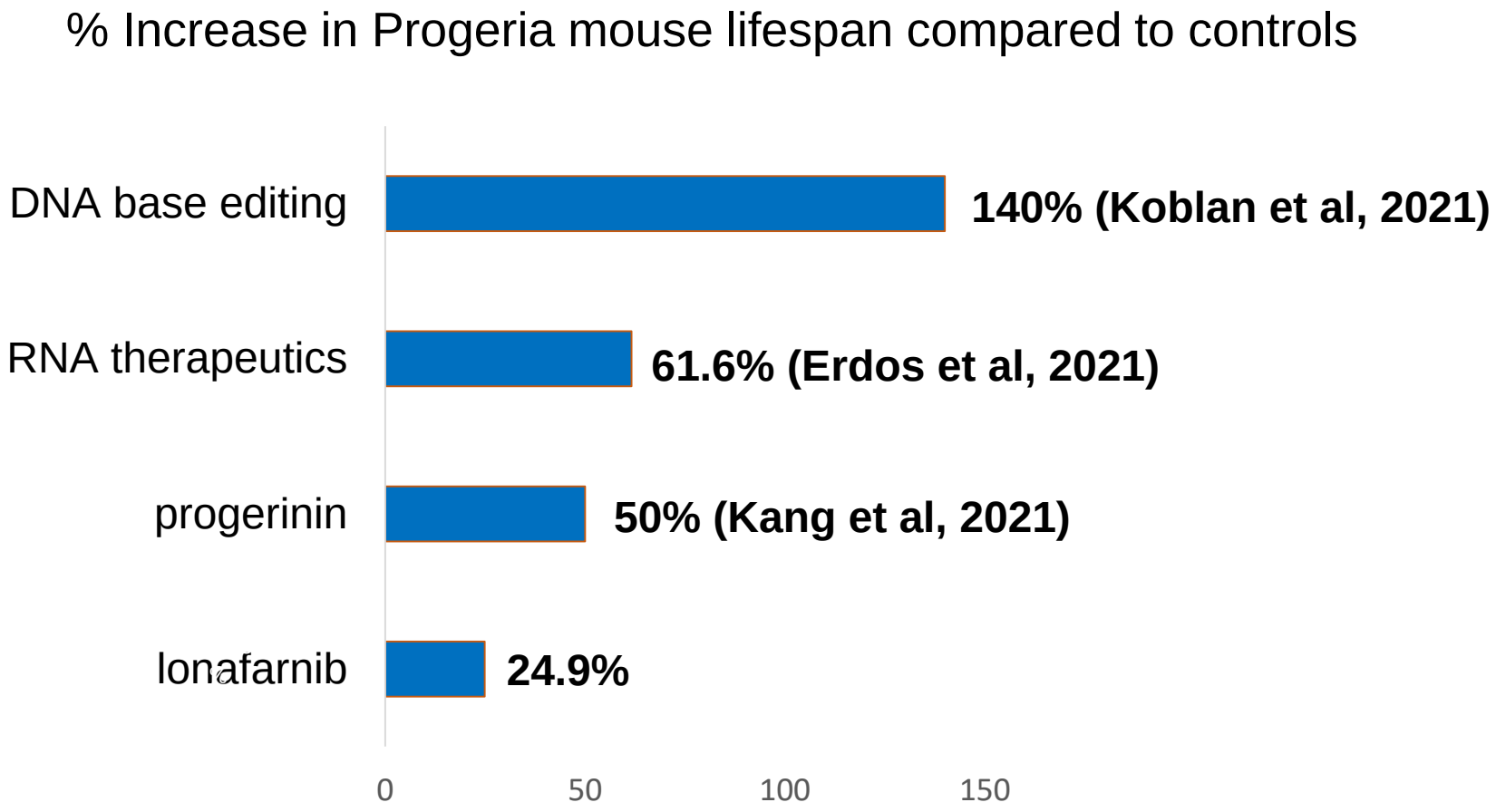
Collection and Distribution of Best Practices and Guidance for Basic Scientists

- New Publications
- Investigator Surveys
- Email Blitz’s with new information
- Resource Center
- Posters at Scientific Meetings

Centralizing Disease-Specific Animal Testing To Optimize Outcomes and Comparability



Potential New Treatments' effects on Progeria Mouse Model Survival*



* **Note that mouse models in use were not the same across all studies**

Determination and Collaboration

Finding…

Diagnosing…

Studying…

Treating…

CURING

Together, we *WILL* find the cure!

www.progeriaresearch.org

Estelle Marrer-Berger

Senior Translational Safety Leader

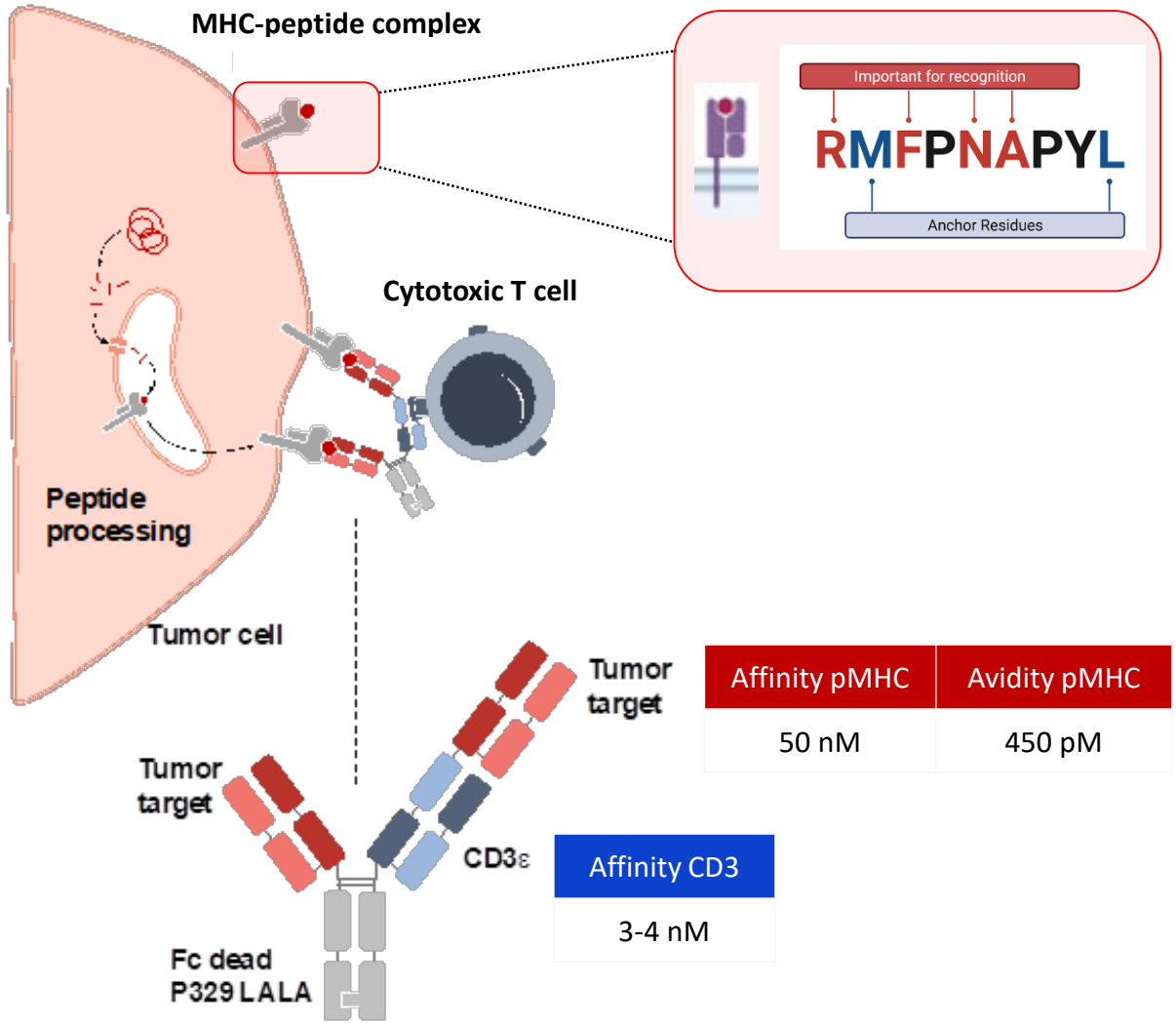
Roche

Optimizing early clinical investigations by increasing the predictive value of non-clinical activities

Estelle Marrer-Berger, Antje Walz, and Imein Bousnina

Duke-Margolis Center for Health Policy / May 24-25, 2022

Targeting intracellular Wilms tumor 1 in AML with a TCR-like T-cell bispecific antibody



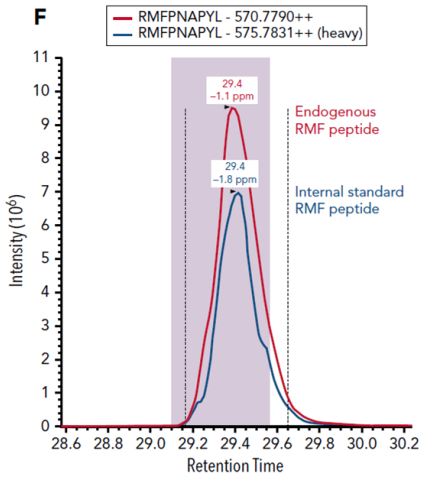
Affinity pMHC	Avidity pMHC
50 nM	450 pM

Affinity CD3
3-4 nM

- WT1 oncoprotein is an intracellular, transcription factor, overexpressed in leukemias (AML, ALL) and solid cancers (ovarian cancer and mesothelioma)

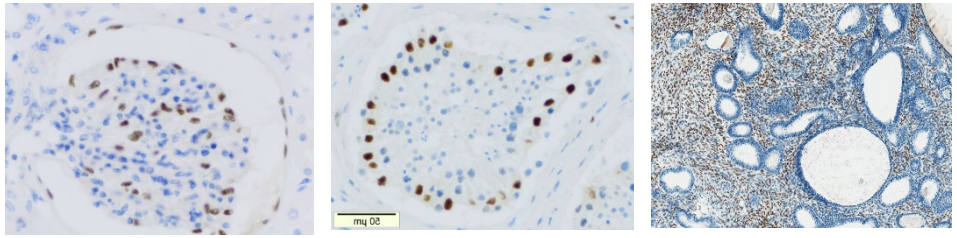
Quantification of the RMF peptide on AML blasts

Augsberger et al., Blood, 2021



- In adults, WT1 expression is restricted to a few tissues: (kidney podocytes, Sertoli and granulosa cells in the testes and ovaries, few mesothelial cells and 1% of bone marrow cells)

Kidney ***Testis*** ***Uterus***



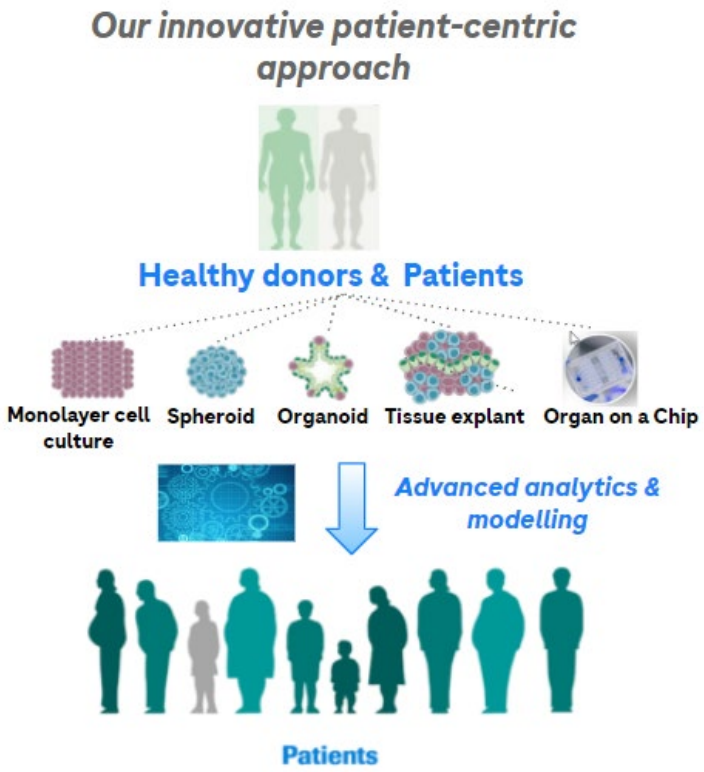
A human/patient-centric non-clinical approach to bring WT1 TCB to patients?

SAFETY

Reduce and manage the «Unknown»

- Lack of cross-reactive TOX animal species and the standard non-clinical toolbox not applicable
- Increased risks for off-target / off-tumor cross-reactivity

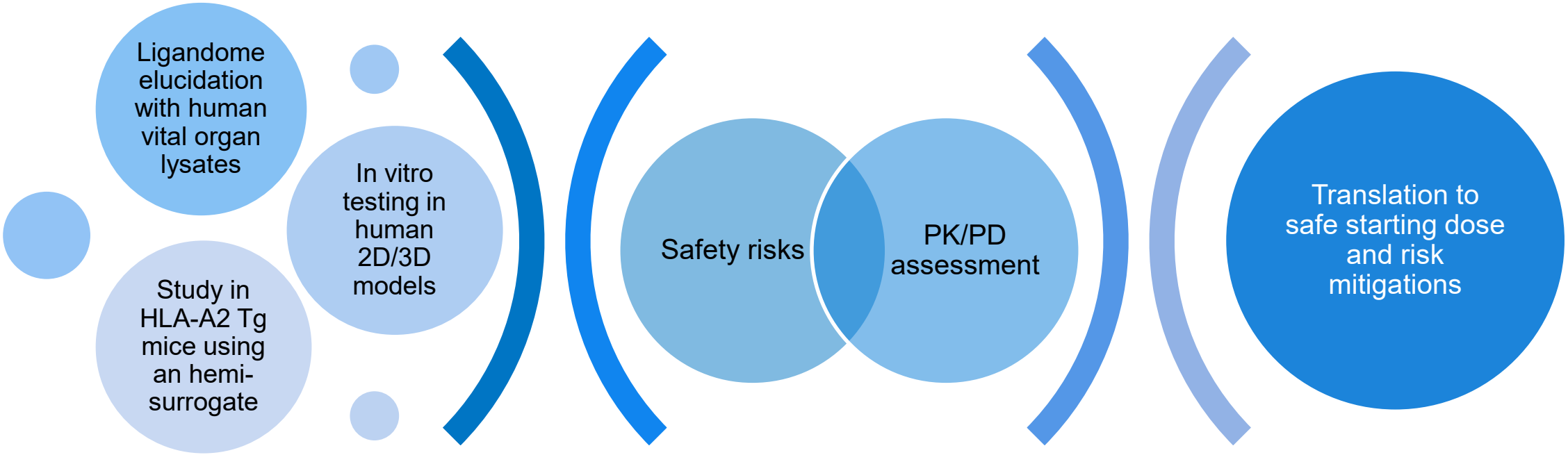
Increase the predictive value: predicting from human to human



PK/PD/SAFETY

Non clinical strategy for Entry into Human based on NAMs

In vitro / ex vivo derived therapeutic index, starting dose, and PAD

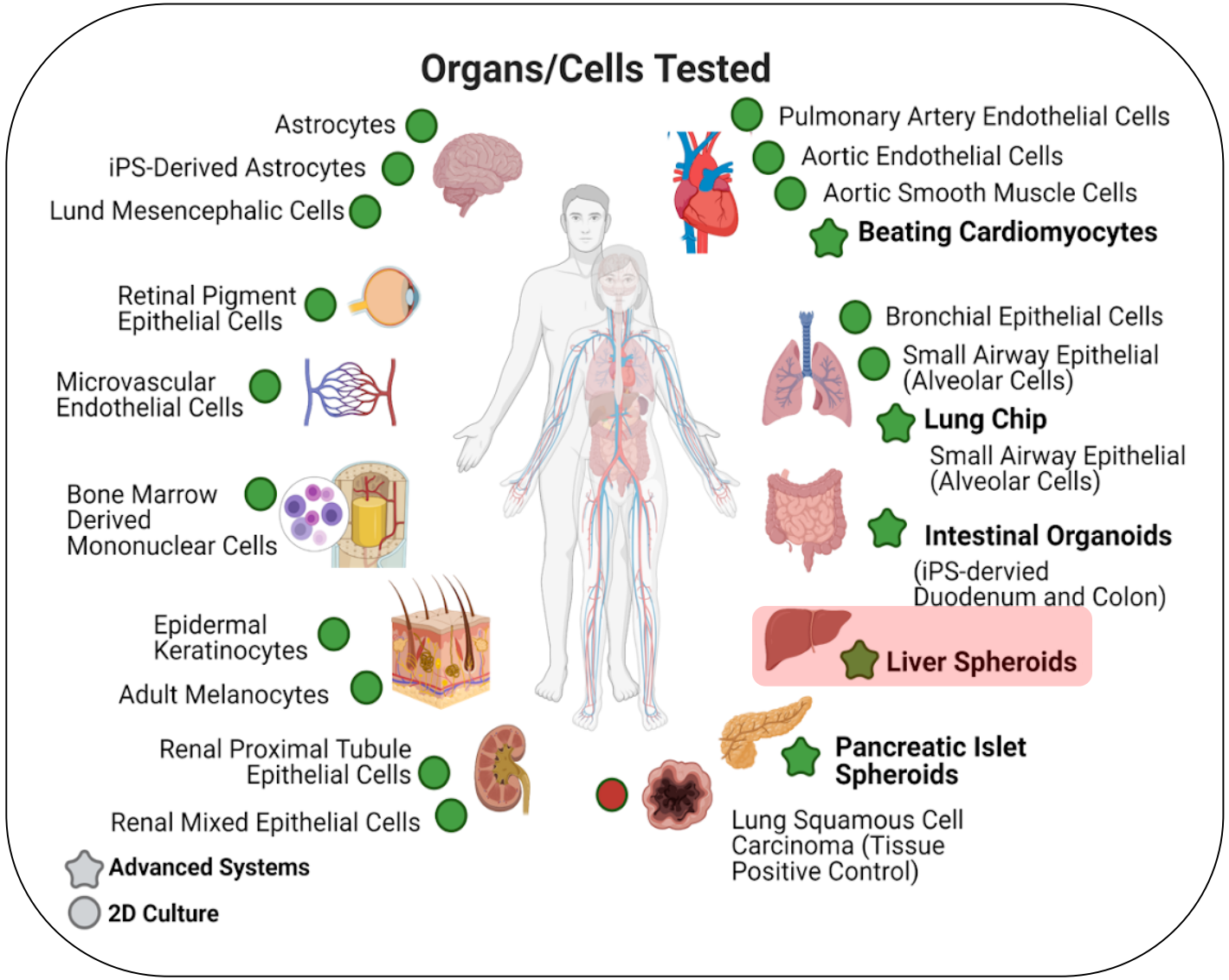


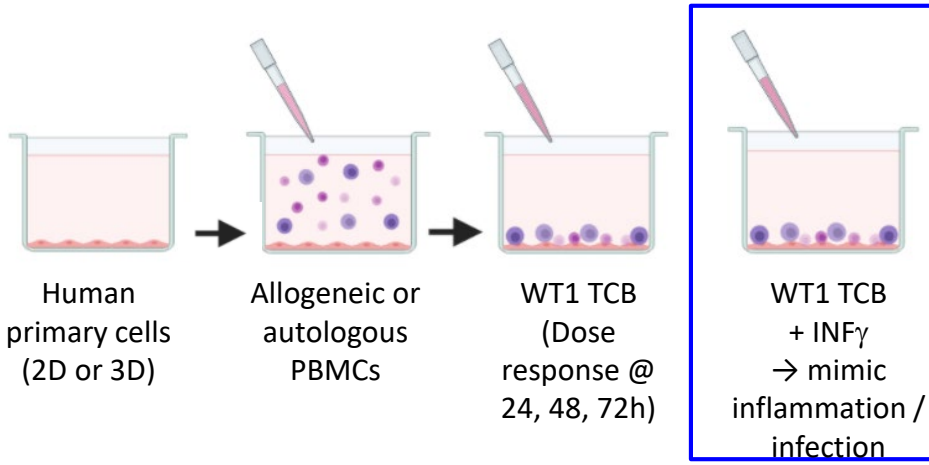
Non-clinical safety strategy combining new «state of the art» activities to potentiate **risk identification** in the **absence of a cross-reactive species**

Integration of qualitative and quantitative assessments to define a **therapeutic index**

Define **starting dose** and **risk management plan**

Risk identification using human 2D / 3D in vitro systems





Cell Death

- A LDH
- B Caspase 3/7

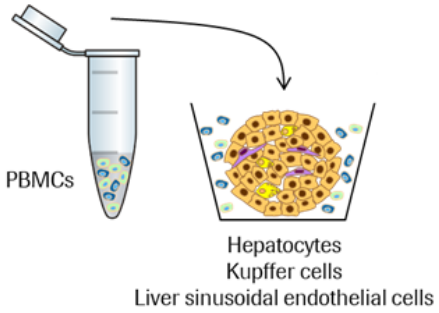
Cytokines

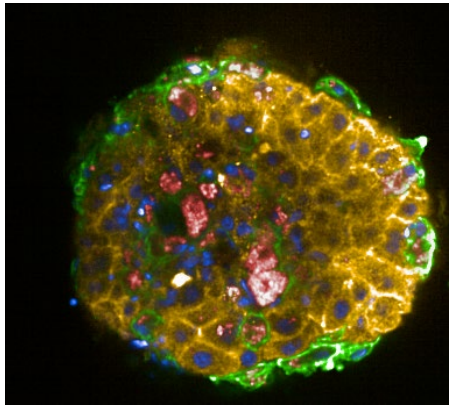
- A Granzyme B, TNF-a, IFN-g
- IL-2, IL-6, IL-8, IL-10

Physiological Parameters

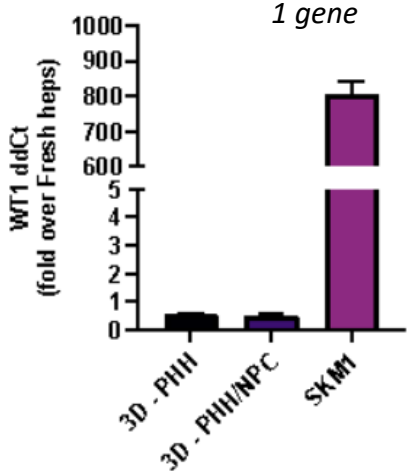
- A AST (Liver)
- C Cardiomyocytes:
  - Beat Rate
  - Base Impedance

WT1 TCB consistently induced minimal (?) lysis in liver spheroids (7 donors) co-cultured with allogenic PBMCs (3 donors)

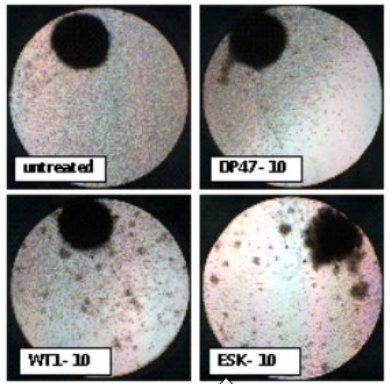


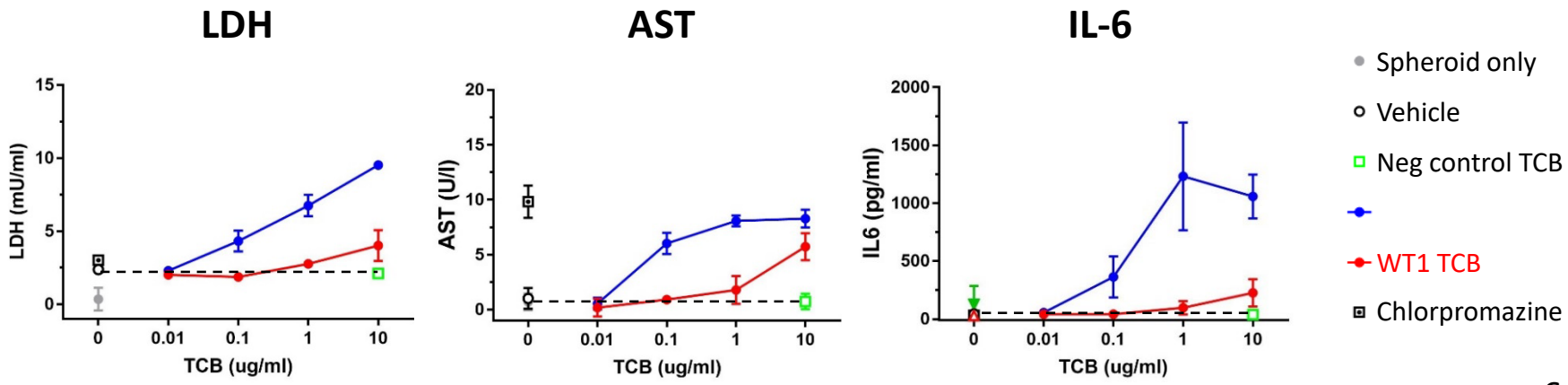


qRT-PCR analysis of Wilm`s tumor-1 gene

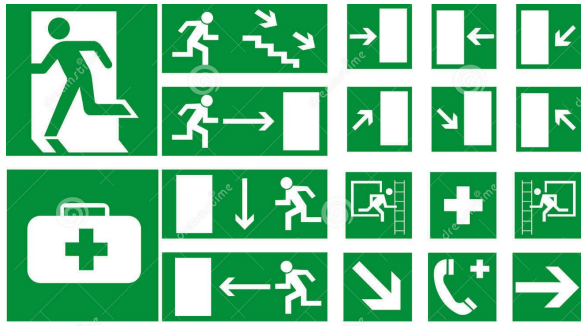


Bright field pictures of liver spheroids in co-culture experiment 72 hours after treatment





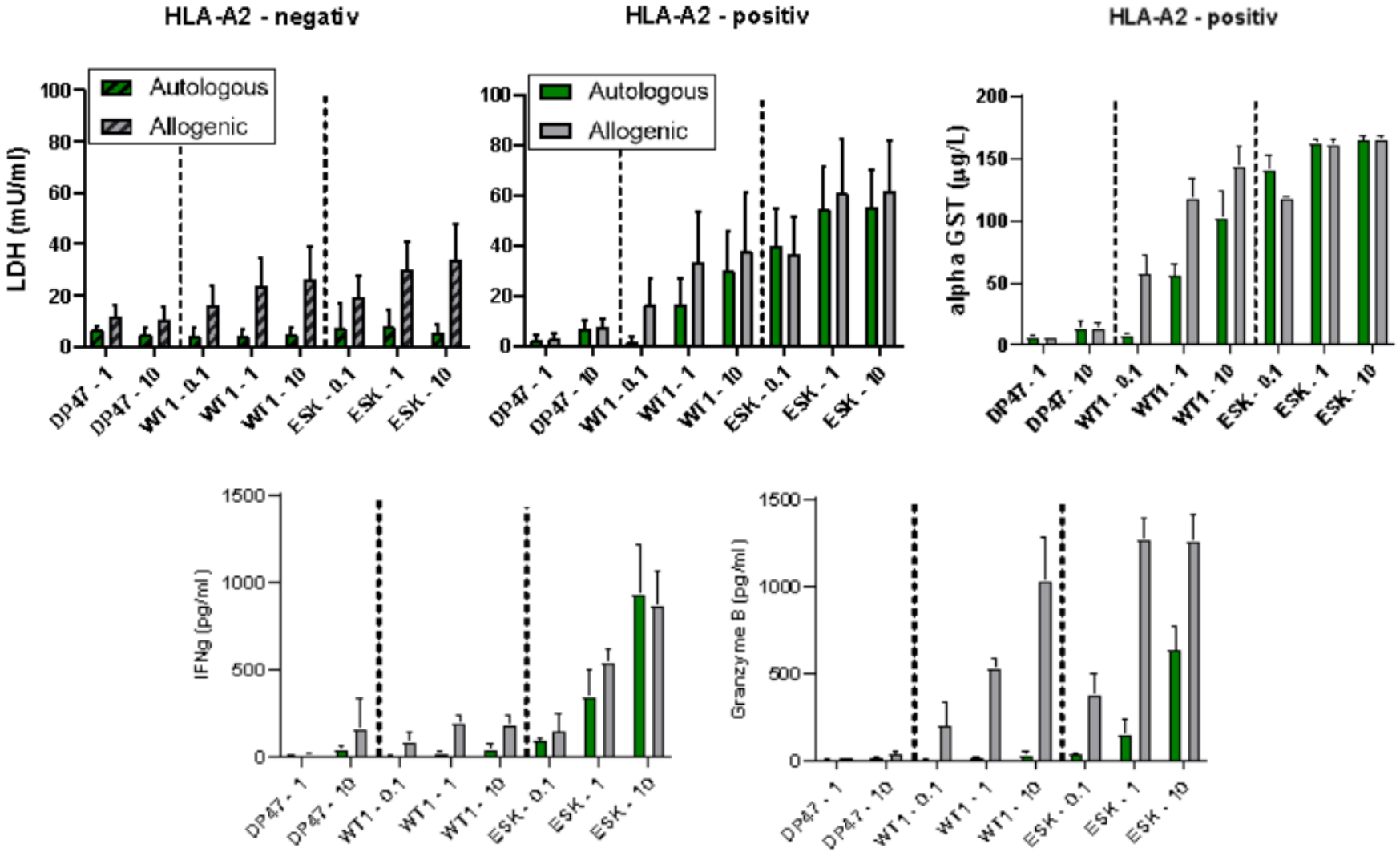
And now what?



- The signal needs to be further assessed, qualitatively and quantitatively
- The in-vitro effect needs to be «translated» to a human body
- A threshold of significance needs to be established and be related to a drug concentration/exposure
- A therapeutic index needs to be defined
- Causality? Exacerbating contexts (pathologies, medications..)?

➢ Exclusion/Inclusion criteria, monitoring and mitigation need to be defined

Safety assessment based on dynamic in vitro killing assays using human liver spheroids (3D): *Mild but consistent signal at 1 µg/ml*



Conclusions

- The signal is **consistent** across donors and endpoints monitored
- The **significance threshold was conservatively defined at 1 µg/mL** based on the increased LDH/caspase3/7, cytokines, and AST observed in the allogenic co-cultures (worst-case scenario)
- **Alloreactivity amplifies the signal**, though, compared to the negative control DP47, 1 µg/mL triggers a minimal effect

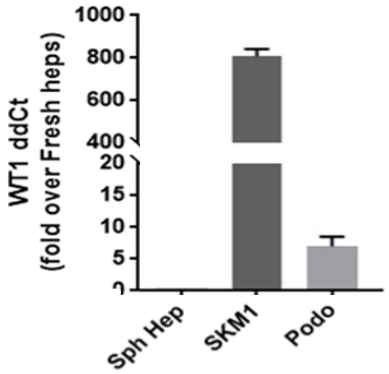
➢ **Causality? Do we have a therapeutic window?**

Causality of the signal observed: a CYP8B1 epitope?

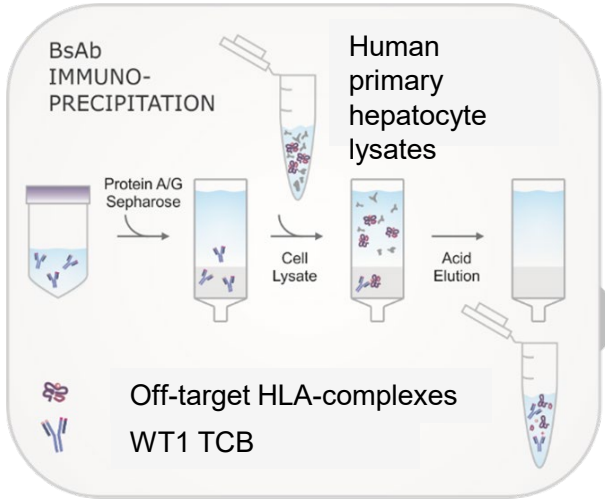
WT1 TCB interactome elucidation to identify potential off-targets

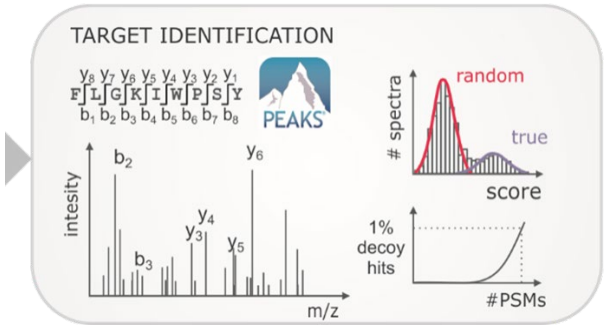
Go after causality of the signal: technical, biological artefact or REALITY?

NO WT1 expression in liver spheroids

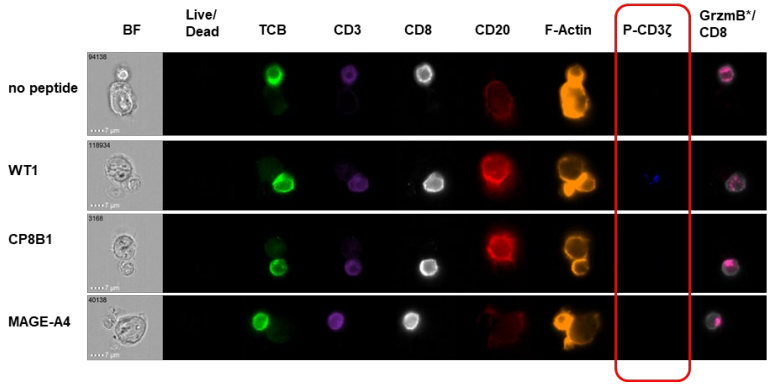


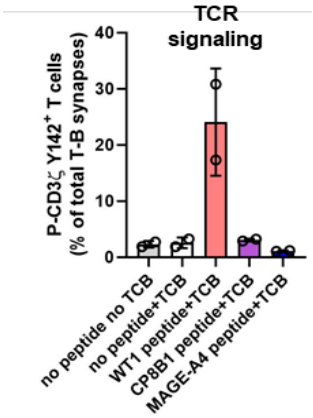
Ligandome elucidation





Synapse stability evaluation



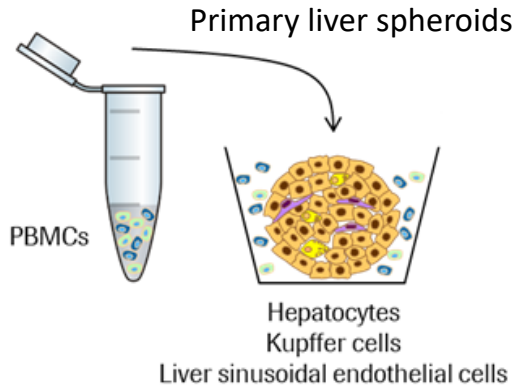


Stable synapse formation only obtained ***with the targeted RMF peptide***

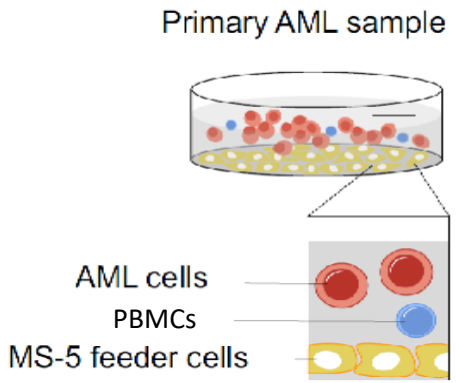
Confirmation that the safety threshold at 1 µg/mL is conservatively defined

Deriving a TI from an harmonized in vitro / ex vivo dynamic testing using diseased and healthy human systems

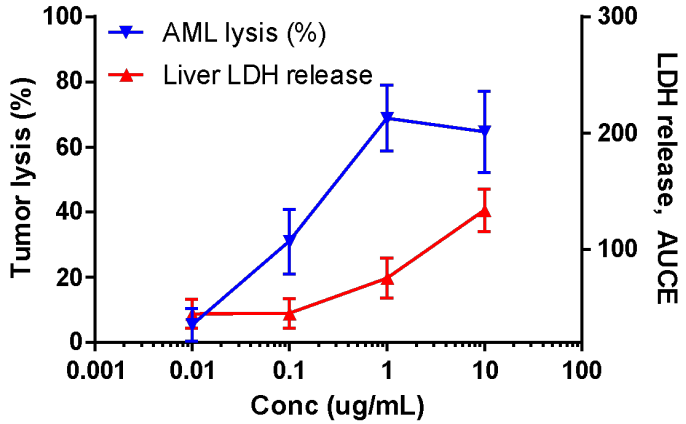
Safety



Efficacy



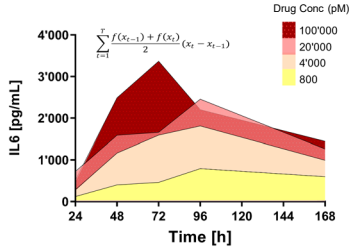
Therapeutic Index



With harmonized experimental design

Time course: 24, 48, 72h
E:T (5:1)
PBMCs (allogeneic vs autologous)
Readouts: killing, cytokines, T cell activation

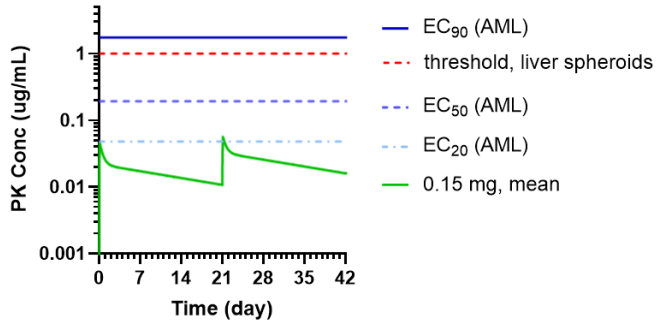
PKPD with AUCE



*Van De Vyver A & Eigenmann M et al. AAPS J. 2021 Dec 3;24(1):7

Translational PKPD strategy

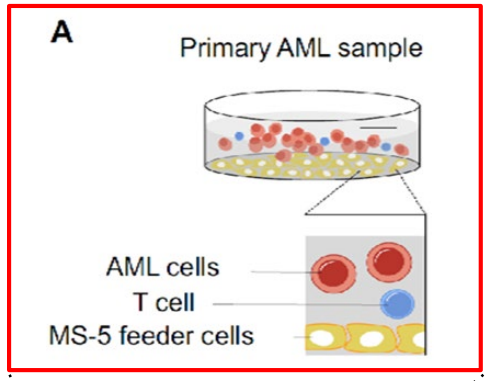
- Patient-centric MABEL starting dose
- Safety margin prediction
- Prediction of efficacious exposure



Augsberger C, et al. Targeting intracellular WT1 in AML with a novel RMF-peptide-MHC specific T-cell bispecific antibody. Blood 2021

Patient-centric starting dose prediction

Reducing the number of patients treated with sub-therapeutic doses



Patient-centric

Classical

	ExVivo-AML	OCI-AML3	SKM1
E:T	5/1	5/1	5/1
EC50 (ug/mL) median	0.193	0.184	0.0059
Min	0.0310	0.0782	0.00079
Max	0.406	2.36	0.011
N	7	10	7

Higher **starting dose: 5 µg** (standard MABEL) **to 150 µg** (patient-centric MABEL)

Increased relevance for patients

Classical *in vitro* MABEL

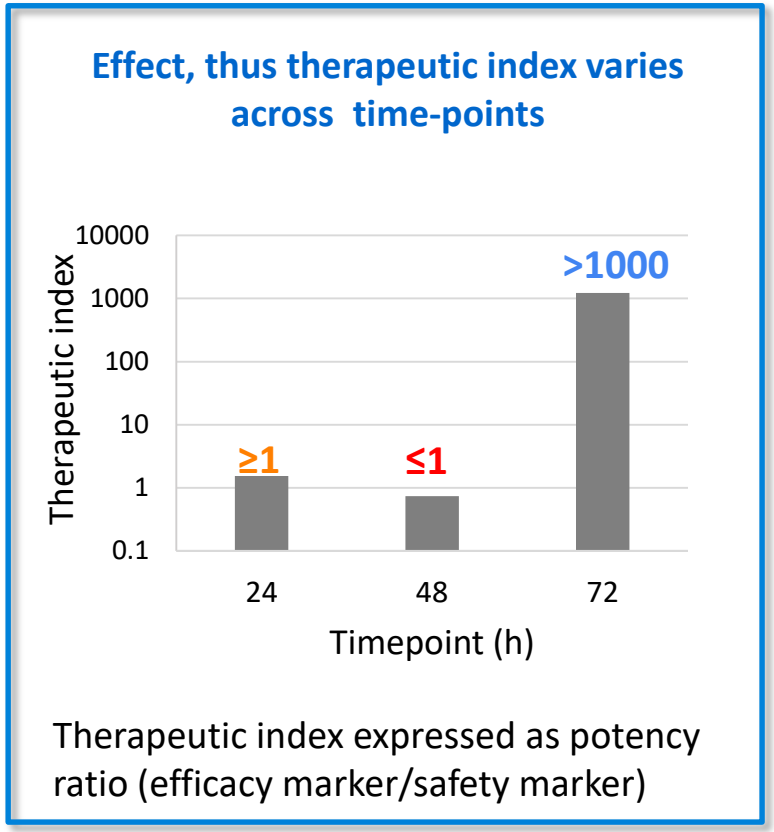
- Uses the most sensitive tumor cell line, most sensitive readout (T cell activation) to derive a safe starting dose
- Starting dose safe BUT much lower than expected therapeutic dose

Patient centric MABEL

- Efficacy prediction using patient-derived material (ex vivo)
- Safety prediction based on primary healthy and diseases in vitro systems
- Starting dose is close to therapeutic dose and reflects a balanced risk/benefit

→ Saved **3 additional cohorts** of patients with sub-clinical doses

WHAT WE LEARNT



Therapeutic index expressed as potency ratio (efficacy marker/safety marker)

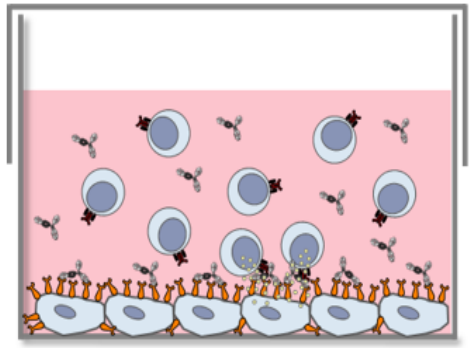
Understand your system and your testing framework (1)

Leverage the systems' strengths, be aware of its limitations

Biological systems are highly dynamic and respond dynamically to stimuli

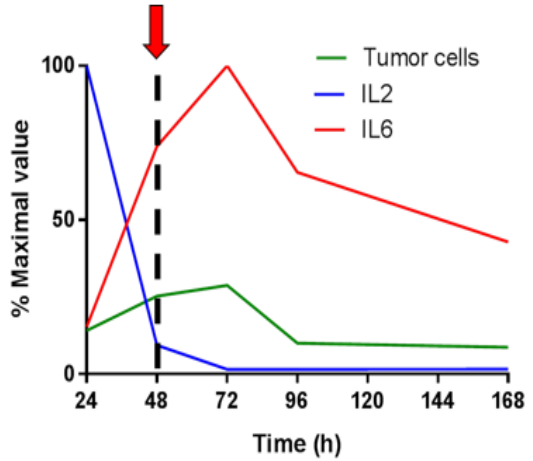
It is critical to evaluate concentration / effect relationships throughout a time-course, for as long as the system allows

Experimental system routinely applied



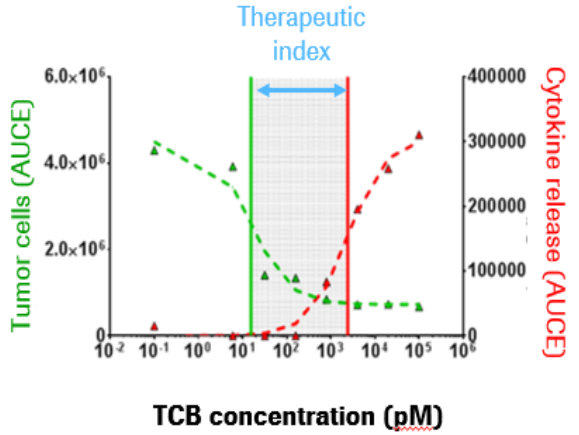
Co-culture of Tumor cells & PBMCs

T-cell mediated drug response is highly dynamic



Capture highly dynamic drug response

PKPD analysis over full time course



Relate tumor killing to PD readouts

Understand your system and your testing framework (2)

Leverage the systems' strengths, be aware of its limitations

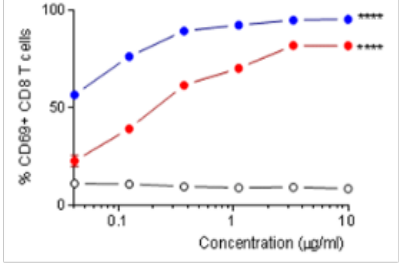
Consistency of the signal

The full cascade of events is observed with WT1 TCB: T cell activation, target cell killing, cytokine and AST increase; controls trigger the expected effects

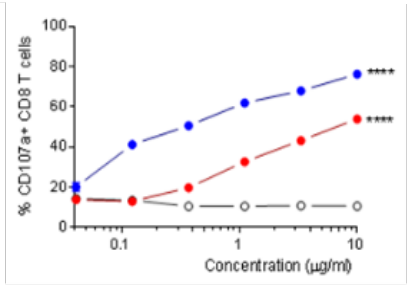
Real-time

T cell activation and synapse formation

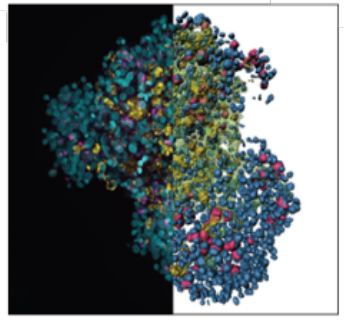
CD69 early activation marker



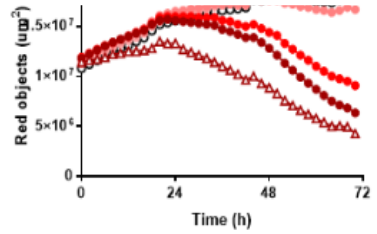
CD107a degranulation marker



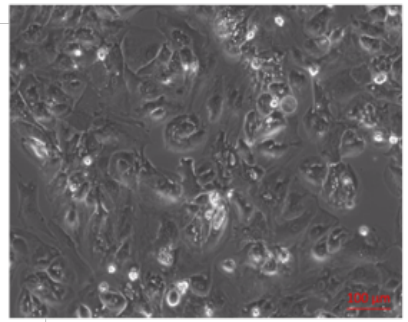
Target cell killing



PODO/SVRed + PBMC (#237): Target cell nuclei (red)

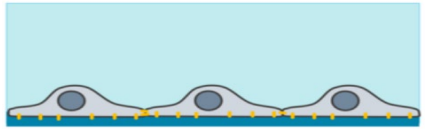


Physiological function



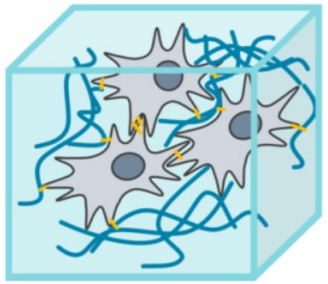
Patient-derived material enables the balancing act to achieve the highest safe starting dose for CD3 bispecifics

2013



Most **sensitive** readout in most **sensitive** cancer cell line; starting dose targets **EC20**

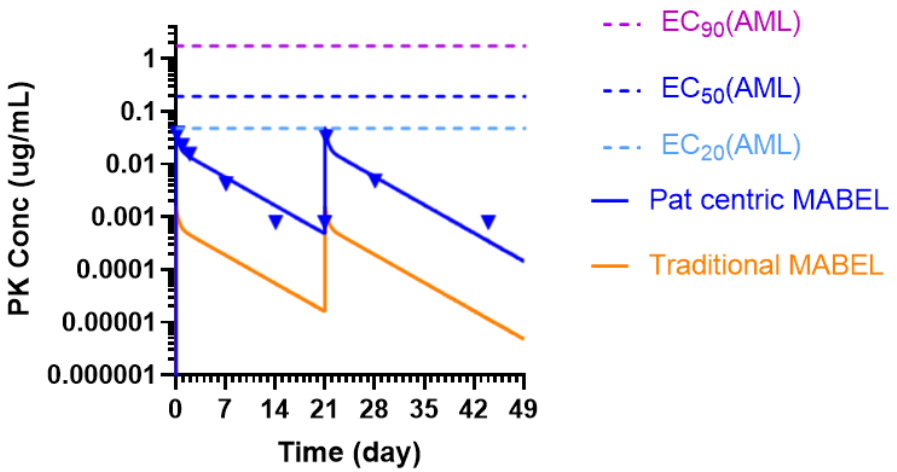
2020



Most **relevant** readout in most **relevant** test system: bone marrow from AML patients; starting dose targets **EC20**

	Blinatumomab	WT1 TCB
Starting dose to efficacious dose	10 000 fold	~100 fold

WT1 TCB PK/PD predictions



- ➔ Patient-centric starting dose (2020) vs Standard MABEL starting dose (2013): **0.150 mg vs 0.005 mg**
- ➔ Patient-centric based efficacious dose range prediction: 10 to 15 mg
- ➔ In the clinic, the starting dose was safe & CRs are observed at predicted exposures

WT1 TCB Ph1 Study WP42004 in acute myeloid leukemia ongoing

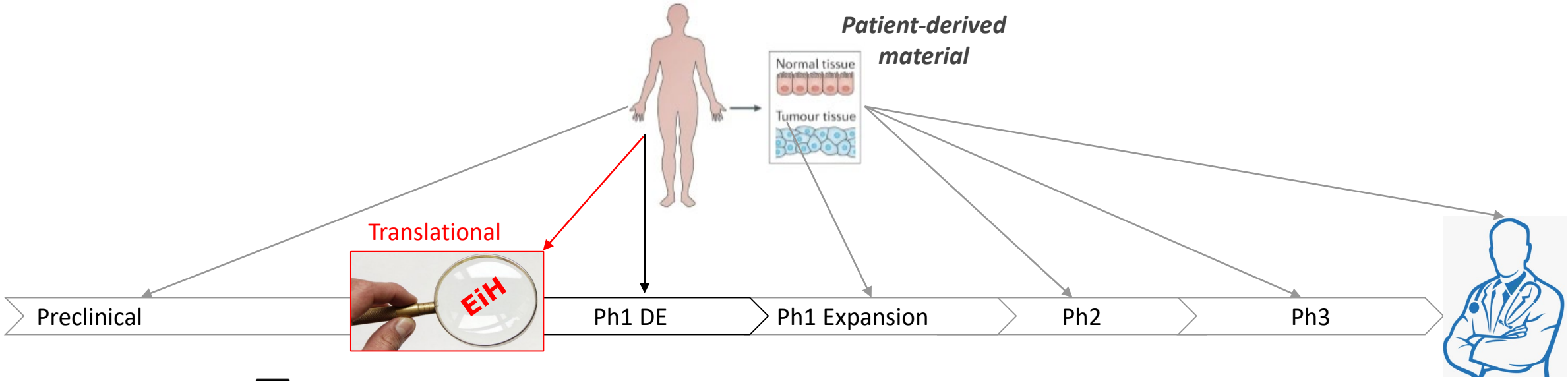
Broad regulatory approval on a novel non-clinical approach & innovative IMP

- First patient dosed in November 2020; the EiH dose predicted from the patient-derived AML blasts + autologous PBMCs was **SAFE**
- So far, no evidence of liver toxicity up to the dose of 12 mg (***Cmax >1 ug/mL***)
- The patient-centric framework is of high predictive value for the estimation of the pharmacologically active dose range

OUTLOOK

Our accomplishments and vision

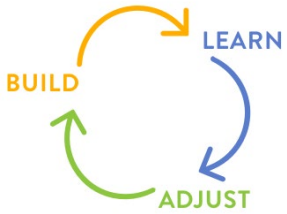
Embrace the uniqueness of the patient to match drug and dose



- Understanding disease mechanisms
- Validate drug target & MoA
- Understanding dose / effect relationships

- Efficacy prediction based on tumor tissues
- Safety prediction based on healthy tissues

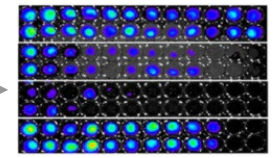
→ Safe starting dose, close to therapeutic dose → Safety assessment; risks and mitigation measures



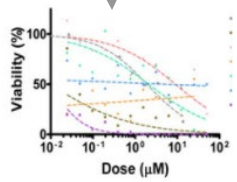
- **Ex-vivo testing** on tumours from patients enrolled in the DE and expansion in parallel to in-vivo testing to:

→ identify responders and predict the efficacious dose

→ verify the predictive value of the EiH data and of power of the model+framework

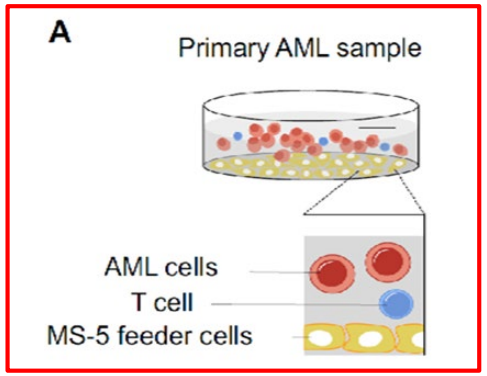


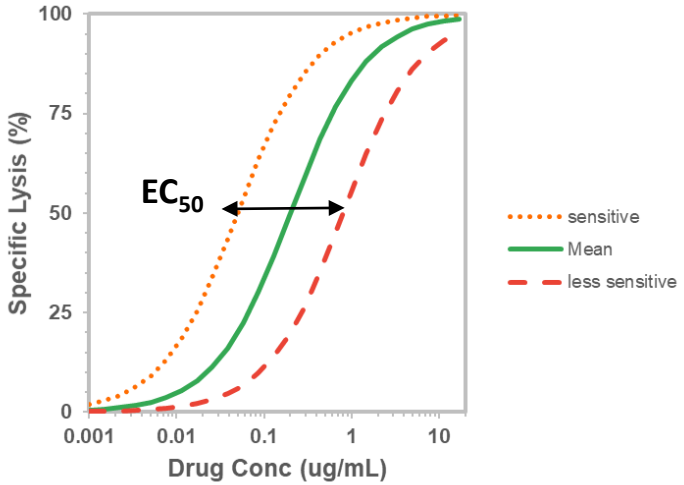
Responder **A** & **B**
Dose **A**: 1 mg
Dose **B**: 2 mg
Schedule: Q3W

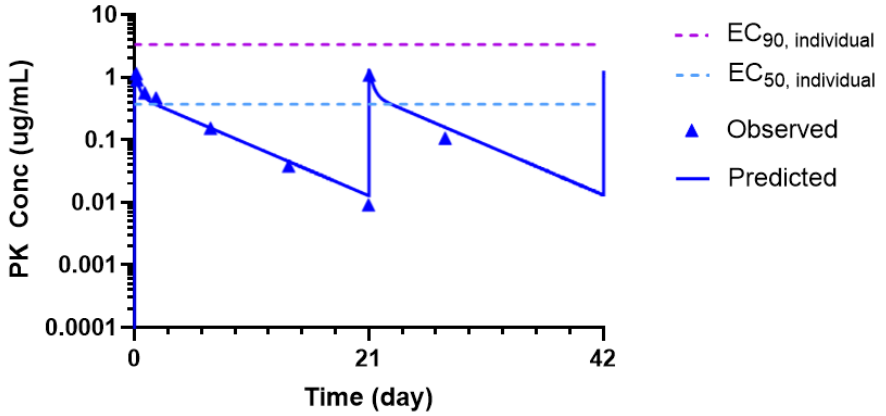


Individual ex vivo / clinical in vivo PKPD approach

Predict individual target exposure based on individual ex vivo EC_{90}







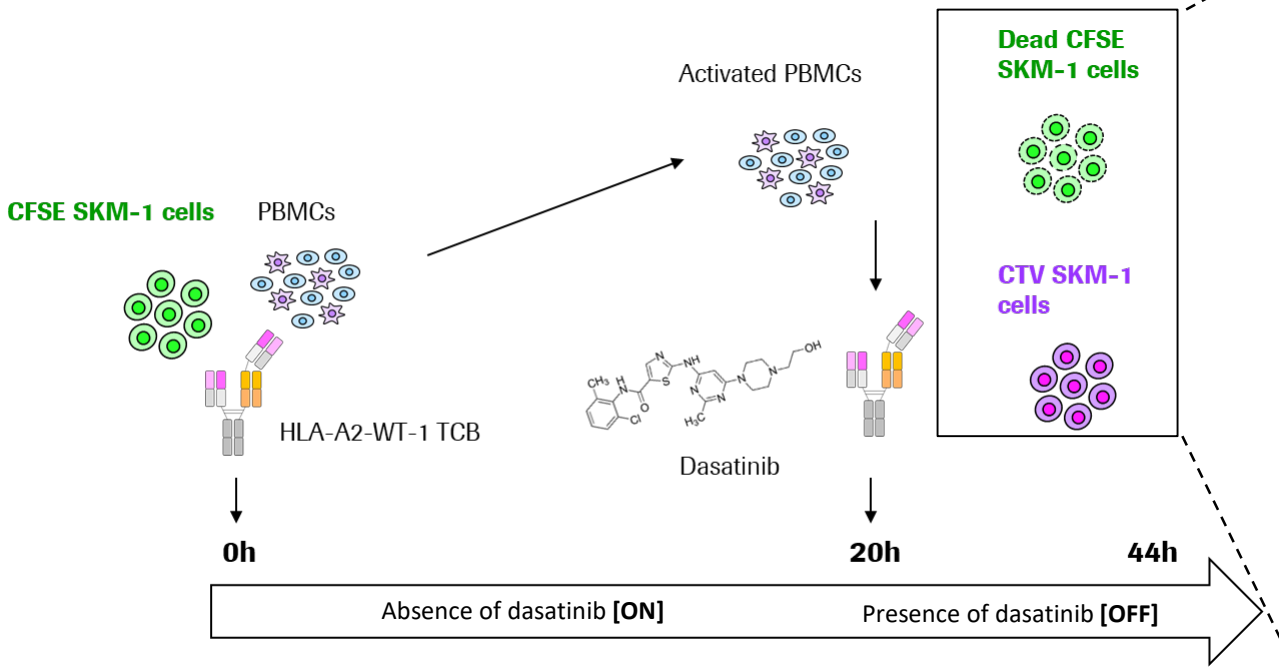
Assess individual ex vivo potency (EC_{50})

Combine ex vivo EC_{50} with individual PK


Academic collaborators
University Hospital, LMU Munich
• Prof Marion Subklewe
• Gerulf Hänel
125 YEARS
Celebrate Life

Doing now what patients need next

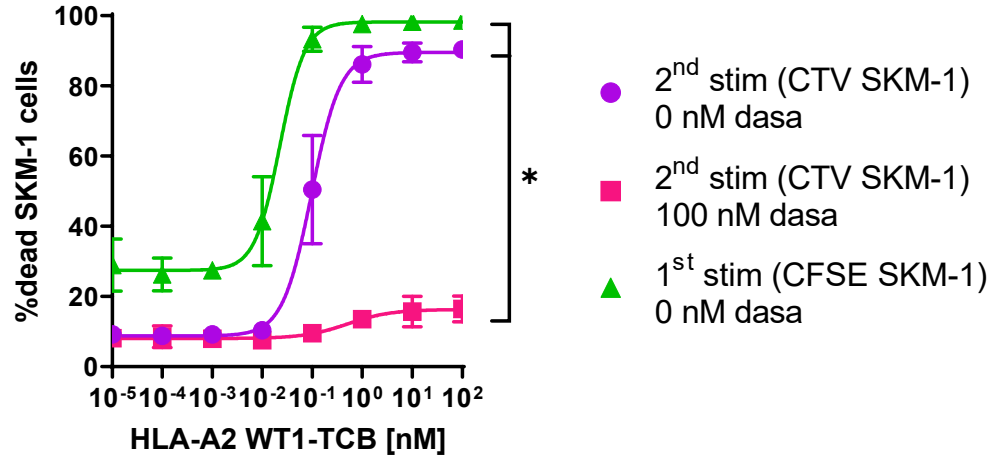
Safety mitigation for off-tumor mediated killing: Dasatinib "switches off" the CD3 signaling and rapidly neutralizes TCR engagement



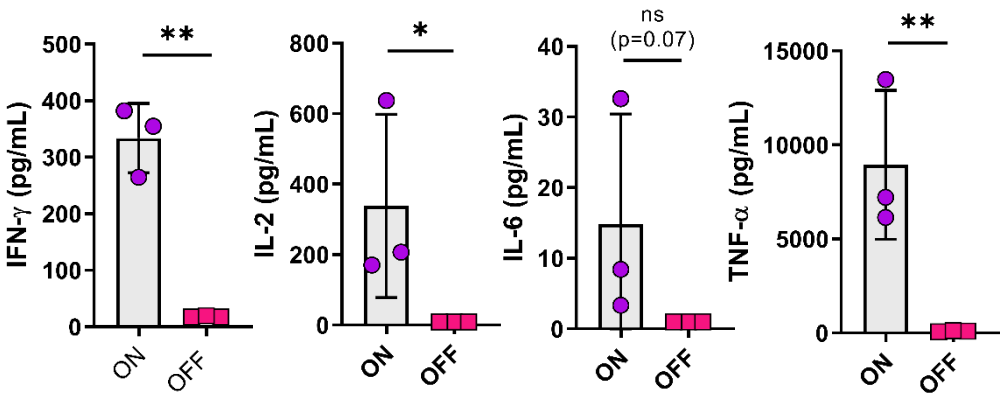
***In vitro* "T cell dependent cellular cytotoxic assay"**

Leclercq G, et al. Src/lck inhibitor dasatinib reversibly switches off cytokine release and T cell cytotoxicity following stimulation with T cell bispecific antibodies - Journal for ImmunoTherapy of Cancer 2021

Dasatinib prevents target cell killing from pre-activated PBMCs



Dasatinib prevents cytokine release from pre-activated PBMCs



Doing now what patients need next

Christine Garnett

Clinical Reviewer

Division of Cardiology and Nephrology

U.S. Food and Drug Administration

Clinical Translational Science: Leveraging Adult Efficacy Data for Pediatrics using Bridging Biomarkers

Christine Garnett, PharmD

Division of Cardiology and Nephrology, OND, CDER, FDA

Disclaimer and Acknowledgements

My presentation reflects my opinion and is not considered official FDA guidance.

I am grateful to Drs. Norman Stockbridge, Lynne Yao and Tom Fleming for their insights and contributions to this presentation.

Pediatric Extrapolation

An approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

Factors Influencing Extrapolation Approaches

- Common pathophysiology, disease definition, course of disease

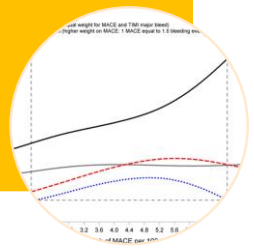
Disease Similarity

- Similar pharmacology, response endpoints
- Exposure-response relationship

Response Similarity

- Quantity and quality of existing data
- Sources: clinical, nonclinical, real world, registries, experience with similar drugs

Existing Data



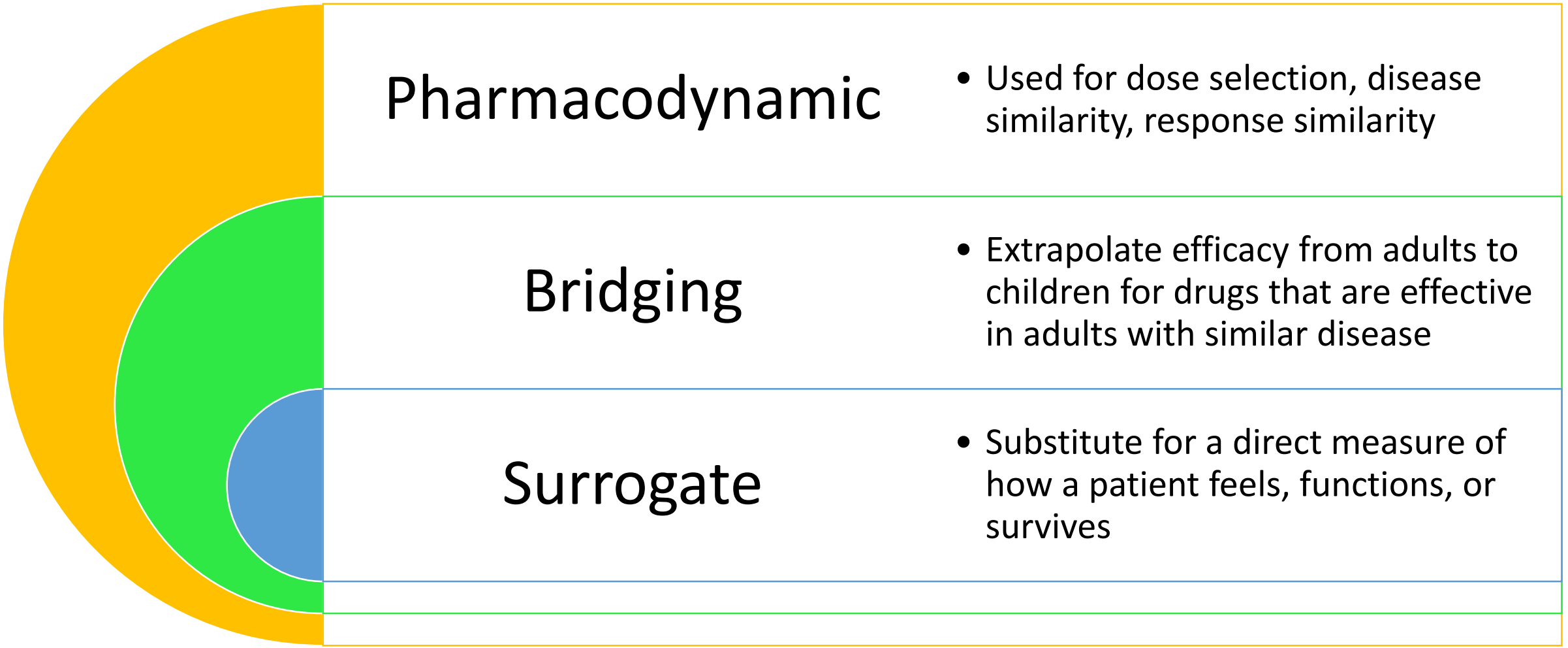
Pediatric Extrapolation Approaches

Pharmacokinetic and safety study using exposure matching

Controlled trial using bridging biomarkers
*confidence in similarity of disease
*less confidence in similarity of exposure-response in children

Adequate and well-controlled trial(s) using clinical or surrogate endpoints

Use of Biomarkers in Pediatric Extrapolation



Criteria for Establishing Bridging Biomarker

1. **Disease processes in pediatric and adult settings are closely related biologically**
2. **In adults, intervention is safe and has substantial effects on FFS measures and biomarker**
3. **Effects on the bridging biomarker capture effects on the principal causal pathway through which the disease process meaningfully influences FFS measures**
4. **Intervention does not have important unintended effects on FFS measures that are not captured by the bridging biomarker**
5. **In adults, intervention's net effect on FFS measures is consistent with what would be predicted by the level of intervention's effect on the bridging biomarker**

FFS = Feels, functions, survives

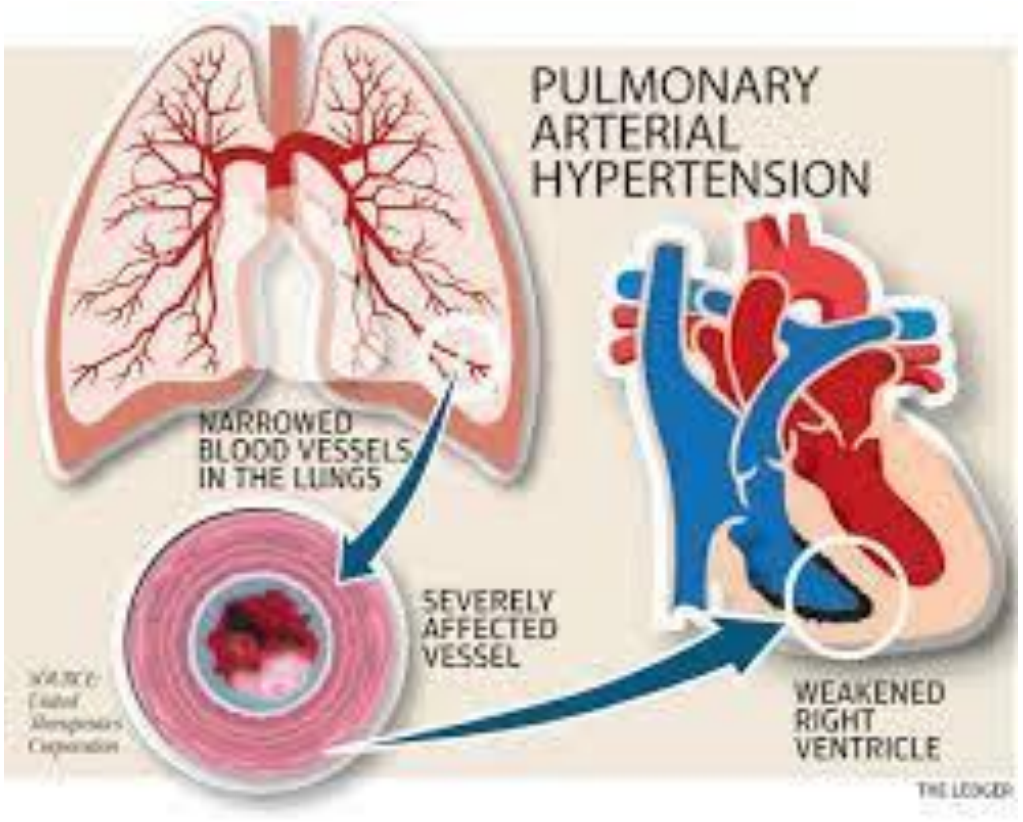
FDA Uses Bridging Analyses of Pediatric Hemodynamic Data to Adult Exercise Capacity in the Approval of Tracleer® (Bosentan) for Pediatric Pulmonary Arterial Hypertension Patients 3 Years of Age and Older

On September 5, 2017, the US Food & Drug Administration (FDA) approved Tracleer (bosentan) for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in pediatric patients aged 3 years and older. This is the first approval of a drug for the treatment of pediatric PAH with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability. FDA's efficacy evaluation relied on the findings from one of the trials − BREATHE-3, an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years which measured PVR, a cardio-pulmonary hemodynamic variable. FDA conducted analyses using data from previously approved programs in adults that established the relationship between improvements in the 6-minute walk distance (6MWD) and PVR in adults and showed that the relationship was consistent across different approved drug classes (e.g., endothelin receptor antagonist, prostanoids, PDE5 inhibitor, and soluble guanylate cyclase stimulator). The observed reduction in PVR in pediatrics from the BREATHE-3 study was used to bridge the bosentan efficacy findings in adults.

–American College of Clinical Pharmacology, 2017

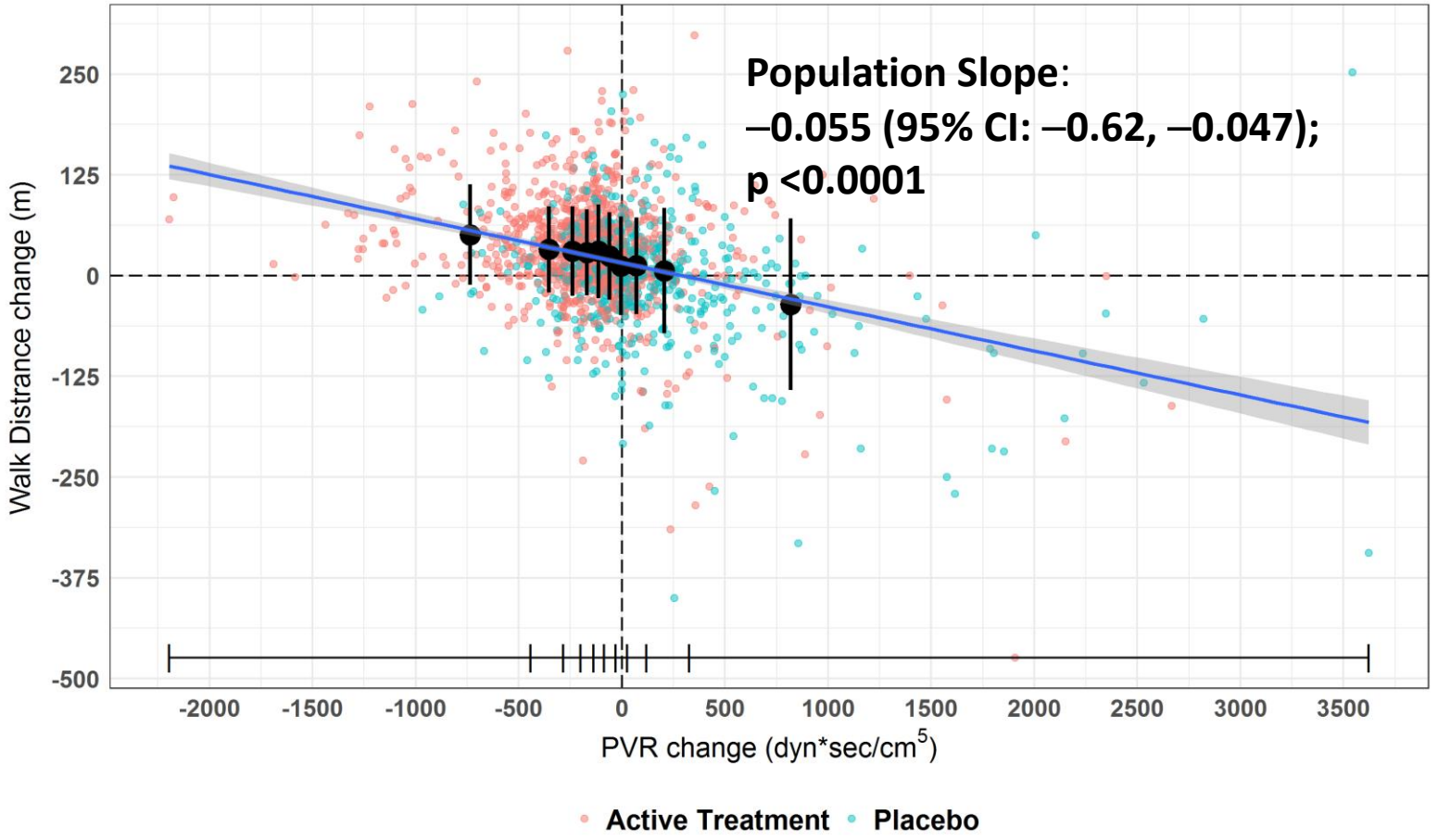
PVR as Bridging Biomarker for Pulmonary Arterial Hypertension

- Adult and pediatric PAH subtypes of idiopathic, heritable and associated with congenital heart disease are similar in pathophysiology
- PVR is a hemodynamic measure of pulmonary arterial pressure and cardiac output. PVR is on the causal pathway through which the disease process impacts how patients feel, function and survive



PVR = Pulmonary vascular resistance

Improvement in Δ6MWD Corresponds to Decrease in ΔPVR in Adults



Shown are the observed data by treatment assignment overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ6MWD within each decile of ΔPVR.

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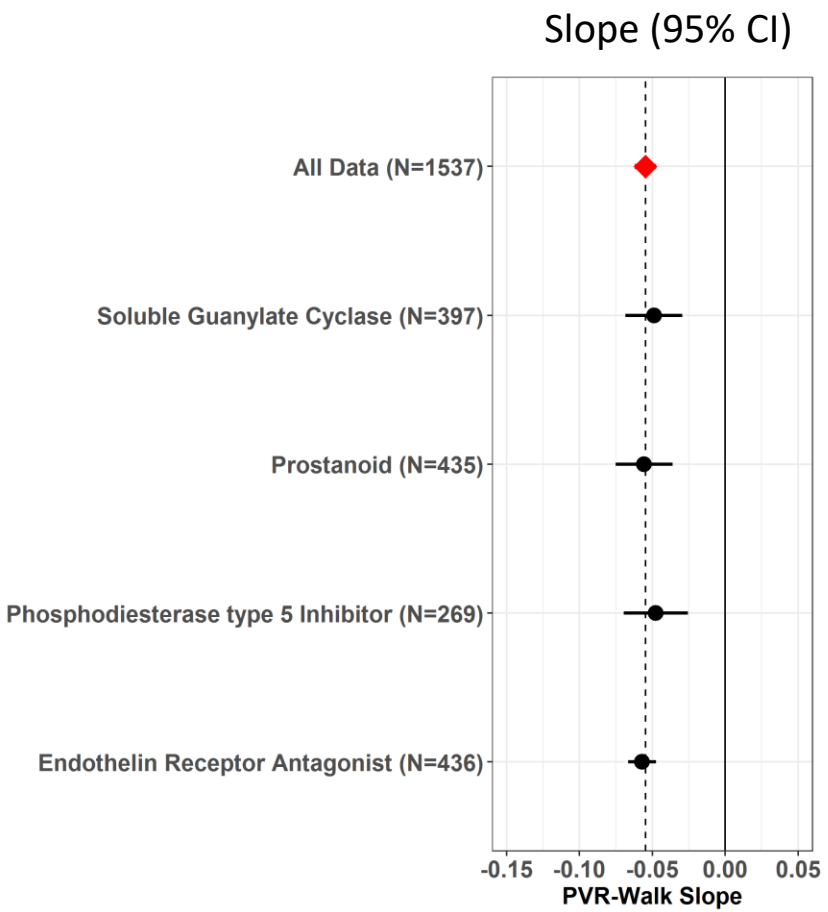
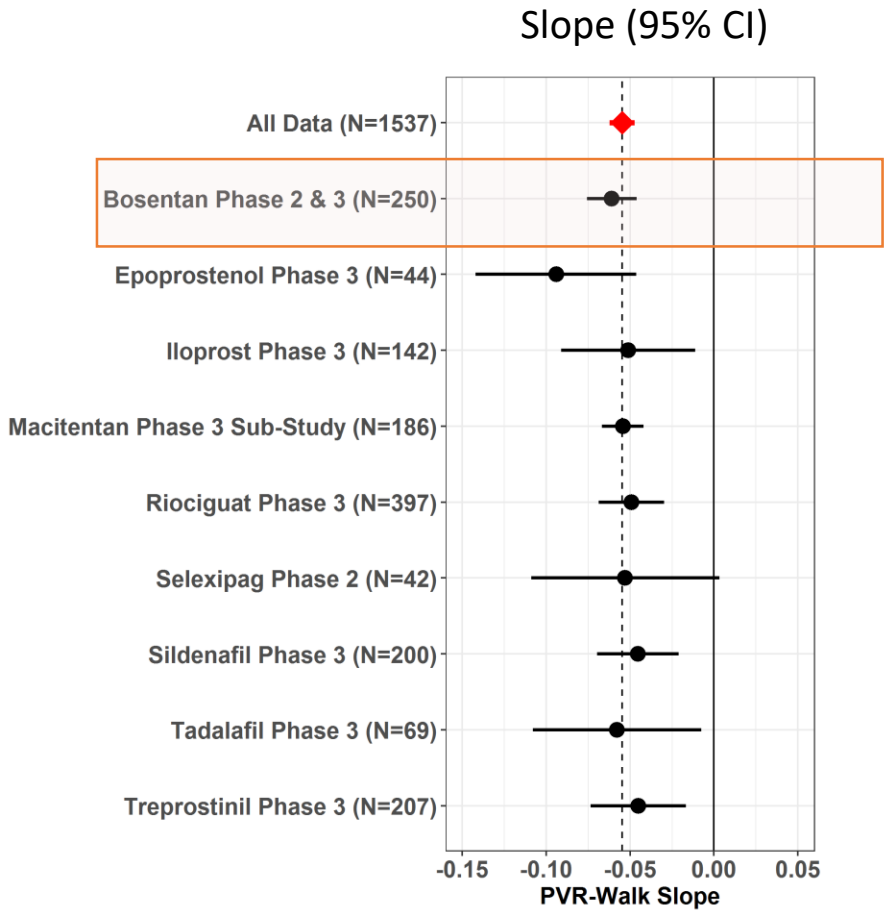
Consistent Relationship Across Drug Classes and Drugs in Adults





Forest plot of mean (95% CI) regression slopes shown by drug class (left) and individual drugs (right). The dashed line is the mean slope of pooled data.

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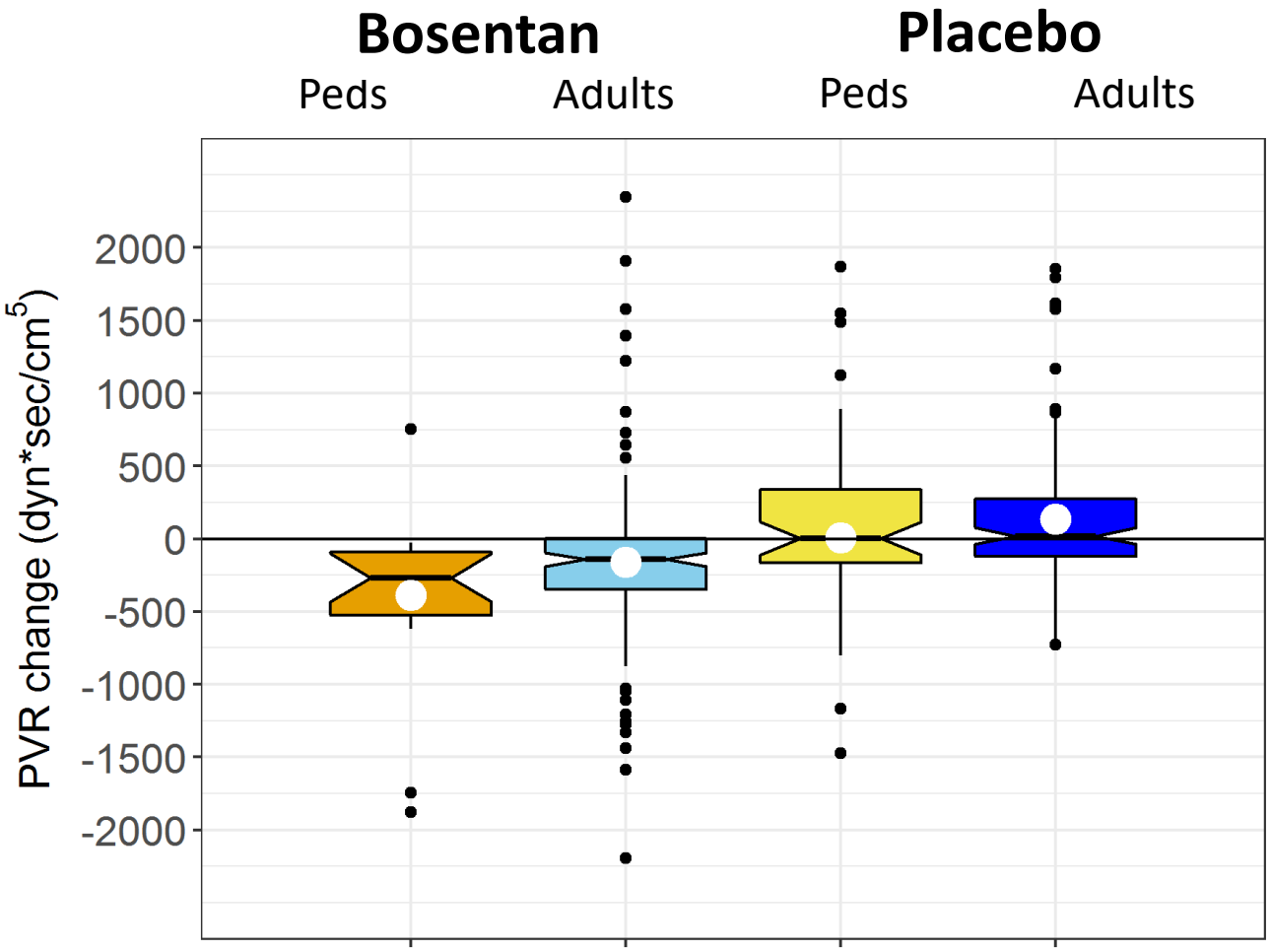
PVR explains the treatment effect on 6 min walk distance in adults

- Bosentan had significant effects on Δ6MWD and ΔPVR:
  - Clinical endpoint, Δ6MWD : +35 m
  - Biomarker, ΔPVR : -250 dyne*sec/cm^5
- 50% treatment effect on Δ6MWD explained by ΔPVR in the data analytical model with and without treatment
- No imbalance of deaths or serious adverse events in both adults and children

Bosentan significantly reduced ΔPVR in children and adults



Box plots show the mean (white circles), median (notch); 95% CI of median (width of notch); 25th and 75th percentile (width of box); 1.5* interquartile range (whiskers); and outliers (filled circles).

Bosentan Indication

- Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):
  - in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
  - **in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.**

Conclusions

- Use of bridging biomarkers in pediatric extrapolation is distinct from other roles for biomarkers:
  - Not PD marker that is used to support dose selection
  - Not validated surrogate endpoint that can reliably predict the net effect of the intervention on feels, functions, or survives outcomes.
- To establish a bridging biomarker in registrational decision-making, the biomarker should satisfy the 5 core criteria
- Pediatric extrapolation using a bridging biomarker has been used to approve drugs for pediatrics
  - Bosentan for pediatric PAH

References

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- ICH E11A: Pediatric Extrapolation Guideline (draft, currently under public consultation)
- ADEPT 7 workshop (September 1, 2021) https://cersi.umd.edu/2017-drug-development-pediatric-heart-failure-workshop
- Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996;125(7):605-613. doi:10.7326/0003-4819-125-7-199610010-00011
- Clinical Review of NDA020927. TRACLEER (bosentan) dispersible tablets.2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209279Orig1s000MedR.pdf.

Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

Moderator:

- David Strauss, US Food and Drug Administration

Panelists:

- Leslie Gordon, Brown University
- Estelle Marrer-Berger, Roche
- Christine Garnett, US Food and Drug Administration
- Anthony Durmowicz, Cystic Fibrosis Foundation
- Lynne Yao, US Food and Drug Administration

Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

Discussion Questions:

1. What translational approaches assist in drug development programs beyond use of surrogate endpoints?
2. What benefits and challenges exist in using these translational approaches to support drug development?
3. How can translational science approaches support regulatory submissions for accelerated approval or traditional approval?
4. Is there more that can be done to encourage use of these approaches?

Session 5: Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

3:30 pm – 4:15 pm EST

Session 5: Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

Moderator:

- Michael Pacanowski, US Food and Drug Administration

Panelists:

- Jeffrey Siegel, US Food and Drug Administration
- David Reese, Amgen
- Jen Farmer, Friedrich's Ataxia Research Alliance
- Steve Hoffmann, Foundation for the National Institutes of Health

Session 5 : Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

Discussion Questions:

1. Reflecting on the meeting, what are key strategies for optimizing the use of surrogate endpoints and other translational approaches for drug development?
2. What are the challenges to taking a biomarker from discovery to validation?
3. Is there more that can be done to facilitate the process? What mechanisms might be able to increase the use of translational research studies?
4. What are key strategies for facilitating collaboration between stakeholders, with the overall goal of improving therapeutic development and approval?
5. What are future considerations and next steps for advancing translational science studies and increasing the use and acceptability of these approaches?

Closing Remarks | Day 2

Michael Pacanowski

Director of the Division of Translational and Precision Medicine

U.S. Food and Drug Administration

Thank You!

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