CHALLENGES IN AD CLINICAL TRIALS
ROLE OF THE ACTC

October, 2019

Latest disappointments

- Crenezumab in sporadic early AD Phase 3 program halted for futility
- Verubecestat in AD, prodromal AD
- EARLY: atabecestat in preclinical AD (liver toxicity, cognitive worsening)
- Lanabecestat
- Umibecestat
- Elenbecestat
- Aducanumab in early AD

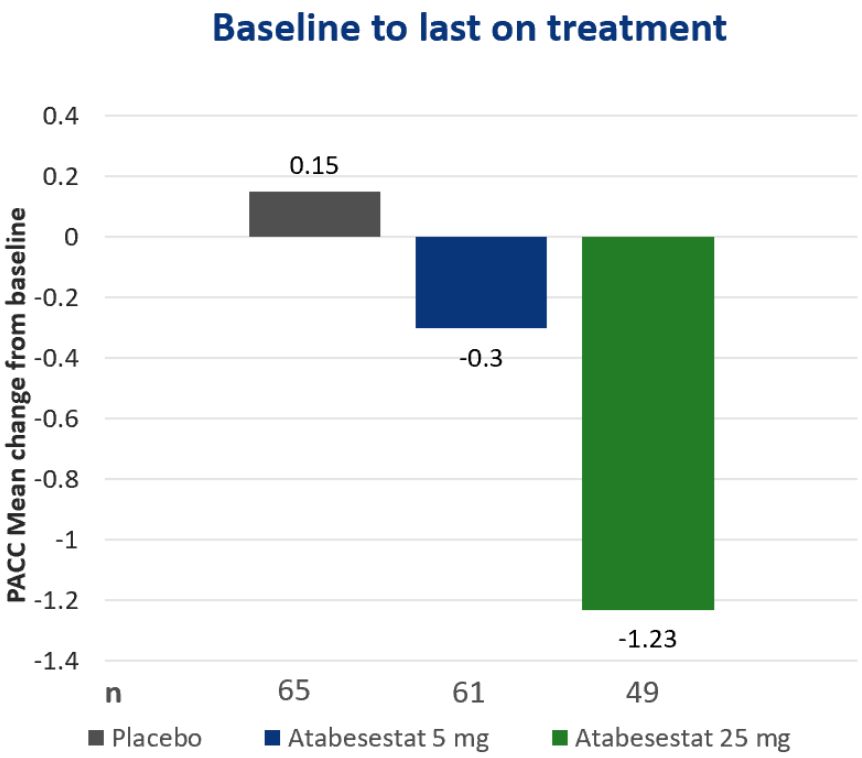
Time to give up on amyloid?

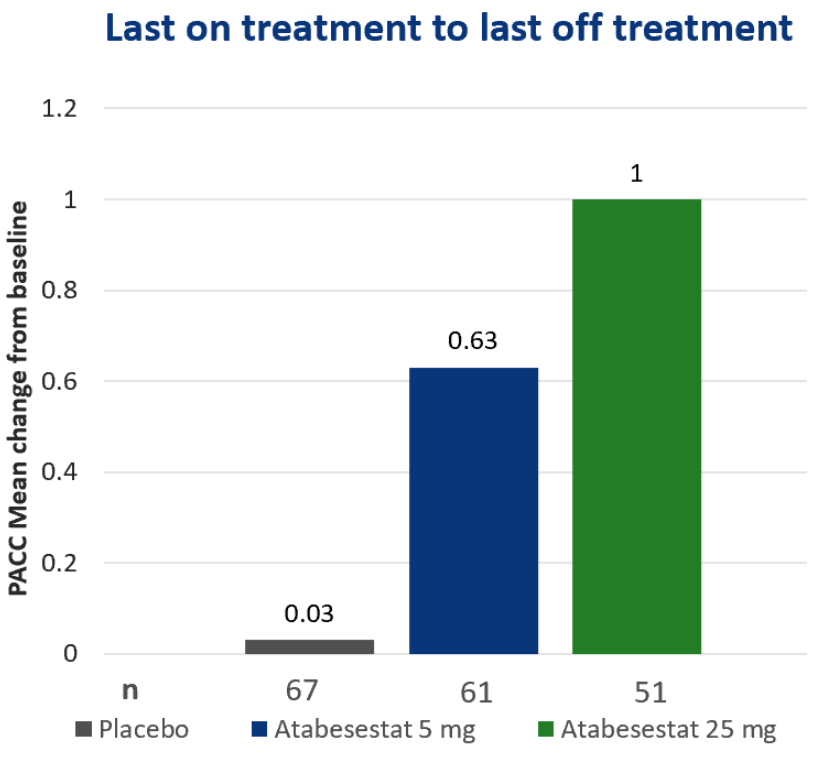
- Growing controversy
- Are alternatives more promising?

Biggest recent disappointment in the field

- BACE inhibitors carry risk of toxicity
  - Rapid onset, dose-related (but non-progressive and possibly reversible) cognitive worsening seen with multiple BACEi
  - Increase in hippocampal atrophy (non-progressive)
  - Narrow therapeutic index
  - Similar to GSI?!

EARLY: cognitive effects of atabecestat





These data suggests that adverse cognitive effects are dose-related and reversible

We should not give up on BACE inhibition

- The amyloid hypothesis remains *by far* the most compelling basis for disease-modification therapy
- BACE inhibition remains a powerful approach to primary prevention and early treatment
- Modest, reversible cognitive toxicity can readily be monitored during a trial
- Modest inhibition (30-50%) should be studied in appropriate populations

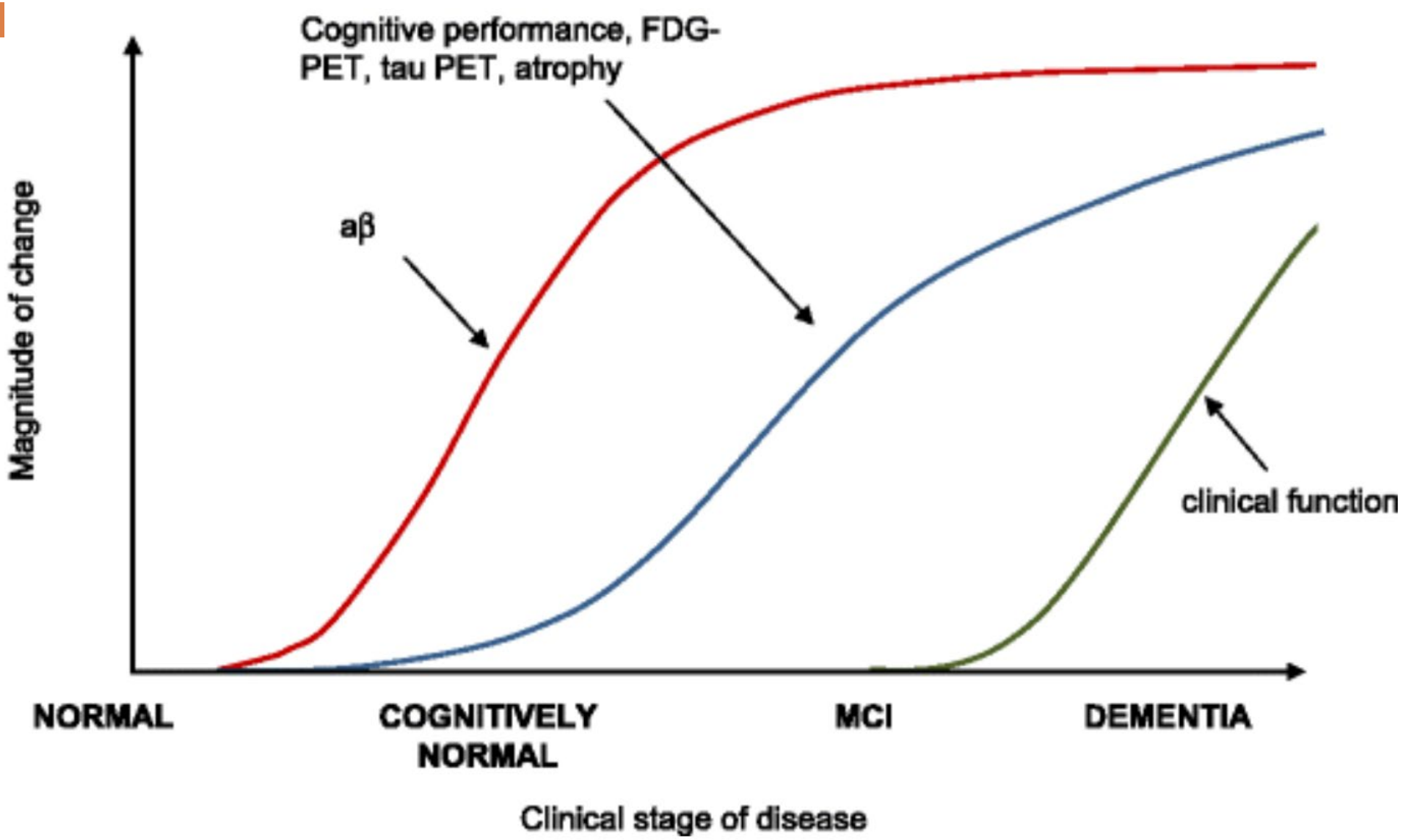
- It will not be easy to move forward with BACEi, but nothing that we do is easy

Data sharing and collaborative analysis is essential (CAP guidance)

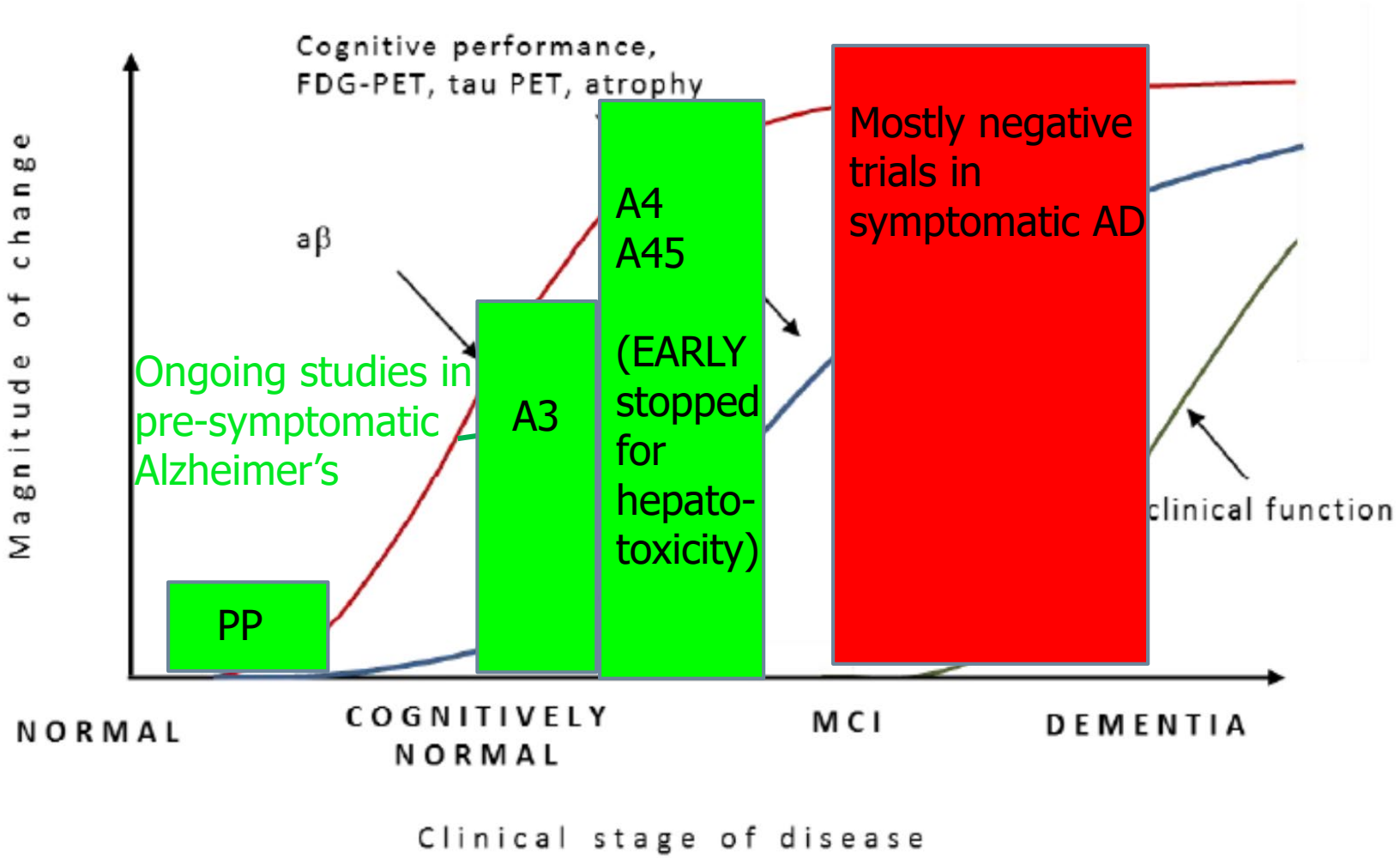
- Aducanumab data
- EARLY
- GENERATION studies
- Elenbecestat

- Were these early discontinuation decisions justified? What exactly are the lessons?

AD Continuum



When should we target amyloid?

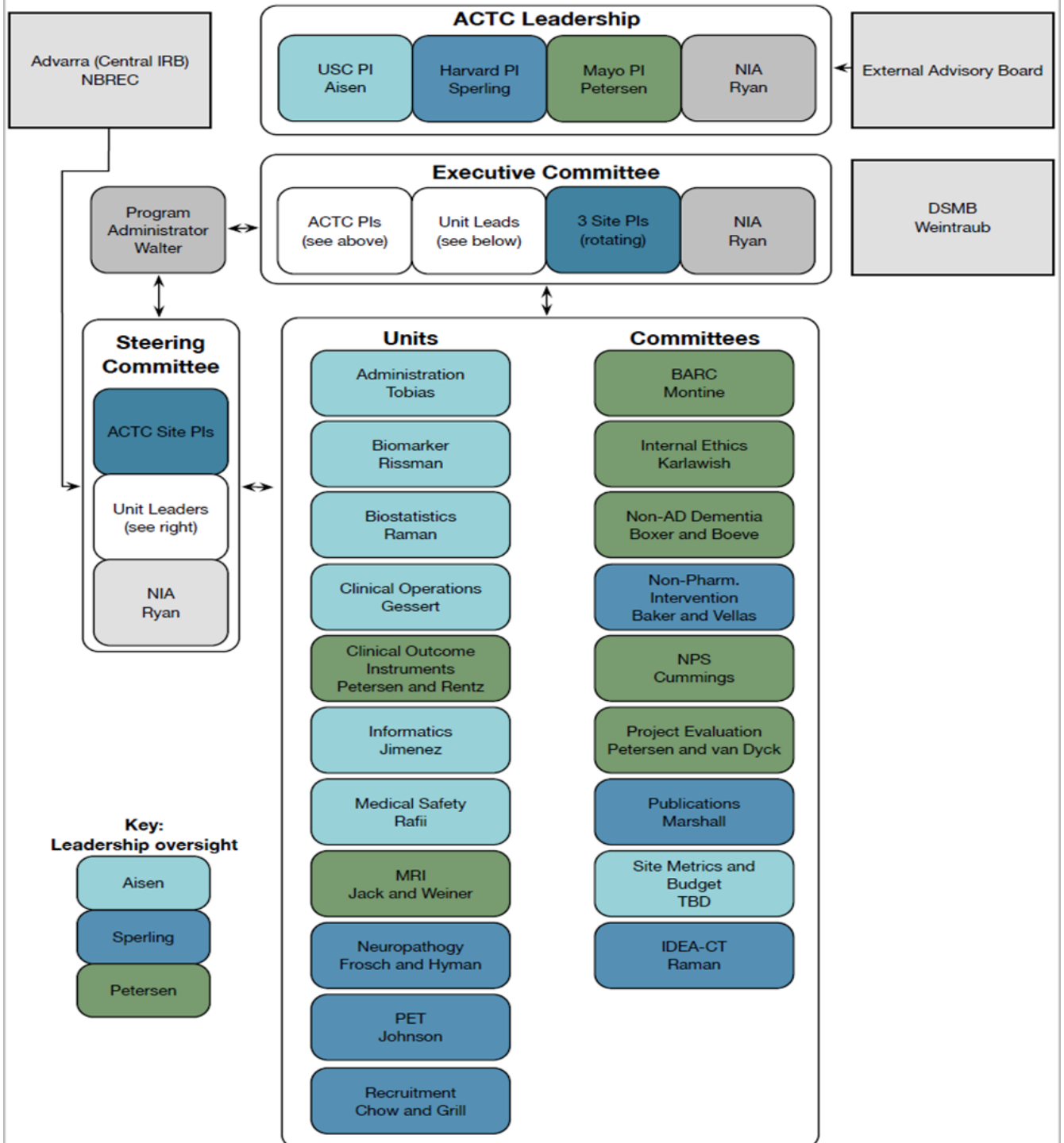


Amyloid studies continue

- A4 continues in preclinical AD, OLE funded, interim cognitive safety analysis
- BAN2401 continues in early AD
- Gantenerumab continues in early AD
- API Colombia study with crenezumab continues
- DIAN-TU solanezumab, gantenerumab continue

ACTC

- Alzheimer's Clinical Trials Consortium


Advarra (Central IRB)
NBREC
ACTC Leadership
USC PI
Aisen
Harvard PI
Sperling
Mayo PI
Petersen
NIA
Ryan
External Advisory Board
Executive Committee
Program
Administrator
Walter
ACTC PIs
(see above)
Unit Leads
(see below)
3 Site PIs
(rotating)
NIA
Ryan
DSMB
Weintraub
Steering
Committee
ACTC Site PIs
Unit Leaders
(see right)
NIA
Ryan
Units
Administration
Tobias
Biomarker
Rissman
Biostatistics
Raman
Clinical Operations
Gessert
Clinical Outcome
Instruments
Petersen and Rentz
Informatics
Jimenez
Medical Safety
Rafii
MRI
Jack and Weiner
Neuropathogy
Frosch and Hyman
PET
Johnson
Recruitment
Chow and Grill
Committees
BARC
Montine
Internal Ethics
Karlawish
Non-AD Dementia
Boxer and Boeve
Non-Pharm.
Intervention
Baker and Vellas
NPS
Cummings
Project Evaluation
Petersen and van Dyck
Publications
Marshall
Site Metrics and
Budget
TBD
IDEA-CT
Raman
Key:
Leadership oversight
Aisen
Sperling
Petersen

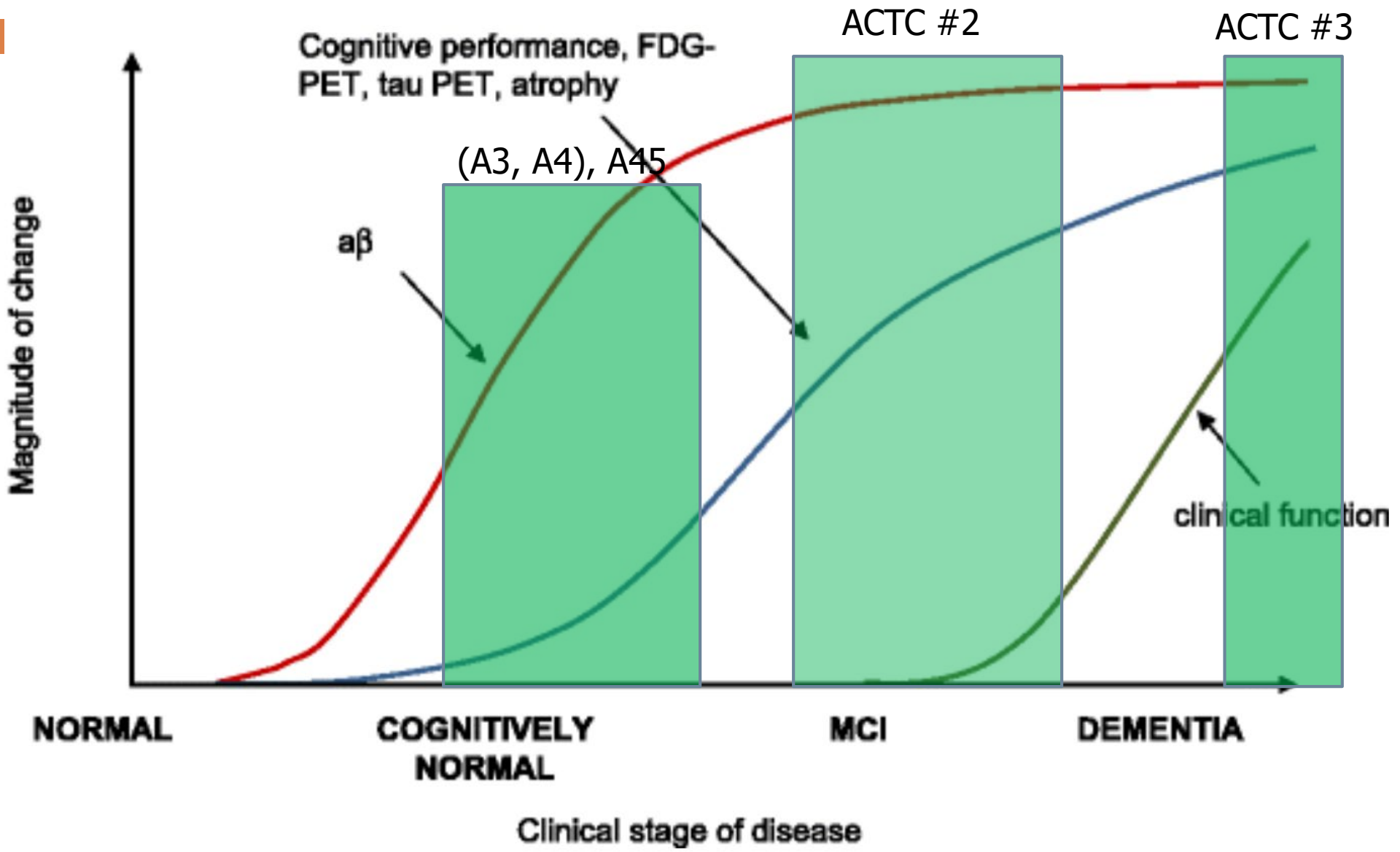
Importance of effective collaboration among clinicians and biostatisticians

- Major unresolved issues:
  - Primary analysis
    - Frequentist v. Bayesian
    - Disease progression models versus MMRM
    - Time-to-endpoint v. continuous measures
  - Interim analysis, cost v. benefit
    - Futility
    - Efficacy
  - Censoring of intercurrent events
  - Missing data
- ACTC/ATRI model v. separation of DCC from CCC

ACTC project development process

- Brief applications, deadlines linked to NIH submission dates
- Project feasibility review at coordinating center
- Project evaluation committee (PEC): scientific review
- Projects approved by PEC are presented to Steering Committee for vote
- Approved projects advance to collaborative NIA application with ACTC Units and Committees

ACTC Projects



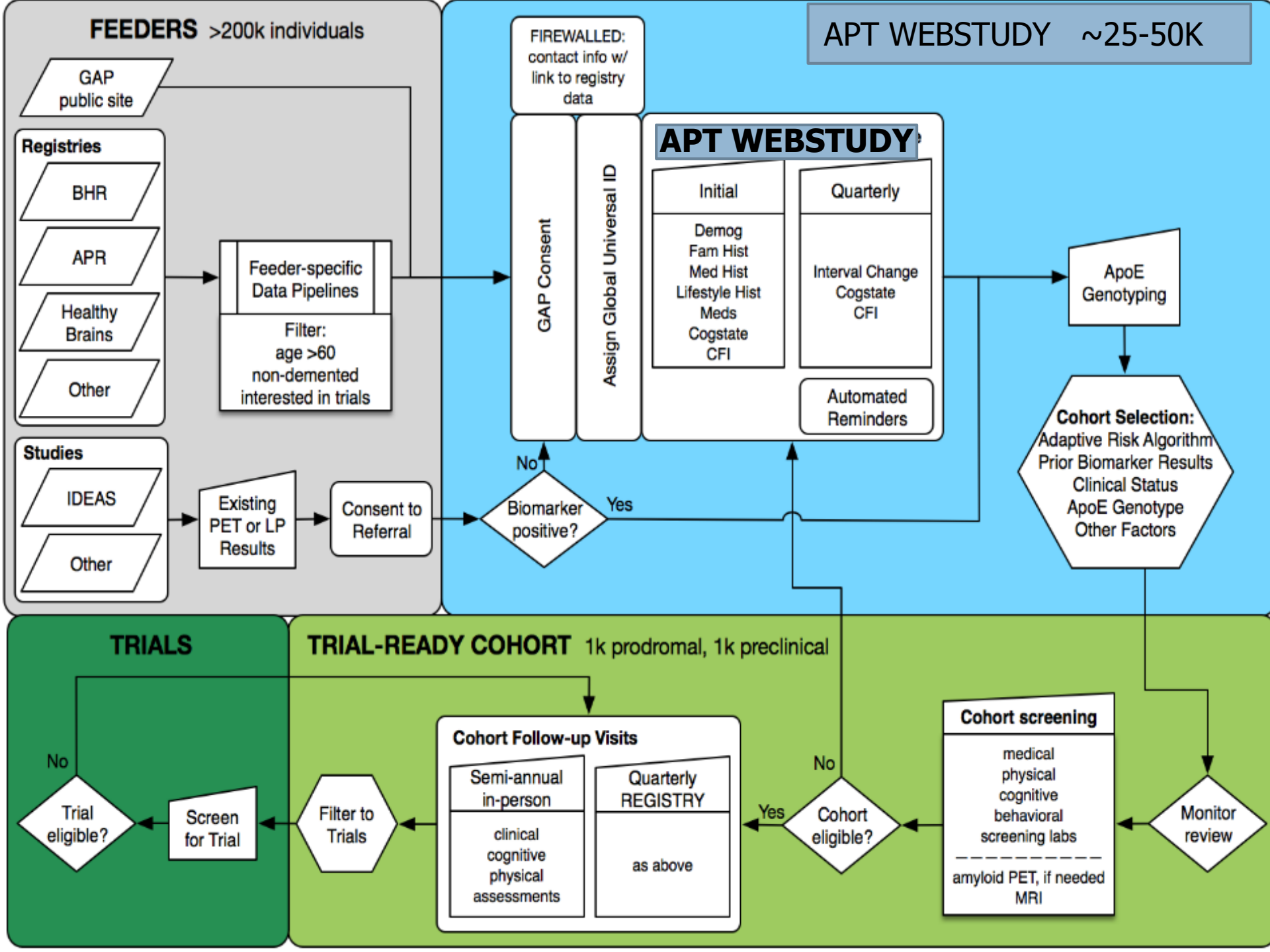
ACTC seeks strategies beyond amyloid

- Tau
- Microglial activation

- Endocrine approaches
- Anti-inflammatories
- Anti-infectives
- Target protein misfolding
- Target APOE
- Non-pharmacologic therapies
- Other age-related dementias

TRC-PAD and the APT Webstudy

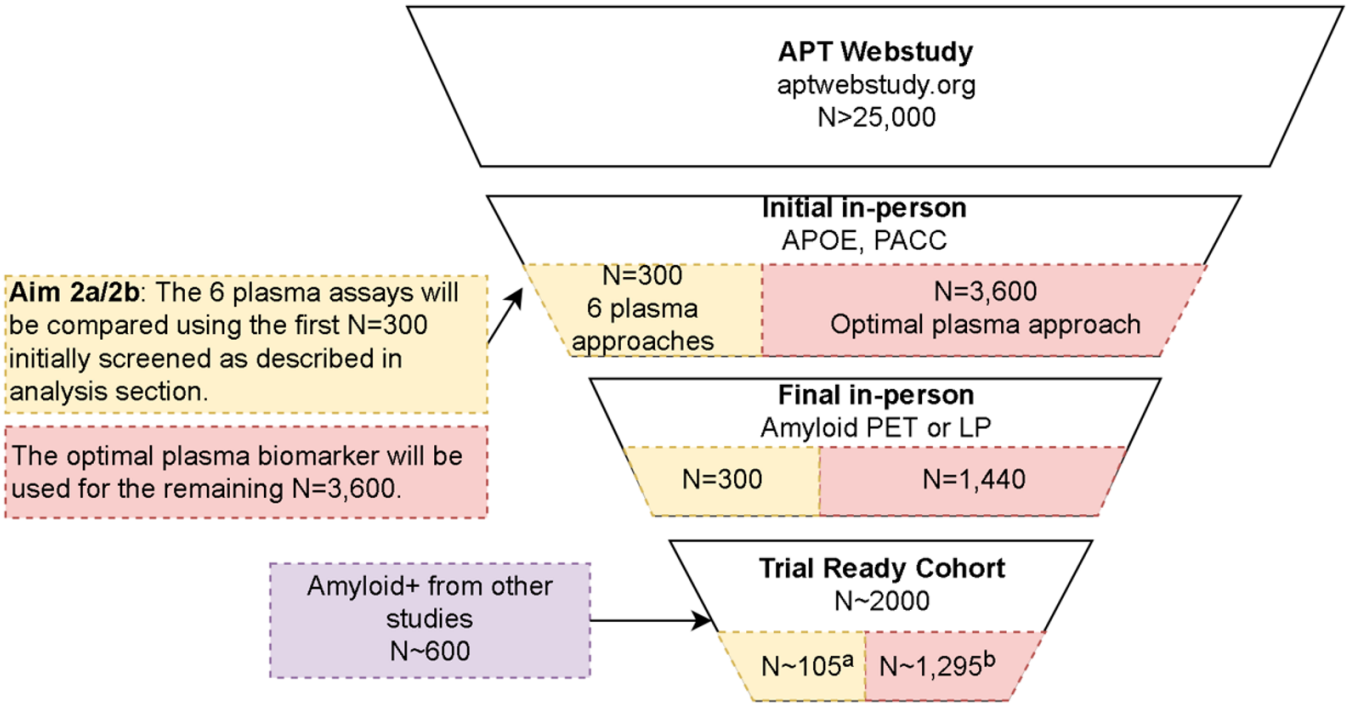
- **Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease**
- MPIs: Paul Aisen, Reisa Sperling, Jeff Cummings


APT WEBSTUDY ~25-50K
FEEDERS >200k individuals
GAP public site
Registries
BHR
APR
Healthy Brains
Other
Feeder-specific Data Pipelines
Filter: age >60 non-demented interested in trials
Studies
IDEAS
Other
Existing PET or LP Results
Consent to Referral
FIREWALLED: contact info w/ link to registry data
APT WEBSTUDY
GAP Consent
Assign Global Universal ID
Initial
Demog
Fam Hist
Med Hist
Lifestyle Hist
Meds
Cogstate
CFI
Quarterly
Interval Change
Cogstate
CFI
Automated Reminders
No
Biomarker positive?
Yes
ApoE Genotyping
Cohort Selection:
Adaptive Risk Algorithm
Prior Biomarker Results
Clinical Status
ApoE Genotype
Other Factors
TRIALS
TRIAL-READY COHORT 1k prodromal, 1k preclinical
No
Trial eligible?
Screen for Trial
Filter to Trials
Cohort Follow-up Visits
Semi-annual in-person
clinical
cognitive
physical
assessments
Quarterly REGISTRY
as above
No
Yes
Cohort eligible?
Cohort screening
medical
physical
cognitive
behavioral
screening labs
amyloid PET, if needed
MRI
Monitor review

TRC-PAD: progress

- APT Webstudy
  - Year 2
  - N>25000
  - Longitudinal Cogstate Brief Battery scores
  - Longitudinal Cognitive Function Index scores
- Risk algorithm generates predicted amyloid SUVr, with high values selected for in-person assessment
- In-person evaluations have started at 8 sites, expanding to 35
- Aim to support enrollment in A3, A45 in 2020

TRC-PAD Revision: plasma Aß ratios



[a] Assuming 35% PPV for amyloid positivity using the APT Webstudy algorithm

[b] Assuming 90% PPV of algorithm including APOE, PACC, and optimal plasma assy; and 40% prevalence of amyloid positivity in initial in-person population (an increase in prevalence compared to [a] due to APT alogirthm improvement with the inclusion of longitudinal data).

Alzheimer's Clinical Trials Consortium (ACTC)

The ACTC is a cooperative agreement between the NIA and the grantees institutions

Call for Ideas and Proposals

Eligibility: Anyone (academic or industry)

Studies: All Phases (Phase 1b-III)

Review Process:

- Contact ACTC to discuss proposed trial **(actcinfo.org)**
- Idea evaluated for mission relevance and feasibility by ACTC protocol feasibility and evaluation committees
- Formal vote by ACTC steering committee
- Approved investigator develops and submits a formal joint application to ACTC FOA.

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ACTC
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CLINICAL TRIALS CONSORTIUM