

# 91<sup>st</sup> AANP Presidential Symposium

## ***PRECISION MEDICINE: Clarity for the Clinical and Biological Complexity of Dementia***

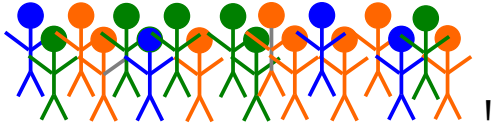

**Thomas Montine, MD, PhD**

**Alvord Professor and Chair  
Department of Pathology  
University of Washington**



# PRECISION MEDICINE

Employ new knowledge and technology to optimize timing and targeting of interventions for maximal benefit ...

!	<i>Traditional Approach</i>
Population of individuals	
Classify by risk	!
Surveillance for pre-clinical disease	!
Signs or symptoms	

# PRECISION MEDICINE

## THE PRECISION MEDICINE INITIATIVE



### LONGER TERM GOALS

Create a research cohort of **> 1 million American volunteers** who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.

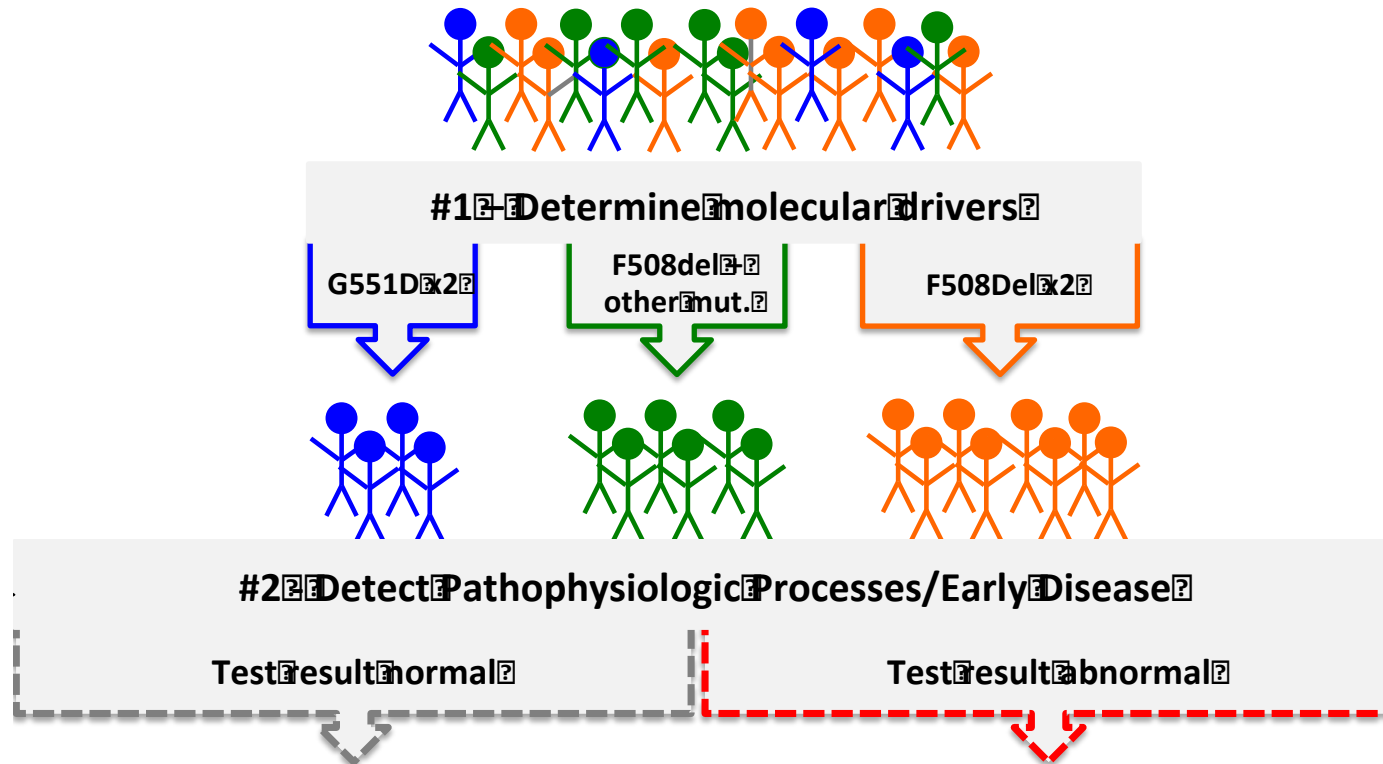


Pioneer **a new model for doing science** that emphasizes **engaged participants, responsible data sharing, and privacy protection.**

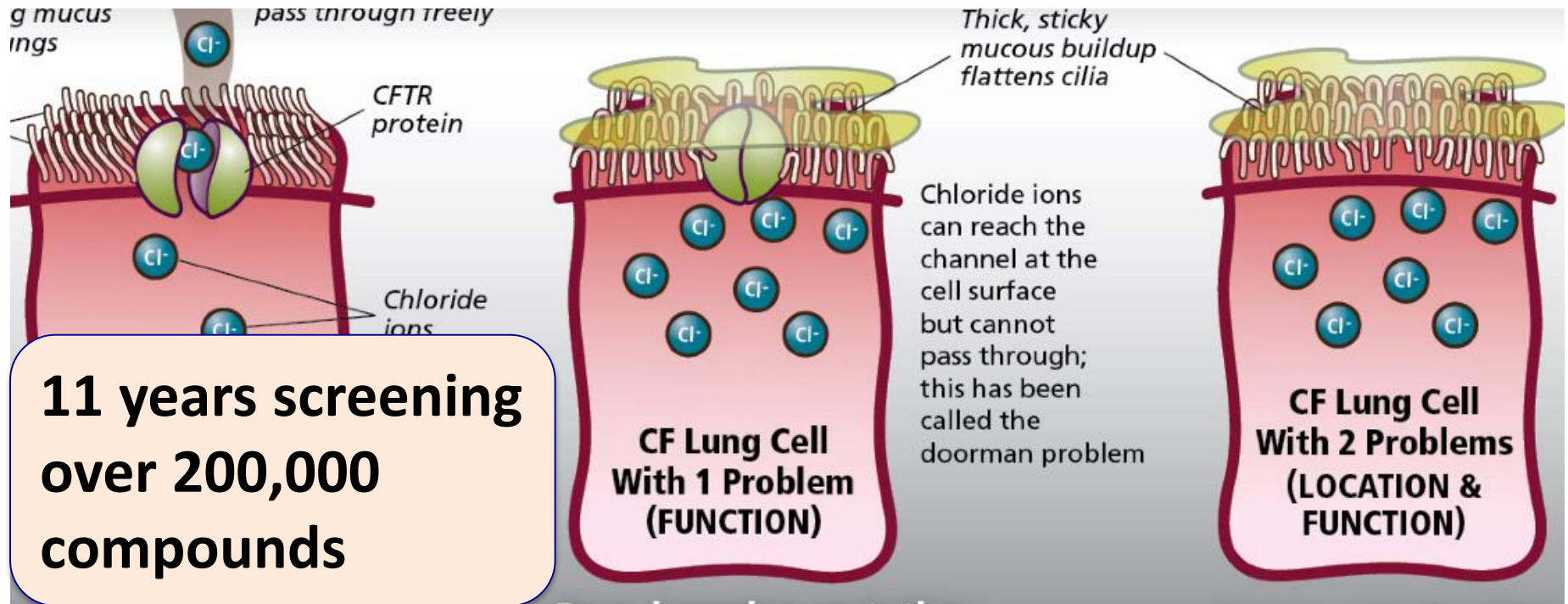
<http://www.nih.gov/precisionmedicine/>

“While significant advances in precision medicine have been made for select cancers, the practice is not currently in use for most diseases ... To accelerate the pace, President Obama unveiled the Precision Medicine Initiative (PMI) — a bold new enterprise to revolutionize medicine and generate the scientific evidence needed to move the concept of precision medicine into every day clinical practice.”

# PRECISION MEDICINE for CYSTIC FIBROSIS

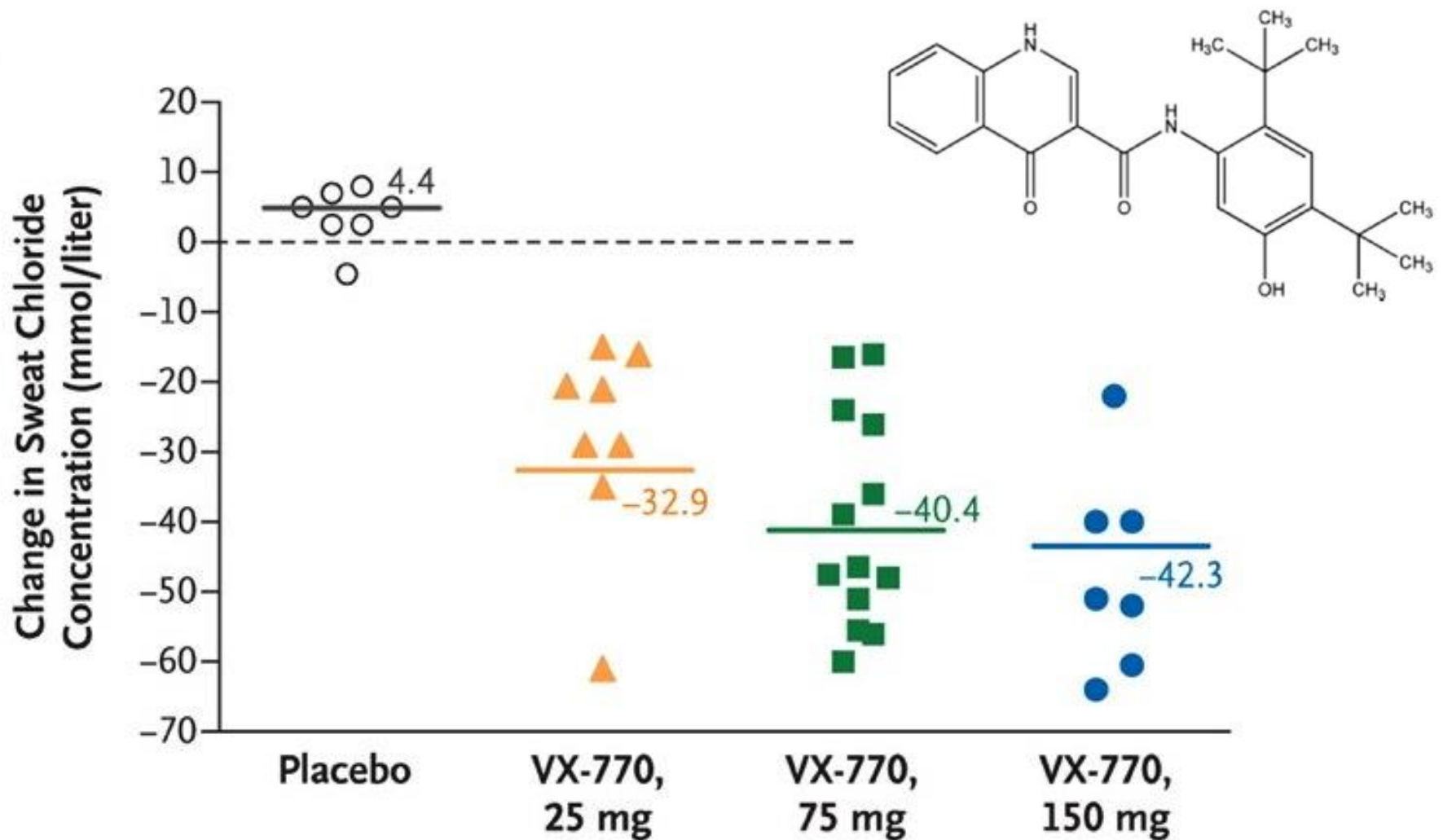


# PRECISION MEDICINE for CYSTIC FIBROSIS



Discover Magazine

# PRECISION MEDICINE for CYSTIC FIBROSIS



## Channel function VX-770

Phase 1

Phase 2

Phase 3

To Patients

Kalydeco™ (also  
known as ivacaftor)

Ataluren (formerly  
known as PTC124)

Lumacaftor +  
ivacaftor

VX-661 + ivacaftor

QR-0

Riocigu

Q

N9TH5

## Folding & Trafficking VX-809

## Folding & Trafficking

**Missense mutations:  
DMD and CF**

# PRECISION MEDICINE for CYSTIC FIBROSIS

G551D, G1244E, G1349D, G178R, G551S,  
S1251N, S1255P, S549N, S549R, or R117H

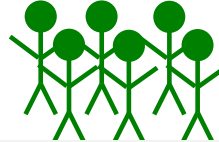


#1 Determine molecular drivers

G551D

F508del  
other mut.

F508Del



#2 Detect Pathophysiologic Processes/Early Disease

Test result normal

Test result abnormal



# PRECISION MEDICINE for DEMENTIA

## CLINICAL COMPLEXITY

- Dementia in > 65 yr olds is a syndrome mostly caused by AD, LBD, and VBI
  - Commonly co-morbid
  - Prevalent latency and prodrome

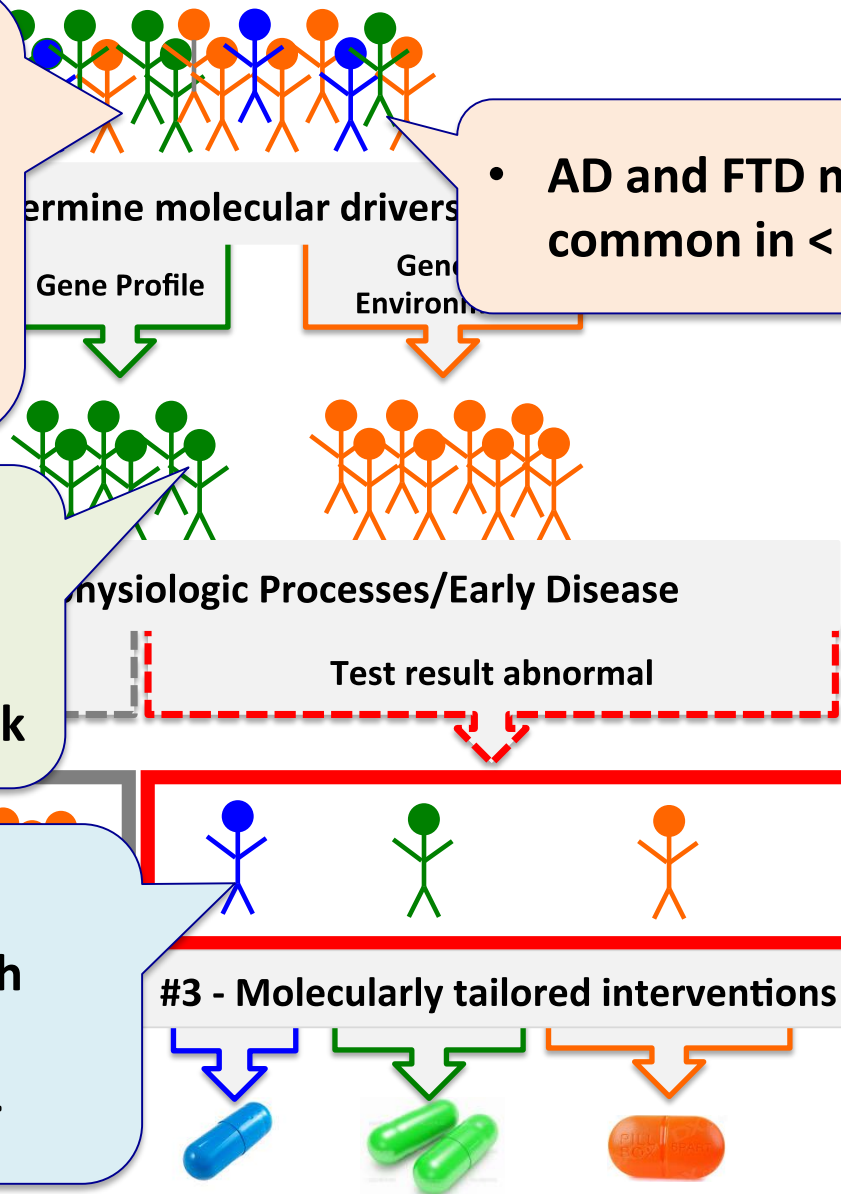
- AD and FTD most common in < 65 yr olds

## BIOLOGICAL COMPLEXITY for AD

- 3 genes with disease-causing mutations
- Over 20 genetic loci impart risk

## DIAGNOSTICS & THERAPEUTICS

- Align diseases and drivers with therapeutic mechanism
  - For AD: API, DIAN-TU, A4

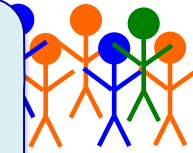


# PRECISION MEDICINE for DEMENTIA at AANP

## Alzheimer's Disease

*Drs. Schneider, Schellenberg, & Reiman*

**Parkinson's Disease  
Aging Brain**

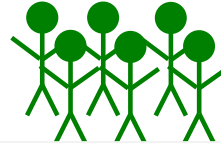


vascular drivers

Gene

Gene Profile

Gene  
Environment



**Vascular Diseases**

*Dr. Gray*

*Dr. Tournier-Lasserre*

*Dr. Frosch*

**FTD/FTLD**

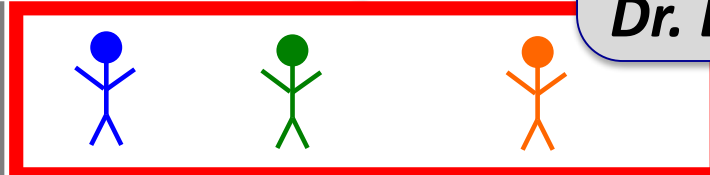
*Dr. Seeley*

**Detection & Surveillance Tools**

disease  
normal

**X-linked  
myopathy**

*Dr. Lawlor*



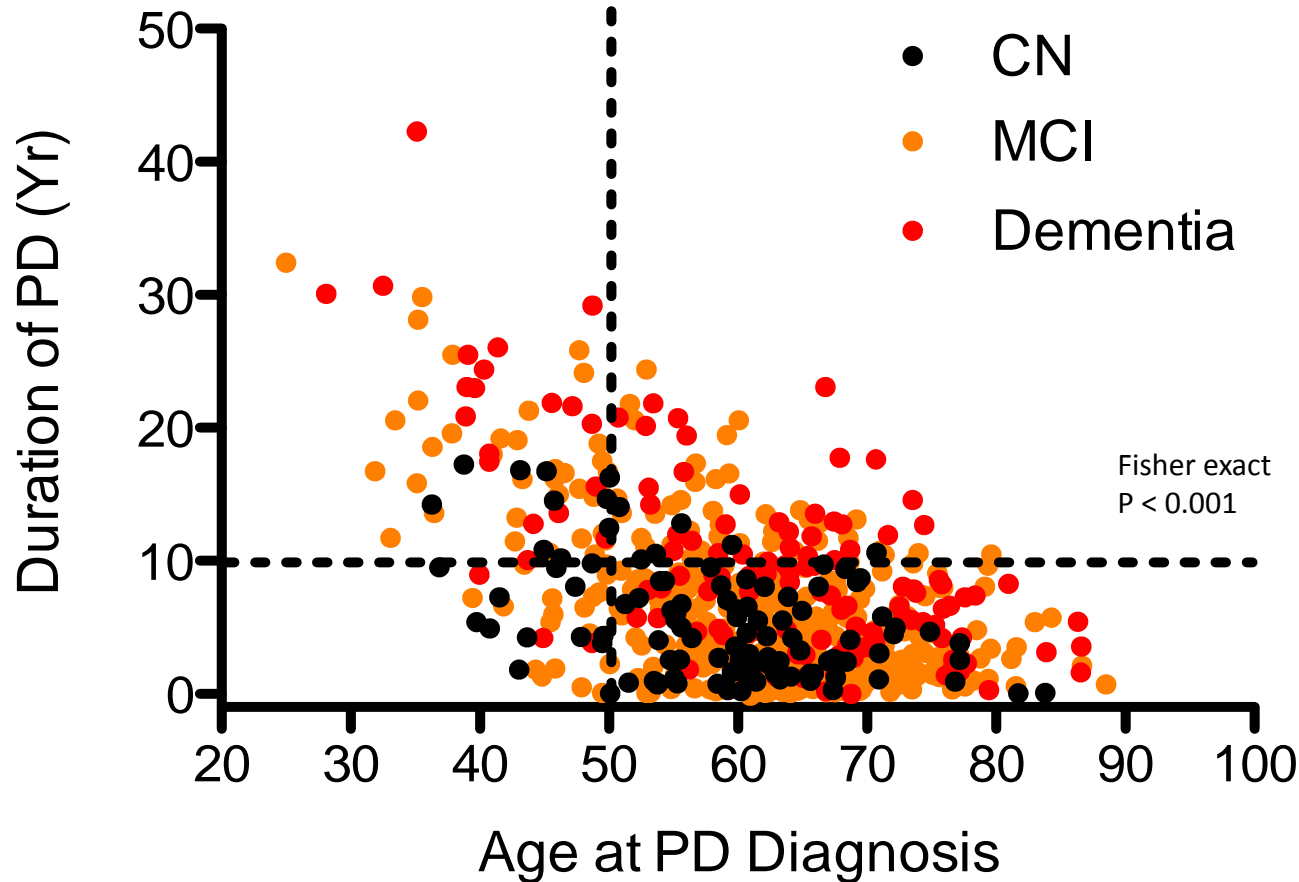
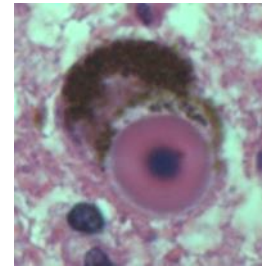
**#3 - Molecularly tailored interventions**



# CLINICAL COMPLEXITY: PARKINSON'S DISEASE

Pacific Northwest Udall Center (PANUC)

## Parkinson's

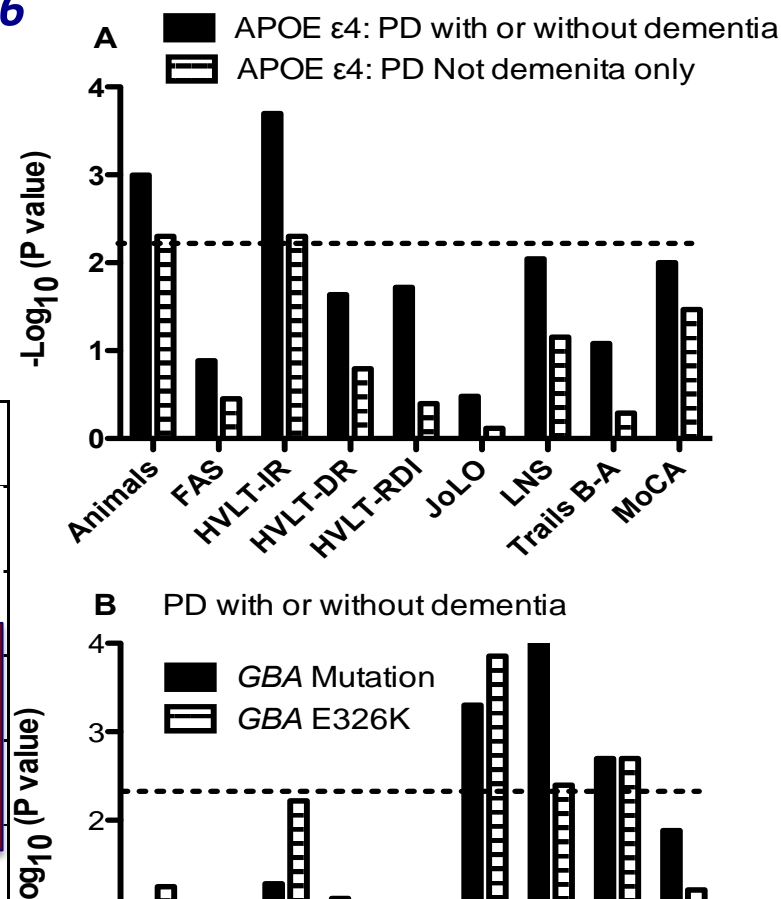


**PD-MCI or PDD: Poor response to DA replacement Tx or DBS. Some response to AChI.**

***Eur J Neurol. 2014 Dec 9***

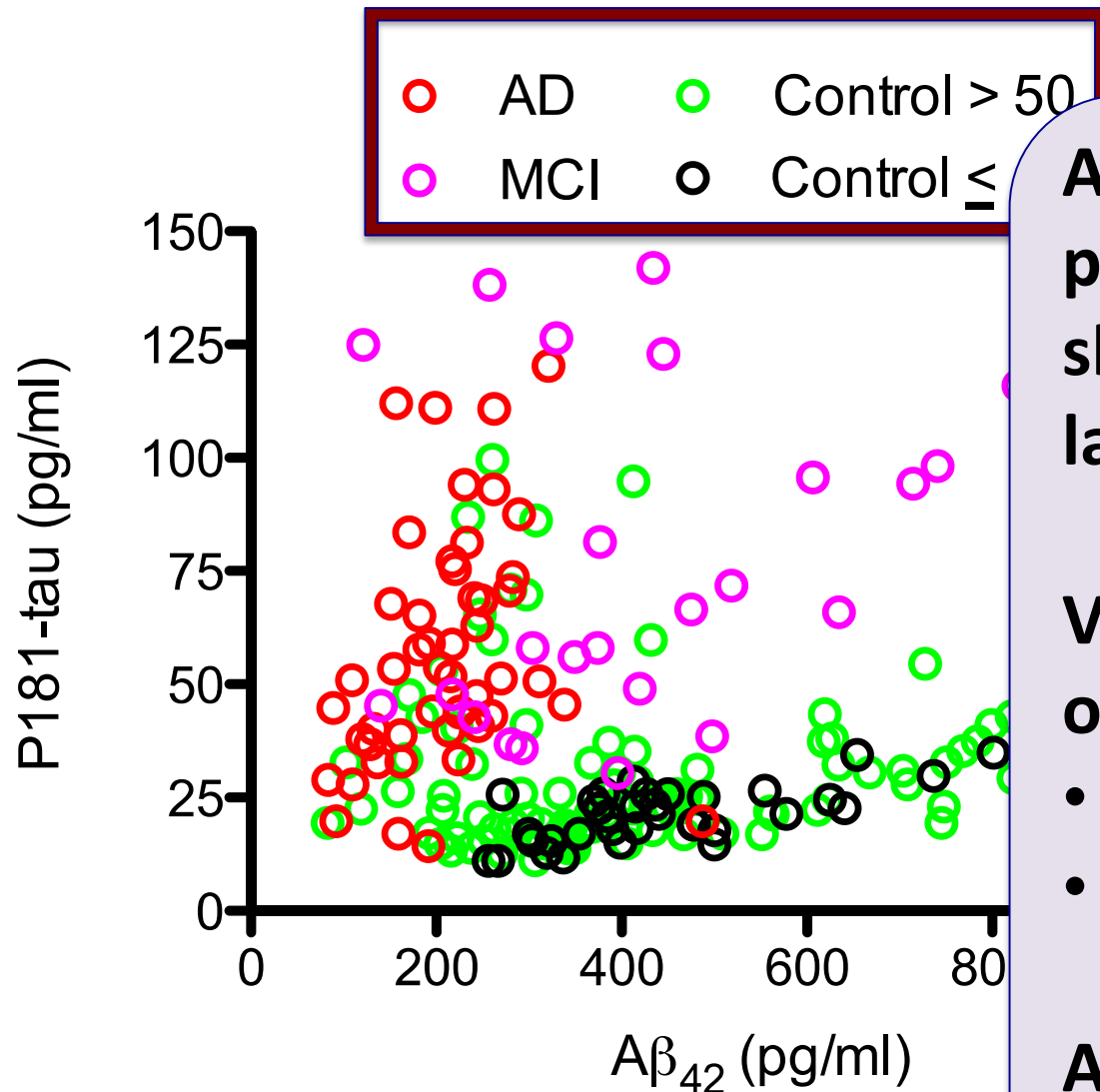
# BIOLOGICAL COMPLEXITY: PARKINSON'S DISEASE

- *PD (Motor) Genetic Risk - Nat Genet 2014;46:989-93 (24 loci)*
- *PD Autopsy GWAS - Neurology 2015 Feb 6*
- *PD Cognitive Genetics Consortium*
  - All Udall Centers and other groups with compatible neuropsych data



Genetic risk for the quantity and quality of cognitive phenotype in PD is different from motor phenotype

# DETECTION and SURVEILLANCE TOOLS



Vertebrae  
Spinal cord

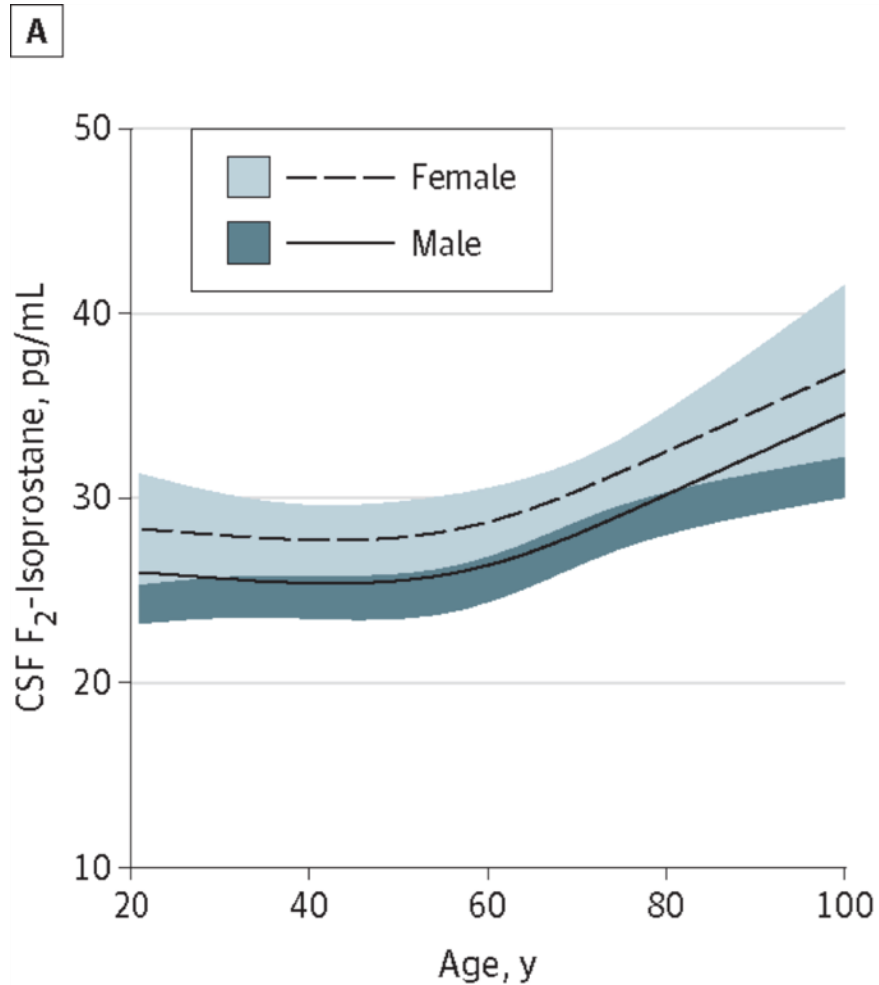
**About 20% of people over 50 yr show evidence of latent AD**

**Validated with other tools**

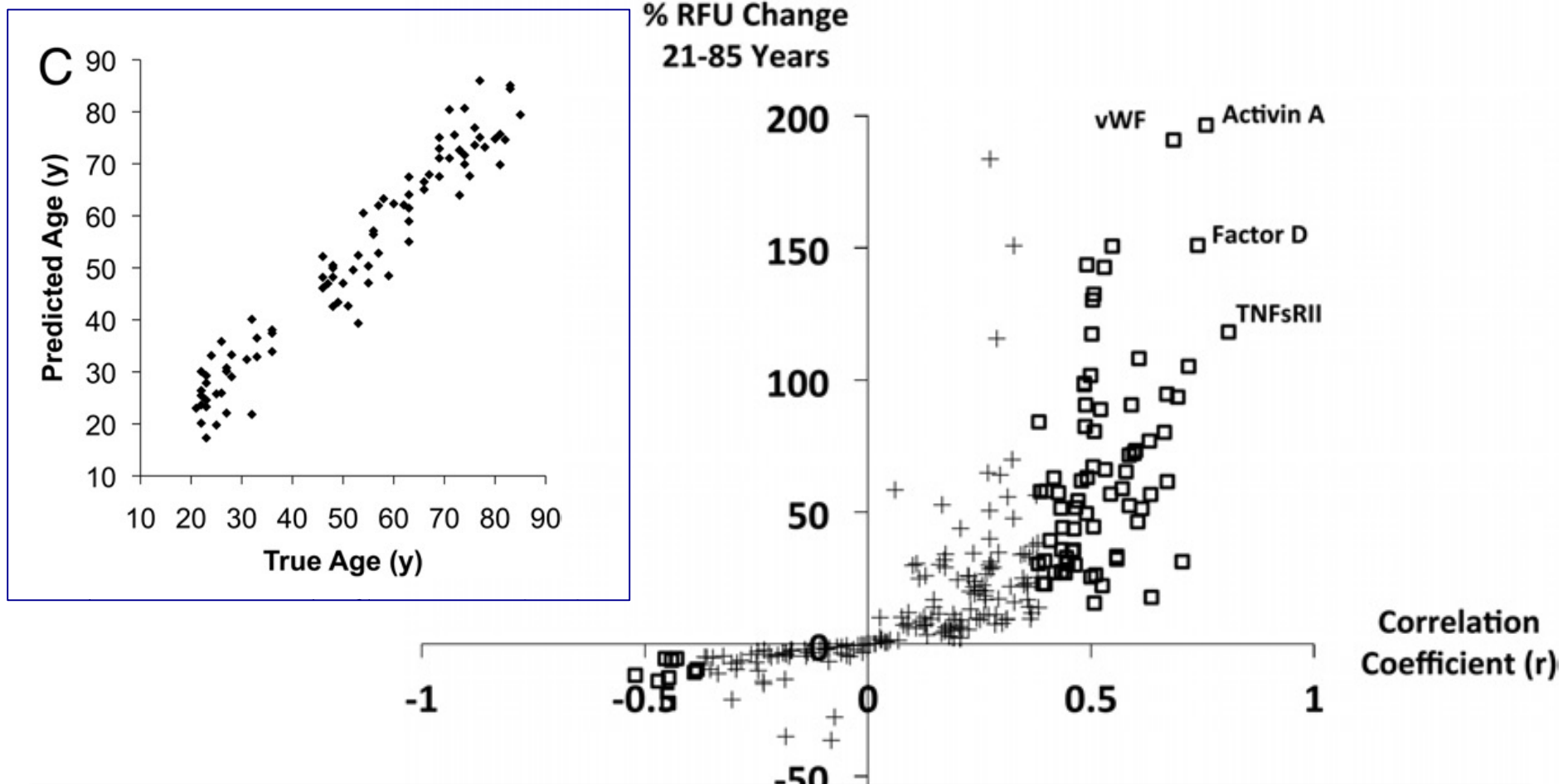
- PET Imaging
- MRI

**Analogous tools for PD**

# AGING BRAIN



# AGING BRAIN

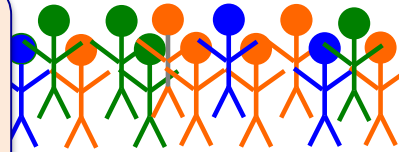


**Aging brain is a progressively pro-inflammatory and pro-oxidative environment that may be modulated by life-style choices.**

# PRECISION MEDICINE for ALZHEIMER'S DISEASE

## CLINICAL COMPLEXITY

Dr. Schneider



#1 – Determine molecular drivers

Gene

Gene Profile

Gene x  
Environment

## BIOLOGICAL COMPLEXITY

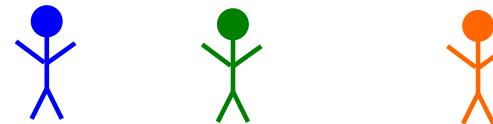
Dr. Schellenberg



#2 – Detect Latent Pathophysiologic Processes/Early Disease

Test result normal

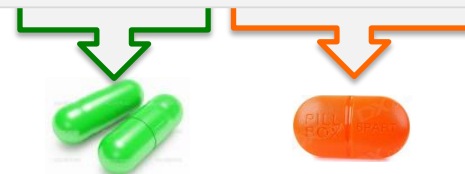
Test result abnormal



## DIAGNOSTICS & THERAPEUTICS

Dr. Reiman

#3 – Molecularly tailored interventions





PANUC  
*Pacific Northwest Udall Center*

