State of Science of Multimodal Biomarkers for CNS Disorders: Parkinson's Disease

A perspective from early clinical drug development

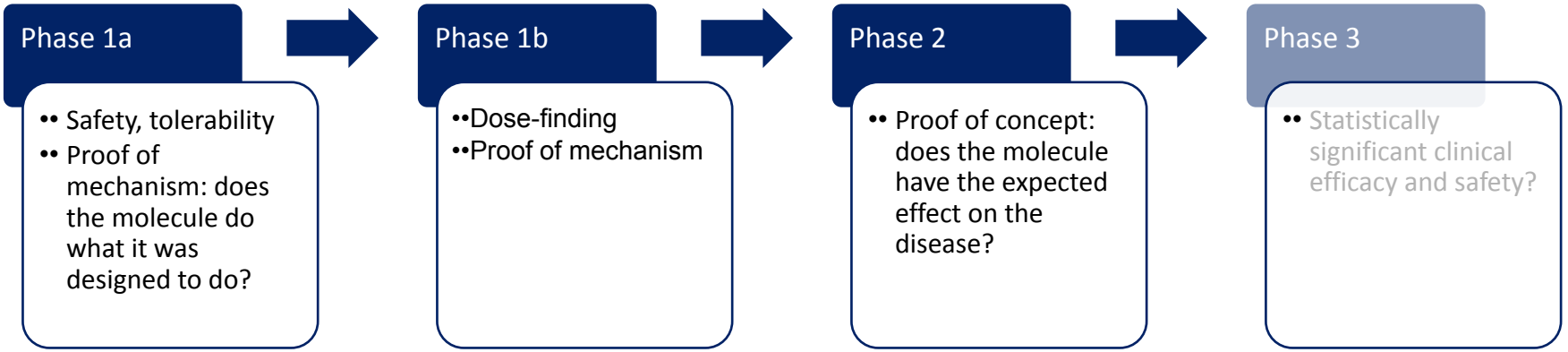
Kirsten Taylor
Expert Scientist
Biomarkers and Translational Technologies
Neuroscience and Rare Diseases
Pharma Research and Early Development
F. Hoffmann-La Roche Ltd.

With special thanks to my Roche biomarker colleagues:
Thomas Kustermann
Thomas Kremer

March 13, 2023

Key biomarkers in early clinical drug development

Terminology and example use cases



Target engagement BM: does the molecule act on the biological target?

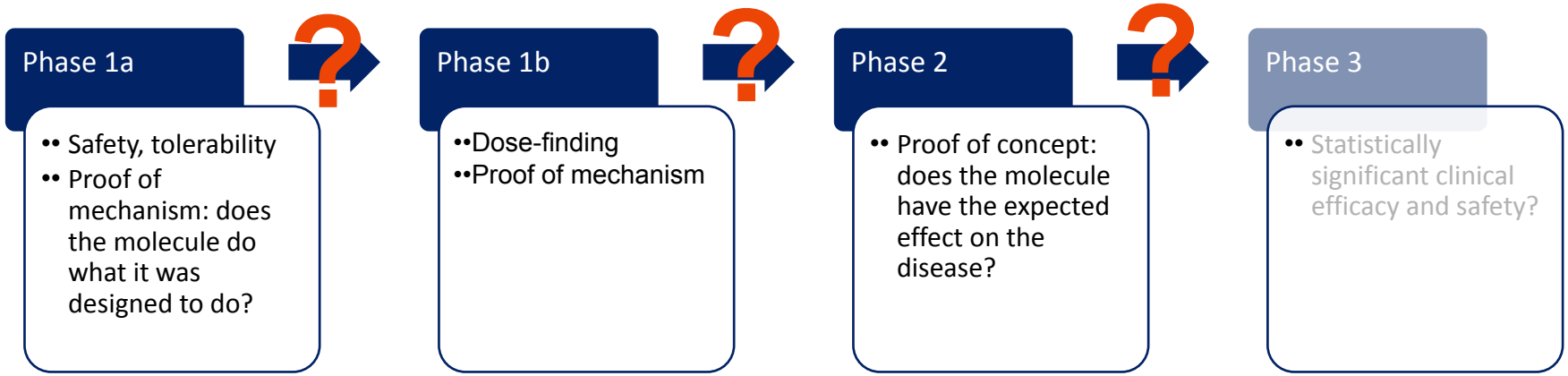
Diagnostic biomarker: identifies the pathognomonic sign

Predictive biomarker identifies future status of patient (e.g. diagnosis, rapid progression)

Disease progression/treatment response BM identifies whether molecule impacts course of disease

Key biomarkers in early clinical drug development

Terminology and example use cases



- Biomarkers must be **robust** to be used in drug development decision-making at each stage:

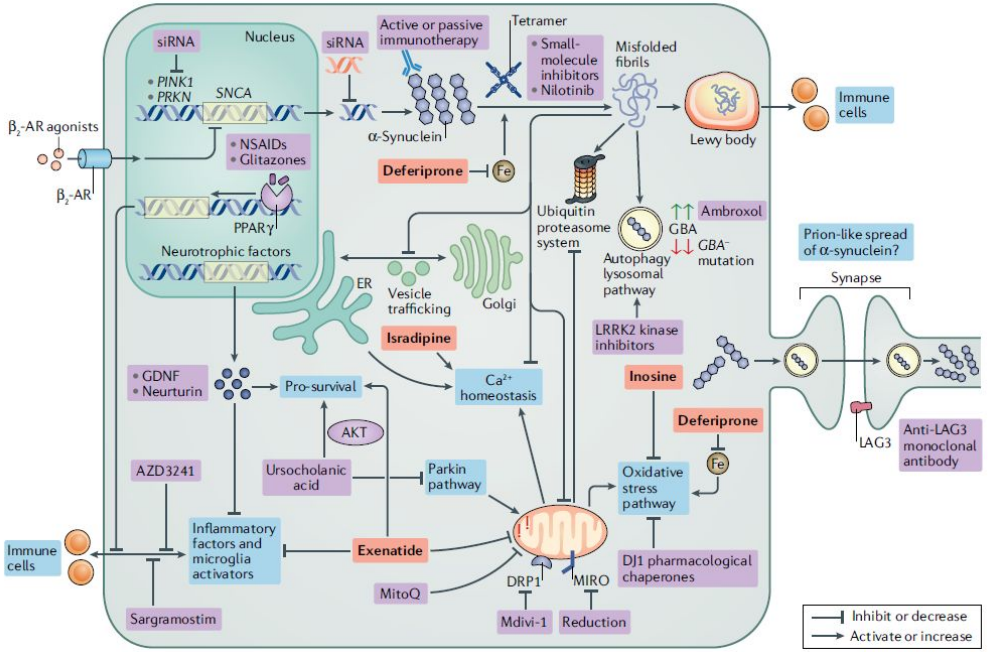
Go: continue develop-m ent

Stop: re-deploy resources to more promising projects, minimize exposure of animals and humans

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

❶ Valid biomarker of target



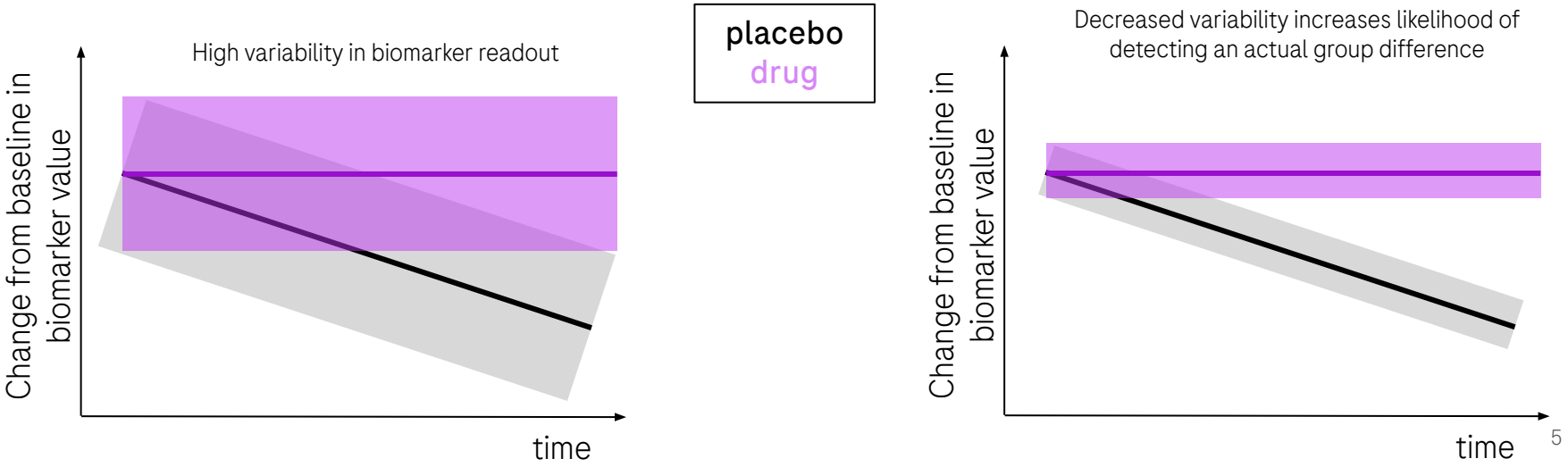
Elkouzi et al (2019). Emerging therapies in Parkinson disease—Repurposed drugs and new approaches. Nature Reviews Neurology, 15(4), 204–223. https://doi.org/10.1038/s41582-019-0155-7.

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

❶ Valid biomarker of target

❷ High test-retest reliability



Biomarkers will only be used in clinical drug development if they are **robust**

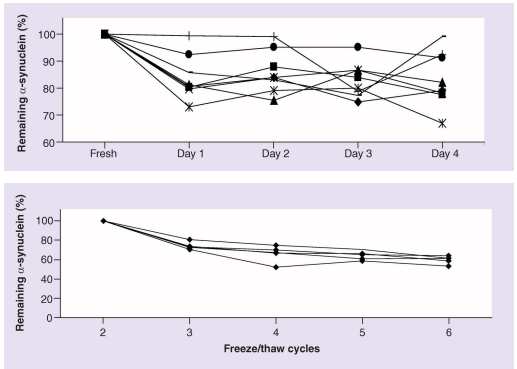
Requirements for use in clinical drug development

❶ Valid biomarker of target

❷ High test-retest reliability

❸ Insensitivity/known sensitivity to confounds; example: **preanalytical conditions** for fluid BM assays

- Tube and tip type (stickiness of proteins to walls)
- Aliquot volume
- Time to and temperature during delay to freeze
- Centrifugation speed
- Number of freeze/thaw cycles
- Thawing speed
- etc



del Campo, Mollenhauer et al. (2012). Recommendations to standardize preanalytical confounding factors in Alzheimer's and Parkinson's disease cerebrospinal fluid biomarkers: An update. *Biomarkers in Medicine*, *6*(4), 419–430. https://doi.org/10.2217/bmm.12.46

Biomarkers will only be used in clinical drug development if they are **robust**

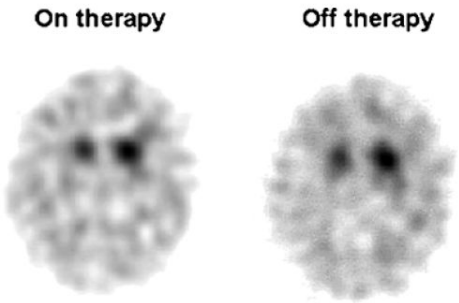
Requirements for use in clinical drug development

❶ Valid biomarker of target

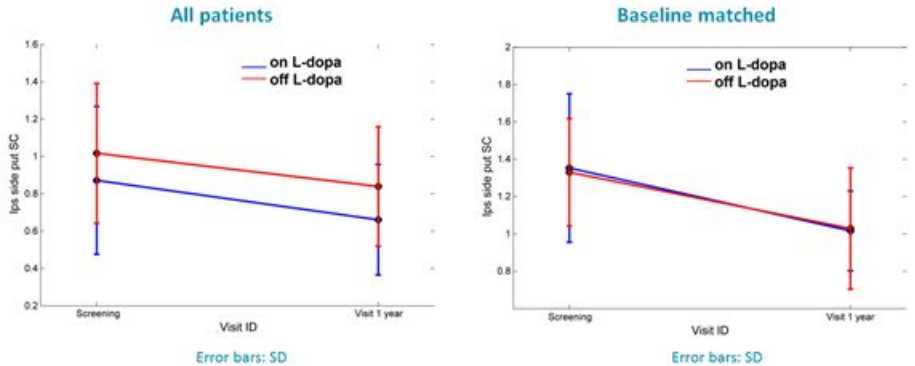
❷ High test-retest reliability

❸ Insensitivity/known sensitivity to confounds; example: sensitivity to **symptomatic medication**

No significant differences in DaT-SPECT in n=15 individuals with PD; example:



PPMI data suggest no effect of levodopa on DaT-SPECT progression
(in-house analyses; J. Dukart)



Schillaci et al. (2005). European Journal of Nuclear Medicine and Molecular Imaging, 32(12), 1452–1456. https://doi.org/10.1007/s00259-005-1922-9

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

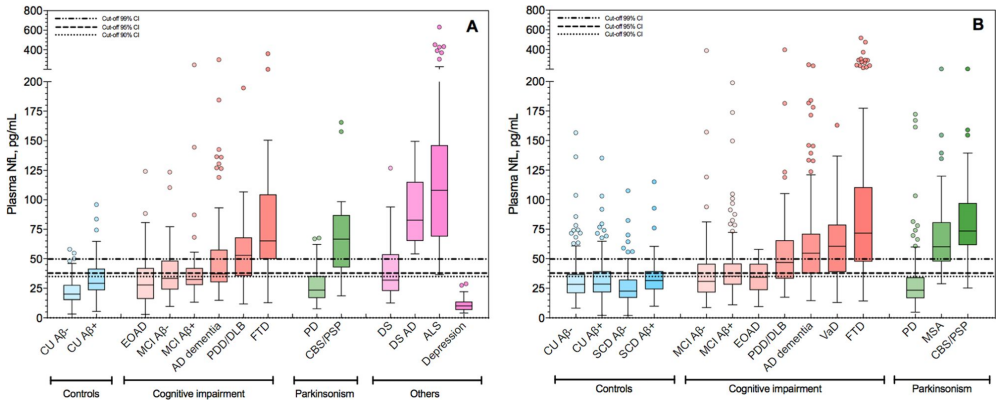
❶ Valid biomarker of target

❷ High test-retest reliability

❸ Insensitivity to confounds (e.g., pre-analytic conditions, concomitant medication)

❹ Specific to disease of interest

- Plasma neurofilament light chain appears robust marker of neurodegeneration
- Less utility as specific biomarker of synucleinopathy in PD



Ashton et al. (2021). A multicentre validation study of the diagnostic value of plasma neurofilament light. Nature Communications, 12(1), 3400. https://doi.org/10.1038/s41467-021-23620-z

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

1. Valid biomarker of target
2. High test-retest reliability
3. Insensitivity to confounds (e.g., pre-analytic conditions, concomitant medication)
4. Specific to disease of interest
5. Findings replicated in an independent dataset

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

❶ Valid biomarker of target

❷ High test-retest reliability

❸ Insensitivity to confounds (e.g., pre-analytic conditions, concomitant medication)

❹ Specific to disease of interest

❺ Findings replicated in an independent dataset

For all, results shown in:

- **Target population of clinical trial** (e.g., early, drug-naïve individuals with PD)
- Robust **sample sizes**

Biomarkers will only be used in clinical drug development if they are **robust**

Requirements for use in clinical drug development

❶ Valid biomarker of target

❷ High test-retest reliability

❸ Insensitivity to confounds (e.g., pre-analytic conditions, concomitant medication)

❹ Specific to disease of interest

❺ Findings replicated in an independent dataset

For all, results shown in:

- **Target population of clinical trial** (e.g., early, drug-naïve individuals with PD)
- Robust **sample sizes**

Biomarkers which do not fulfill all above criteria will likely not be used for decision-making in clinical drug development

- Promising yet unvalidated biomarkers may be investigated in house, if enough confidence potentially included in clinical study for exploratory purposes

Overview of biomarkers in early clinical development for PD

Key gaps = areas for future development

Target engagement BM: does the molecule act on the biological target?

Diagnostic biomarker: identifies the pathognomonic sign

Predictive biomarker identifies future status of patient (e.g. diagnosis, rapid progression)

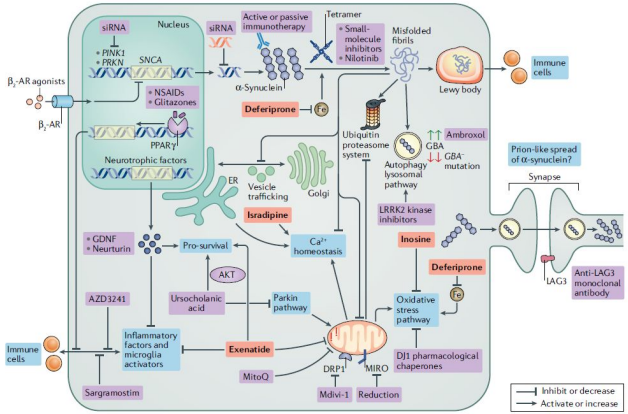
Disease progression/treatment response BM identifies whether molecule impacts course of disease

Target engagement: does the molecule act on the biological target?

Key gap

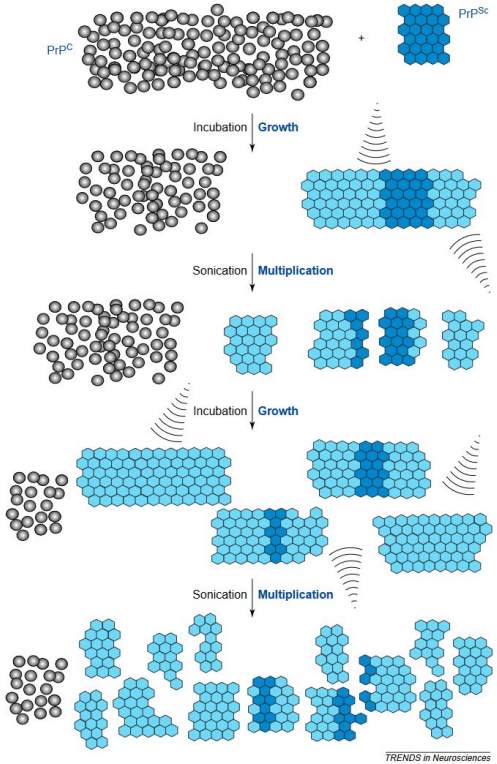
Roche

Example: in search of alpha-synuclein PET tracer



...

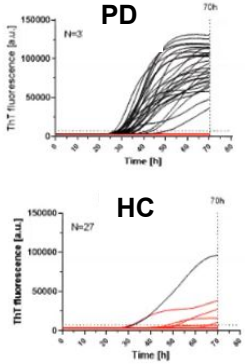
Example: Seeding amplification assay for detection of aggregated alpha-synuclein in CSF

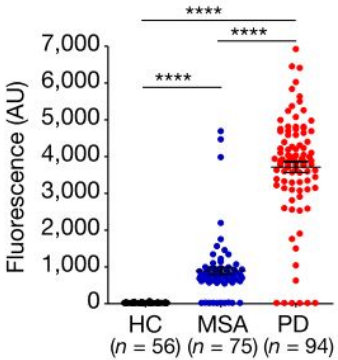


Shahnawaz et al. (2020)

- A template alpha-synuclein aggregate is introduced to a sample
- Cycles of incubation and sonication/shaking induces alpha-synuclein monomers in CSF to aggregate
- Aggregation level measured with Thioflavin-T dye fluorescence

- Qualitative readout (positive, negative, undetermined); kinetic parameters not yet shown to be reliable markers of disease severity



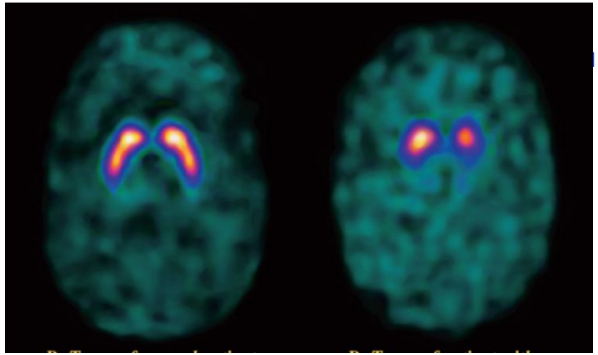


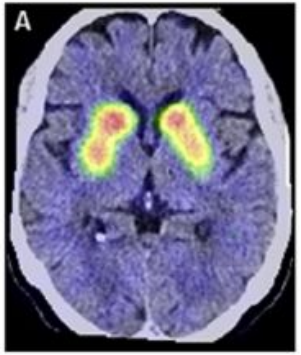
Abbvie @ADPD 2021

1. Valid (no direct measure of pathologic seed and substance of final product)
2. Reliable
3. Insensitivity
4. Specific
5. Replicated

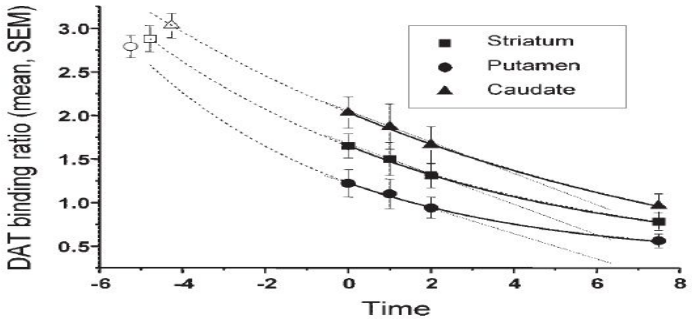
Predictive biomarker: the biomarker identifies future status of patient (e.g. diagnosis, rapid progression)

Example: DaT-SPECT as predictor of future PD diagnosis





HC PD SWEDD



Schwarz 2004

Gap: easily deployable measurements with broad reach and low patient burden

Disease progression/treatment response BM identifies whether molecule impacts course of disease

Key gap

Roche

Lack of biomarkers tracking progressive neurodegeneration

Lack of progression, large variability, over short term

Over short term (ca 1y)

- Show Brit's fluid BM / PPMI readouts
  - lack of progression
  - Sensitivity to pre-analytical factors

examples

- MRI – lack of progression

examples

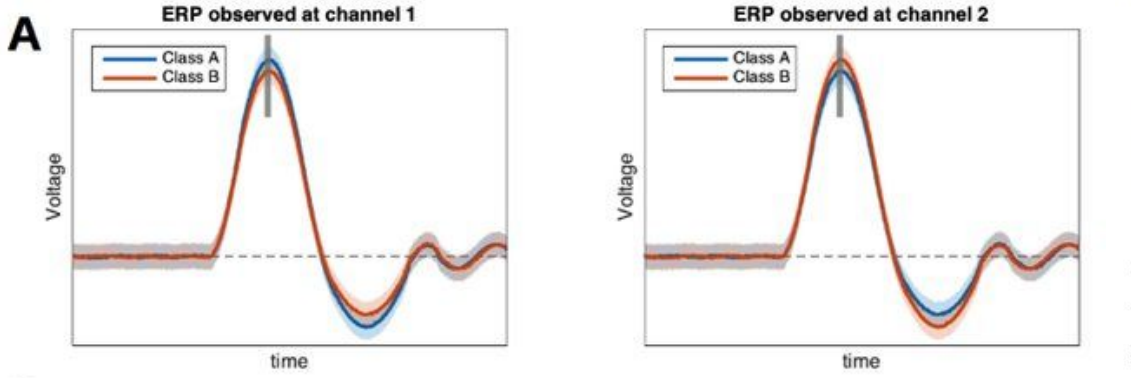
- DaT-SPECT
  - lack of progression
  - Delayed effects

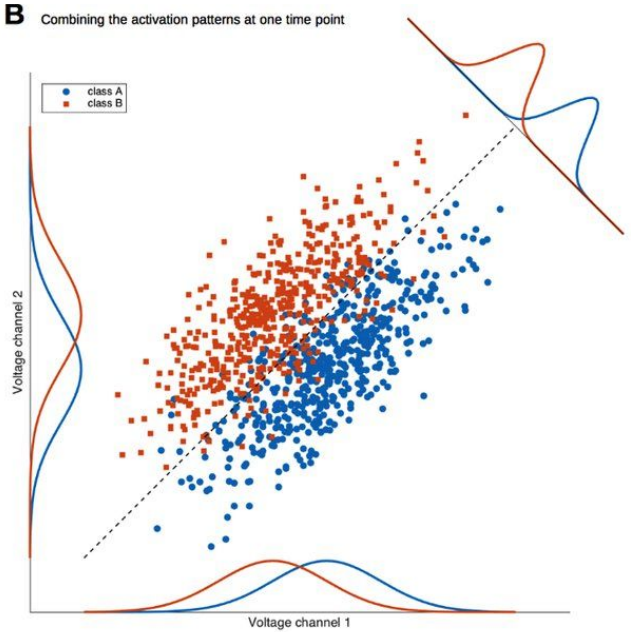
examples

Why multimodal biomarkers for PD (and beyond)

Promise to fill biomarker gaps?

Multivariate:





Multimodal: capturing different aspects of PD

Promises:

Increase signal-to-noise

More representative quantification of PD neurodegeneration

Potential to discover biologically meaningful subgroups

Grootswagers et al. (2017). Journal of Cognitive Neuroscience, 29(4), 677–697. https://doi.org/10.1162/jocn_a_01068.

Promising modalities for multimodal biomarkers in PD

- Genes
- Fluids/tissue
- Imaging
  - DaT-SPECT, VMAT2
  - Structural MRI
  - Functional MRI
- …

examples

examples

examples

Increasing precision in biomarker development by sharpening the clinical signal

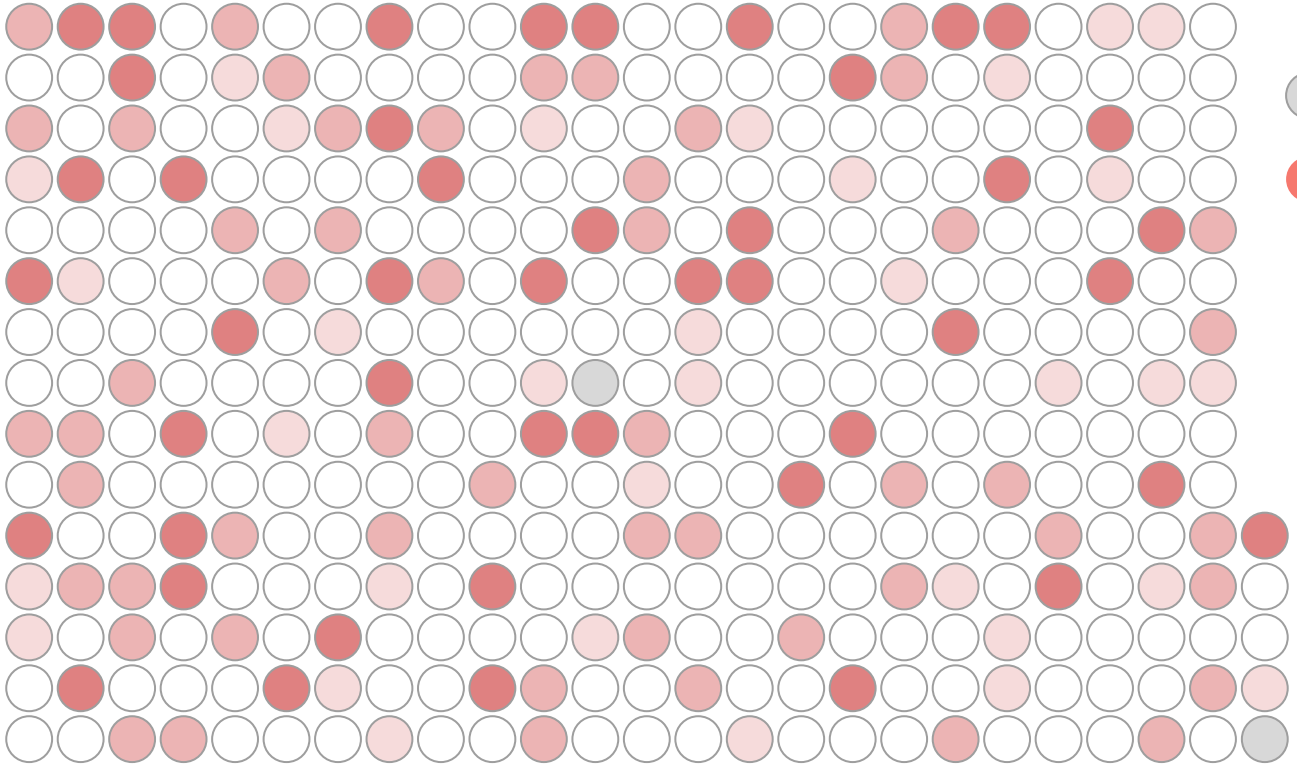
Increasing signal to noise of motor sign readouts

- Many biomarkers are developed using comparisons with 'clinical gold standard'
- The Movement Disorders Society – Unified Parkinson's Disease Rating Scale Part III is standardly used to quantify severity and progression in PD
  - Part 1: XX-item patient-reported outcome (PRO) of activities of daily living
  - Part 2: XX-item PRO of motor activities of daily living
  - Part 3: XX-item clinical exam of motor signs
  - all items rated on 5-point scale (0=absent, 4=most severe)
- The **fluctuating** nature of PD motor signs encumbers the precise quantification of motor sign severity (increased variability)
- Digital Health Technology tools enable remote and frequent assessments of motor sign severity in home environments

Regnault et al. (2019). Journal of Neurology, 266(8), 1927–1936. https://doi.org/10.1007/s00415-019-09348-3; Zolfaghari et al. (2022). Movement Disorders, 37(3), 585–597. https://doi.org/10.1002/mds.28884.

Example: digital biomarkers as disease-related marker of treatment benefit?

Considering fluctuating nature of motor signs in Parkinson's disease



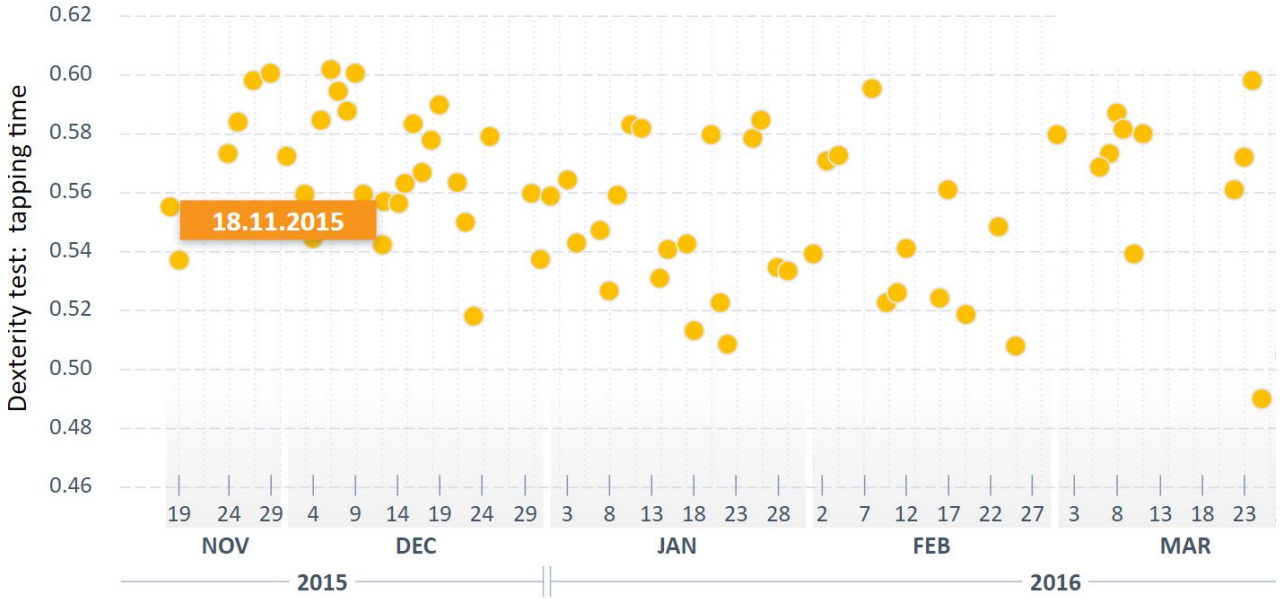
Day in the life of an individual with PD

Severity of symptoms

Digital biomarkers enable remote and frequent assessments

Considering fluctuating nature of motor signs in Parkinson's disease

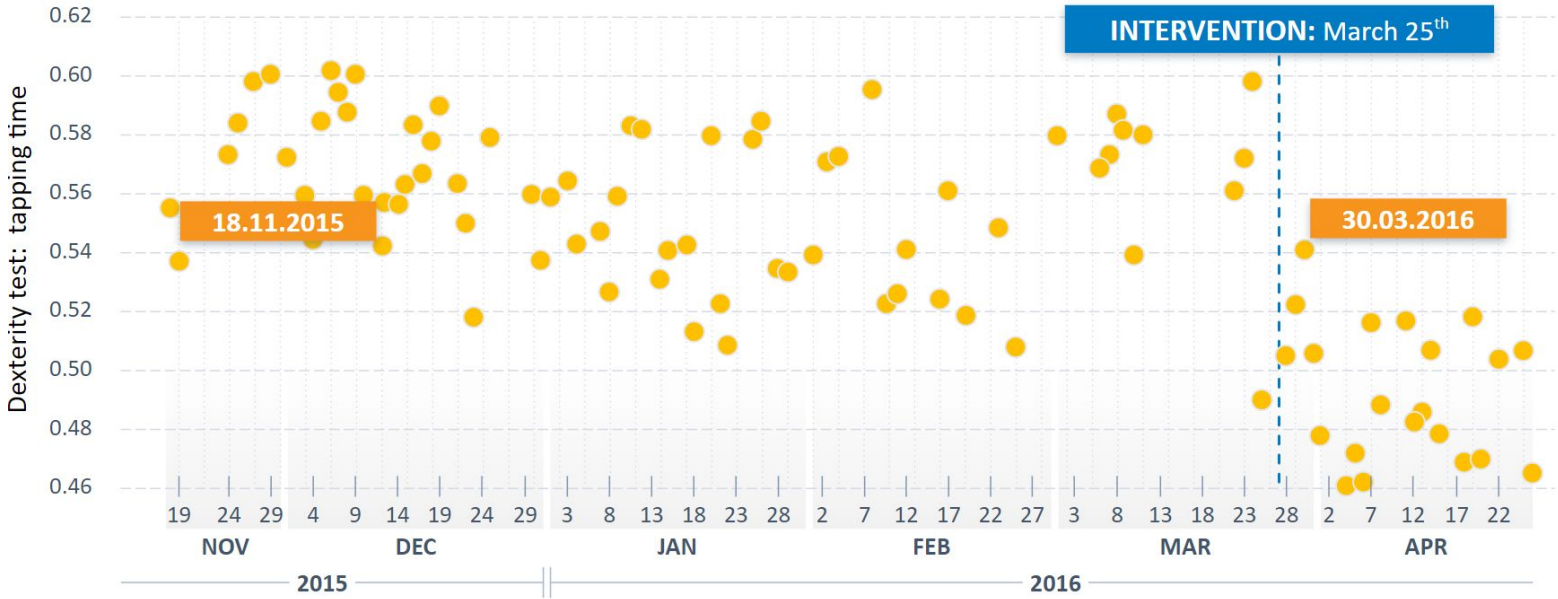
- An individual with Parkinson's disease was asked to perform a finger-tapping test on the smartphone every day
  - Finger-tapping is classic test of bradykinesia (motor slowing), a cardinal sign of Parkinson's disease
  - Higher = slower (worse)



Digital biomarkers enable remote and frequent assessments

Considering fluctuating nature of motor signs in Parkinson's disease

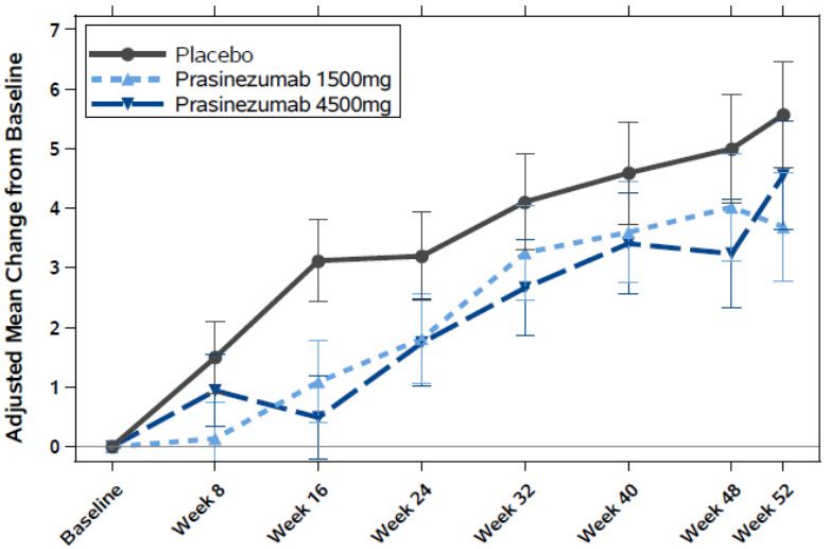
- An individual with Parkinson's disease was asked to perform a finger-tapping test on the smartphone every day
  - Finger-tapping is classic test of bradykinesia (motor slowing), a cardinal sign of Parkinson's disease
  - Higher = slower (worse)



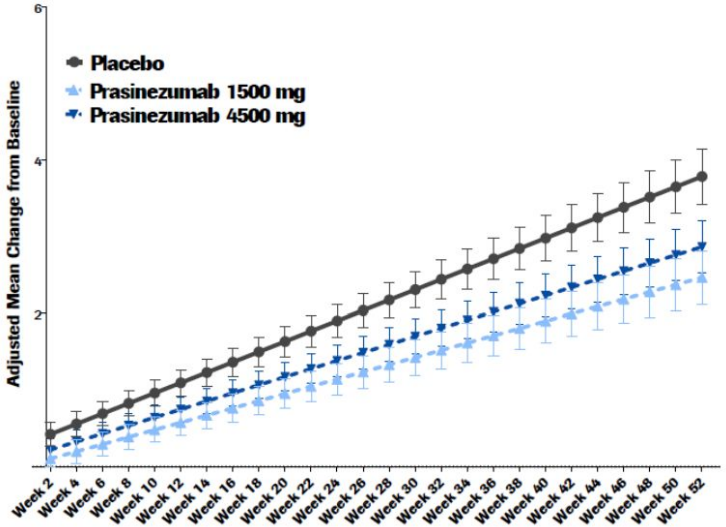
Sharpening the signal of motor sign progression

Results of PASADENA Part 1 phase 2 study of the anti-alpha synuclein monoclonal antibody prasinezumab

Change from baseline in MDS-UPDRS Part 3



Change from baseline in PASADENA Digital Motor score



Pagano et al.(2022). Trial of Prasinezumab in Early-Stage Parkinson's Disease. New England Journal of Medicine, 387(5), 421–432.
https://doi.org/10.1056/NEJMoa2202867

Summary and Outlook

- Any potential biomarker must be proven to be highly **robust** in order to be used for decision-making in clinical drug development
  - E.g. test-retest reliability, insensitivity to confounds (eg preanalytic factors), valid, replicated in independent cohort, insensitivity to symptomatic therapies, changes over time;
  - all findings must be available in (a) large samples which (b) reflect the target population for the clinical trial
- Key biomarker gaps in PD space:
  - Biomarkers of target engagement (e.g. pathological alpha-synuclein)
  - Low burden predictive biomarkers
  - Biomarkers of progressive neurodegeneration/treatment response

  -> patient input critical to design of acceptable biomarkers
- Combining biomarkers from different modalities may:
  - increase signal-to-noise of readouts -> smaller sample sizes, faster studies
  - Aid in understanding heterogeneity of disease sign and progression profiles
  - Produce a more representative measure of disease severity and progression
- Keys to success:
  - Non-profit organizations such as MJFF and CPP spearhead the development of biomarkers for academic and drug development studies in PD in collaborative projects (academia, pharma, non-profits, regulators)
  - Maximally robust (SNR) clinical comparators
  - Data and data sharing

Doing now what patients need next