Session 4: Developing and Advancing Phenotyping and Biomarker Discovery to Enable Patient Stratification

Session Objective:
Discuss opportunities to improve patient stratification by leveraging multi-modal data to identify, validate, and use robust biomarkers, including early biomarkers of disease.

Key Discussion Questions:

- How are novel biofluid-based biomarkers (e.g., genomics, proteomics, and biological pathways) being used for patient stratification in neurodegenerative disorders?
- What lessons learned and similarities can be applied to neuropsychiatric disorders, and when are different approaches required?
- How can well-correlated biomarkers in clinical data be used to identify patient subsets by leveraging natural history studies and opportunities for deep phenotyping with appropriate representation of ancestral diversity?
- Can polygenic scores be integrated with fluid and PET biomarkers to improve stratification?

Biomarker Definition

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.

Types of biomarkers – molecular, histologic, radiographic, and physiologic characteristics

FDA-NIH Biomarker Working Group
Biomarkers, EndpointS, and other Tools Resource (BEST)
https://www.ncbi.nlm.nih.gov/books/NBK326791/

Biomarker Classes from a Drug Development Perspective

Measures of disease presence and status

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker

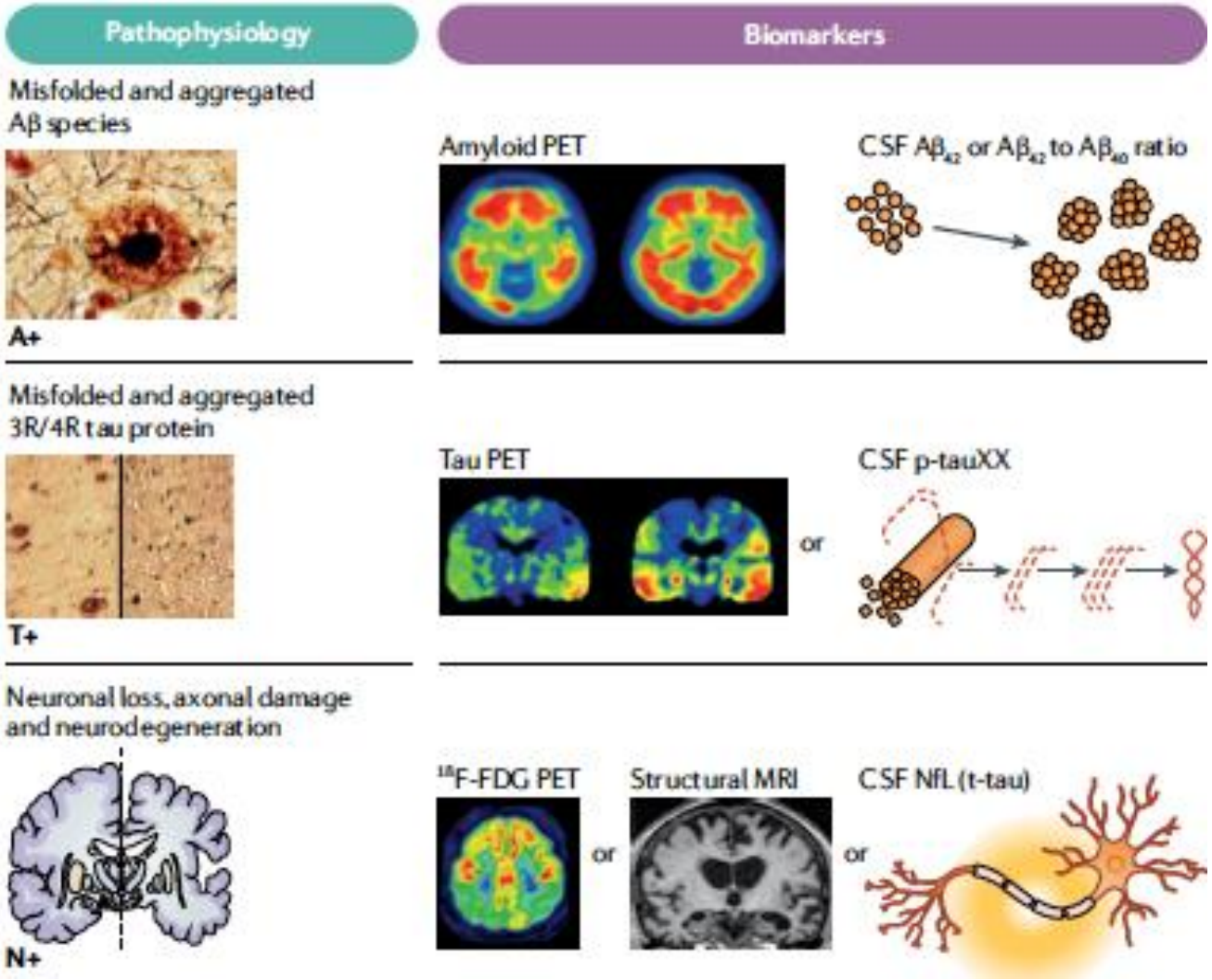
Measures of aspects of response to treatment

- Predictive biomarker
- Pharmacodynamic/Response biomarker
- Safety biomarker

Measures for stratification

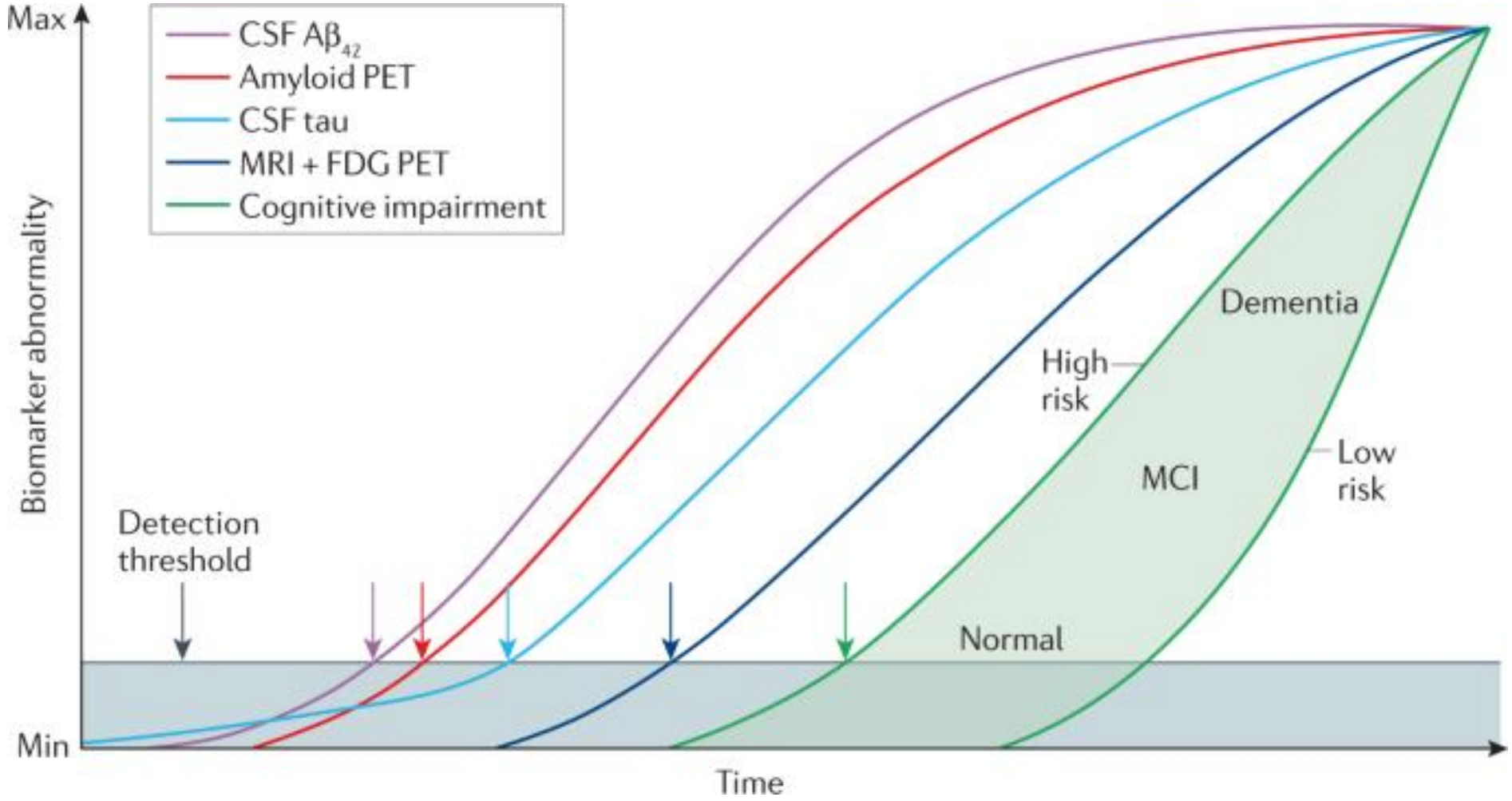
- Biomarkers to identify subjects “at risk” to aid in patient stratification
  - Identify subgroups most likely to benefit, or least likely to experience harm, from an intervention

Biomarker-Based Disease Characterization – Alzheimer's Disease



Current biomarkers of the AT(N) classification system (From Hampel et al., Nature Reviews Neurology 2021)

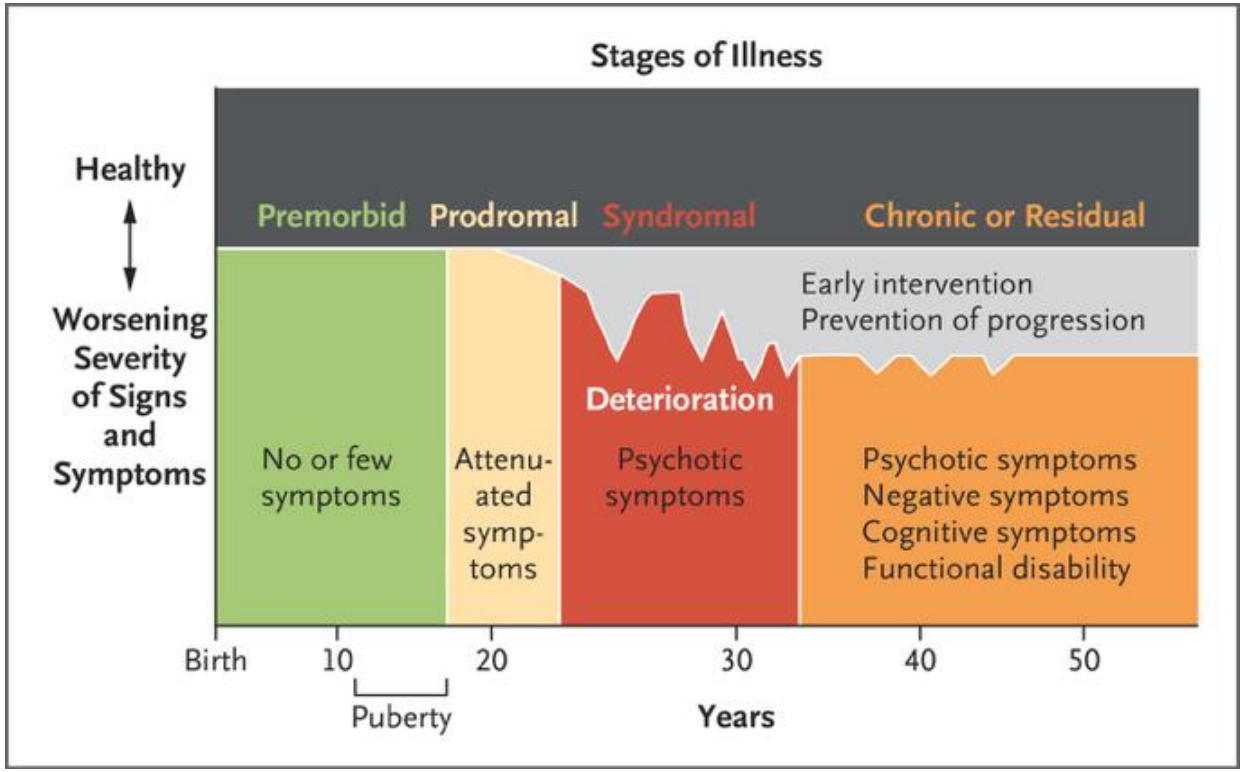
Biomarker-Based Staging of Disease Progression – Alzheimer's Disease



Temporal evolution of AD pathophysiology and biomarkers
(From Jack et al, Lancet Neurology 2010)

Need for Biomarkers to Characterize Early Stages of Disease – Schizophrenia

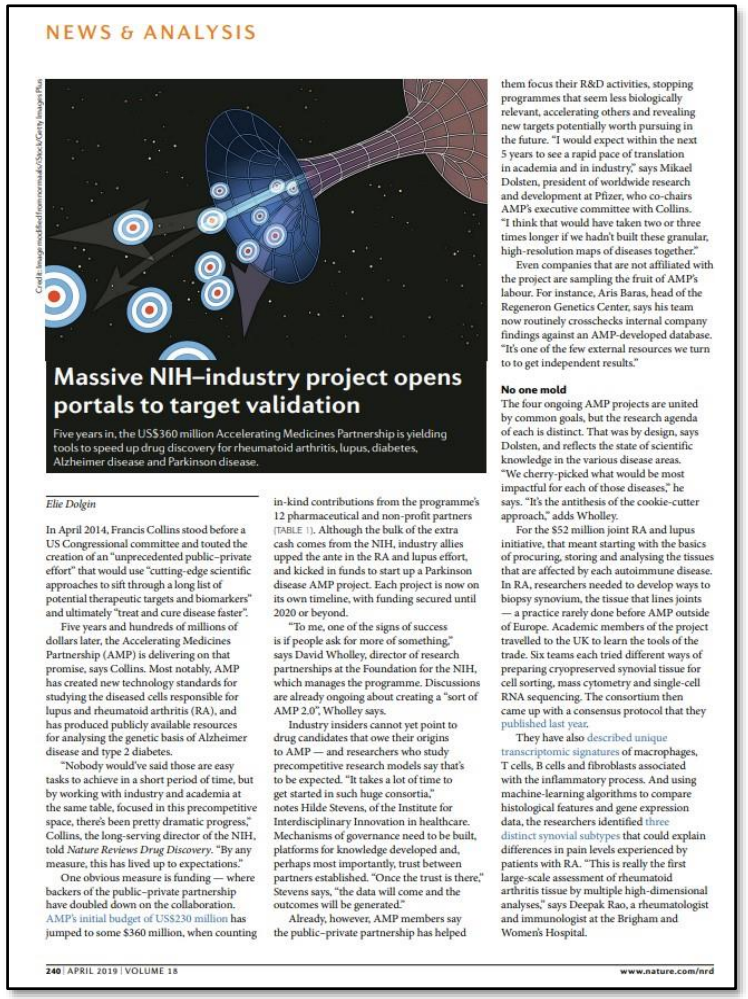
- One of the top 15 leading causes of disability worldwide
- Early onset of symptoms (usually start between ages 16 and 30) and the long-lasting trajectory of this condition exacerbate both the impact and need
- Currently an unmet need for medications to address the disabling negative and cognitive symptoms
- No tools are currently available to identify or stratify populations in the early stages of illness mechanistically, or to evaluate the efficacy of treatments



Natural history of schizophrenia and rationale for preventing chronic disease (from Lieberman, 2018)

Accelerating Medicines Partnership® - a flagship pre-competitive public-private launched in 2014 to accelerate therapeutics development in major diseases

- The Foundation for the National Institutes of Health (FNIH) unites resources of NIH and private partners to improve our understanding of disease pathways to aide in biomarker and targets selection
- The goal is to increase the number of therapies for patients and reduce the time and cost of developing them
- Specific projects launched in five major disease areas to date:
  - Alzheimer's Disease 1.0 and 2.0
  - Parkinson's Disease
  - Rheumatoid Arthritis & Lupus
  - Schizophrenia
  - Type 2 Diabetes and Common Metabolic Disorders
- Current partners include:
  - 16 industry and life sciences members
  - 17 non-profits and other sectors
  - 3 government entities
- Combined funding of over US$450M+



NEWS & ANALYSIS

Massive NIH–industry project opens portals to target validation

Five years in, the US$360 million Accelerating Medicines Partnership is yielding tools to speed up drug discovery for rheumatoid arthritis, lupus, diabetes, Alzheimer disease and Parkinson disease.

Elie Dolgin

In April 2014, Francis Collins stood before a US Congressional committee and touted the creation of an "unprecedented public–private effort" that would use "cutting-edge scientific approaches to sift through a long list of potential therapeutic targets and biomarkers" and ultimately "treat and cure disease faster".

Five years and hundreds of millions of dollars later, the Accelerating Medicines Partnership (AMP) is delivering on that promise, says Collins. Most notably, AMP has created new technology standards for studying the diseased cells responsible for lupus and rheumatoid arthritis (RA), and has produced publicly available resources for analysing the genetic basis of Alzheimer disease and type 2 diabetes.

"Nobody would've said those are easy tasks to achieve in a short period of time, but by working with industry and academia at the same table, focused in this precompetitive space, there's been pretty dramatic progress," Collins, the long-serving director of the NIH, told *Nature Reviews Drug Discovery*. "By any measure, this has lived up to expectations."

One obvious measure is funding — where backers of the public–private partnership have doubled down on the collaboration. AMP's initial budget of US$230 million has jumped to some $360 million, when counting in-kind contributions from the programme's 12 pharmaceutical and non-profit partners (TABLE 1). Although the bulk of the extra cash comes from the NIH, industry allies upped the ante in the RA and lupus effort, and kicked in funds to start up a Parkinson disease AMP project. Each project is now on its own timeline, with funding secured until 2020 or beyond.

"To me, one of the signs of success is if people ask for more of something," says David Wholley, director of research partnerships at the Foundation for the NIH, which manages the programme. Discussions are already ongoing about creating a "sort of AMP 2.0", Wholley says.

Industry insiders cannot yet point to drug candidates that owe their origins to AMP — and researchers who study precompetitive research models say that's to be expected. "It takes a lot of time to get started in such huge consortia," notes Hilde Stevens, of the Institute for Interdisciplinary Innovation in healthcare. Mechanisms of governance need to be built, platforms for knowledge developed and, perhaps most importantly, trust between partners established. "Once the trust is there," Stevens says, "the data will come and the outcomes will be generated."

Already, however, AMP members say the public–private partnership has helped them focus their R&D activities, stopping programmes that seem less biologically relevant, accelerating others and revealing new targets potentially worth pursuing in the future. "I would expect within the next 5 years to see a rapid pace of translation in academia and in industry," says Mikael Dolsten, president of worldwide research and development at Pfizer, who co-chairs AMP's executive committee with Collins. "I think that would have taken two or three times longer if we hadn't built these granular, high-resolution maps of diseases together."

Even companies that are not affiliated with the project are sampling the fruit of AMP's labour. For instance, Aris Baras, head of the Regeneron Genetics Center, says his team now routinely crosschecks internal company findings against an AMP-developed database. "It's one of the few external resources we turn to to get independent results."

No one mold

The four ongoing AMP projects are united by common goals, but the research agenda of each is distinct. That was by design, says Dolsten, and reflects the state of scientific knowledge in the various disease areas. "We cherry-picked what would be most impactful for each of those diseases," he says. "It's the antithesis of the cookie-cutter approach," adds Wholley.

For the $52 million joint RA and lupus initiative, that meant starting with the basics of procuring, storing and analysing the tissues that are affected by each autoimmune disease. In RA, researchers needed to develop ways to biopsy synovium, the tissue that lines joints — a practice rarely done before AMP outside of Europe. Academic members of the project travelled to the UK to learn the tools of the trade. Six teams each tried different ways of preparing cryopreserved synovial tissue for cell sorting, mass cytometry and single-cell RNA sequencing. The consortium then came up with a consensus protocol that they published last year.

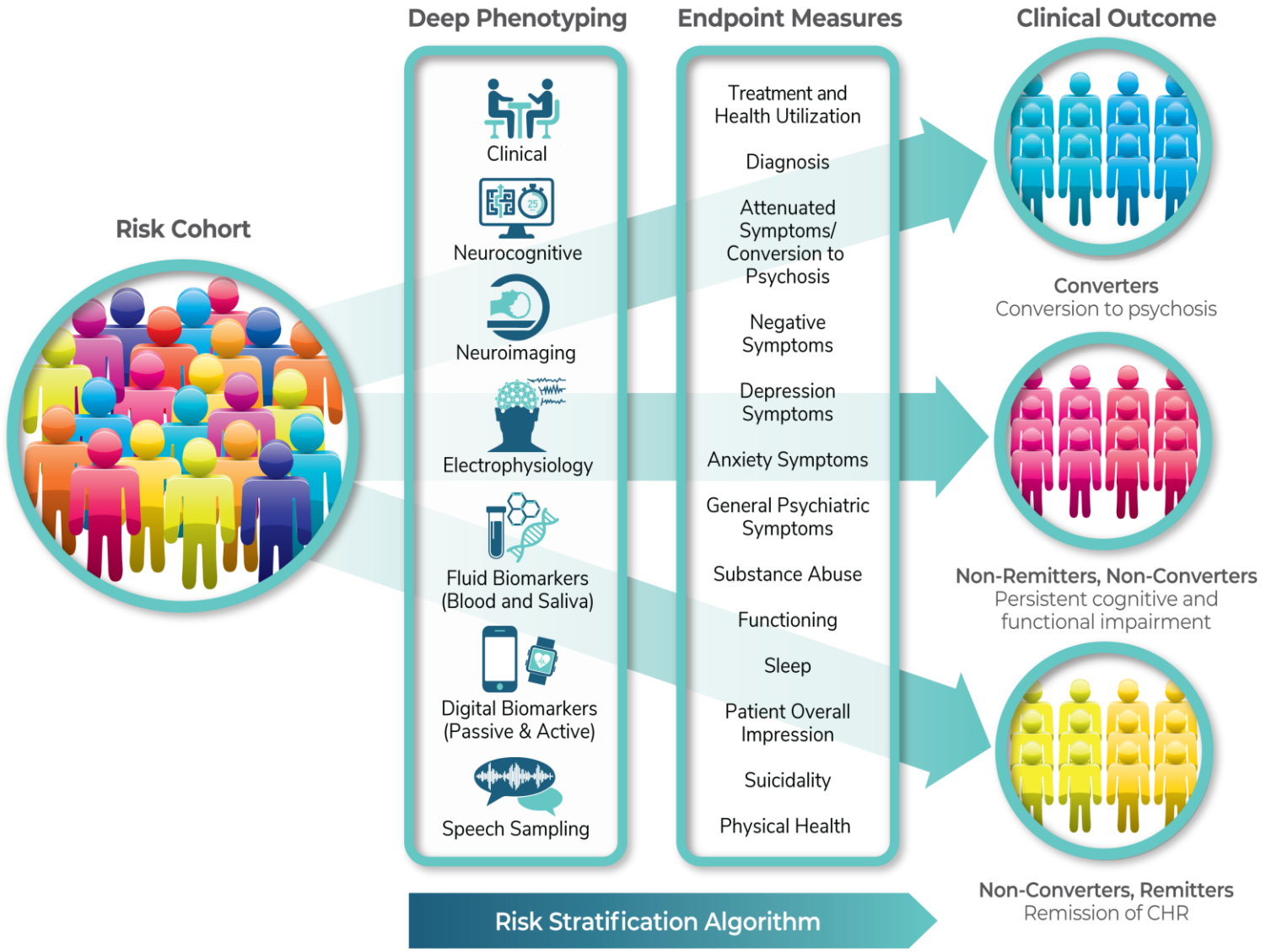
They have also described unique transcriptomic signatures of macrophages, T cells, B cells and fibroblasts associated with the inflammatory process. And using machine-learning algorithms to compare histological features and gene expression data, the researchers identified three distinct synovial subtypes that could explain differences in pain levels experienced by patients with RA. "This is really the first large-scale assessment of rheumatoid arthritis tissue by multiple high-dimensional analyses," says Deepak Rao, a rheumatologist and immunologist at the Brigham and Women's Hospital.

For an overview of the AMP Initiative, see:
Nature Reviews Drug Discovery - February 27, 2019
https://www.nature.com/articles/d41573-019-00033-8

Accelerating Medicines Partnership® - Schizophrenia

The overall goal of the AMP® SCZ program is to provide tools to considerably improve success in developing pharmacologic treatments for patients with Clinical High Risk for psychosis

Aim 1: Provide tools to enable the selection of enriched patient populations, to considerably improve success in developing pharmacologic treatments for patients with CHR for psychosis



https://fnih.org/our-programs/AMP/schizophrenia

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Speakers:

- Charlotte Teunissen, Amsterdam UMC
- Danielle Graham, Biogen
- Pamela Horn, Food and Drug Administration
- Ernest Fraenkel, Massachusetts Institute of Technology
- Nikos Koutsouleris, Kings College London and Ludwig-Maximilian-University