Multimodal biomarkers as a bridge from the past to the future of precision neuroscience

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Disclaimer and Disclosure

Employee of J&J	Clinical trials and/or marketed products for Alzheimer's, Parkinson's, Depression and Psychosis Spectrum Disorders	No products mentioned

I do not bear any direct or indirect financial interest in products or concepts quoted in this talk.

On classification of disease, biomarkers bridge the past to the future

Diagnostic ***Mechanistic***

"[One] must advance from one formulation of tentative conclusions to another in progress toward the truth.… [B]esides the symptoms of any present attack, we [must] take into account the course of the disease through the patient's life-time together with the final outcome of the disease"

Prognostic

– Edward Cowles, Progress in the Clinical Study of Psychiatry, 1899

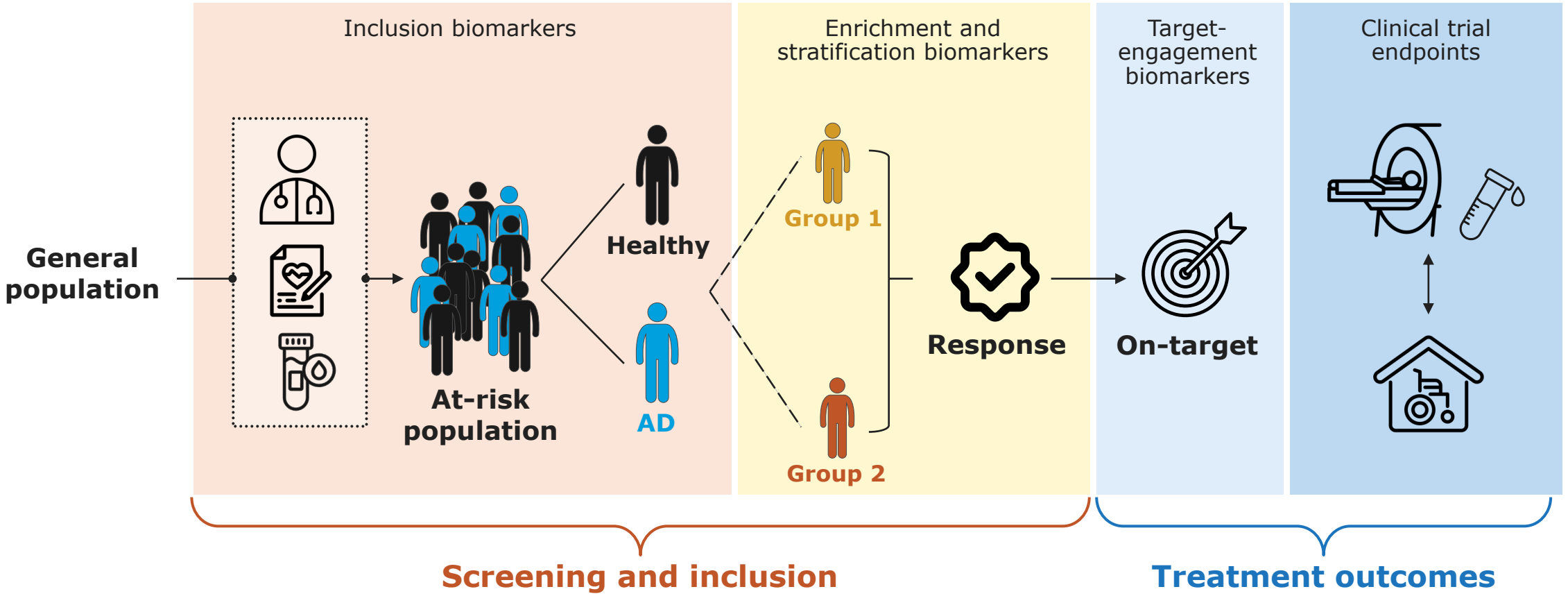
The promise of biomarkers:

Understand disease

Apply understanding to develop therapeutics

Improve clinical care

Alzheimer's disease: Biomarkers may predict clinical benefit, positioning them as an efficacy measure and surrogate endpoint for registration

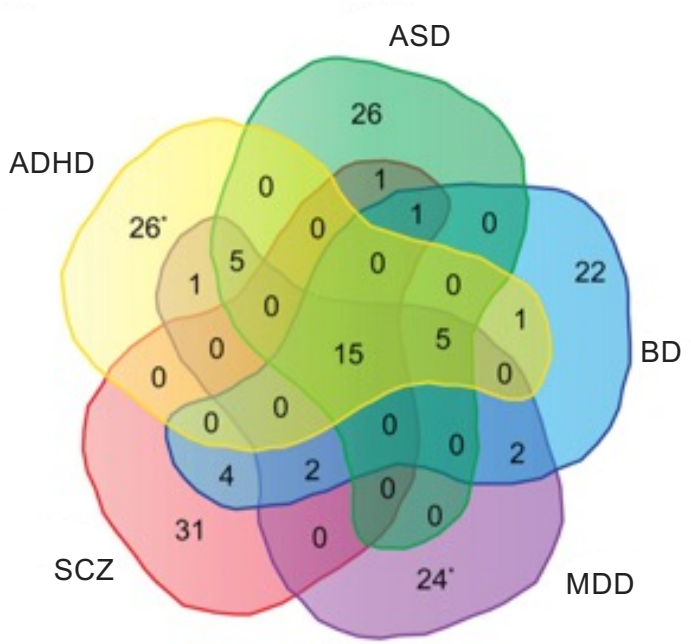


Adapted from Hansson et al., 2022

Neuropsychiatric disorders: historical constructs hinder progress

- Genetic overlap: ~20 genes shared among at least 4 disorders
- Symptom overlap: comorbidity is the rule, rather than exception
- No systematic overlap between genes and behavioral symptoms

Important to shift from "understand [category]" to identifying multimodal predictive and prognostic biomarkers based on biologically-defined subtypes.



Genes shared among	N genes
6 disorders	0
5 disorders	15
≥ 4 disorders	20
≥ 3 disorders	28
≥ 2 disorders	39

Lotan et al, 2014

Regulatory pathways and challenges for the integration of biomarkers in drug development

Center for Drug Evaluation & Research (CDER) Biomarker Qualification Program

Critical Path Initiative's (C-Path) creation of Drug Development Tools (DDTs)

CRITICAL PATH INSTITUTE

Questions & Challenges:

- Is a multimodal biomarker path captured by "single COU should be associated with each biomarker qualification effort"?
- Which regulatory pathway is best fit for a specific biomarker in the early stages of drug development?
- Evidence required for biomarker qualification is not standard for all biomarkers submitted to CDER; rather, "evidentiary criteria are dependent upon the potential impact on patients."
- Lack of harmonization across regulatory health authorities increases cost and uncertainty of global development programs
- How to think about biomarkers for mental health conditions, and distinctions between biomarkers and measures of a clinical outcome assessment (COA)?

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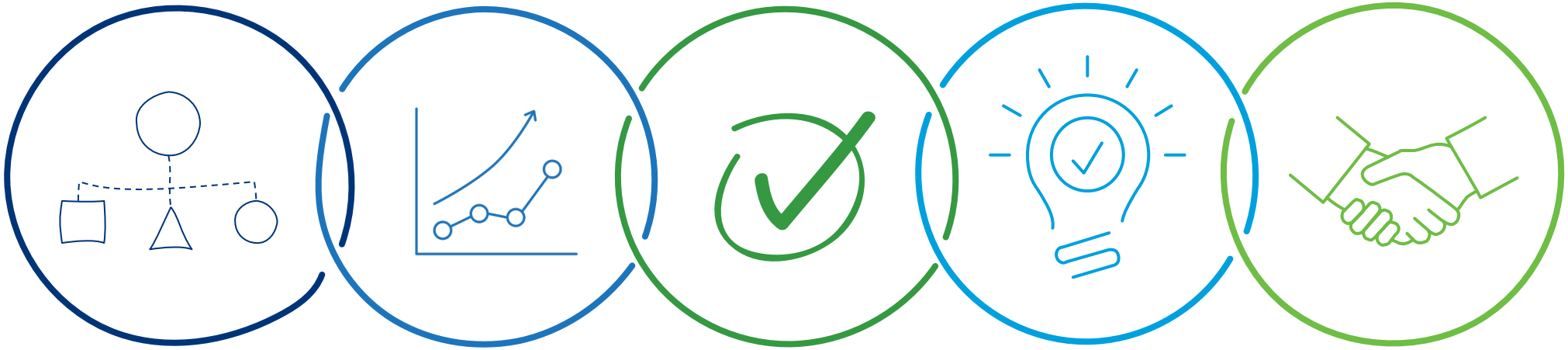
Bridging to the future: What's needed?

Validate surrogate endpoints for clinical progression in Alzheimer's disease [mechanistic, diagnostic, prognostic]

Implement longitudinal, (transdiagnostic) patient cohorts with multimodal measures to understand course of disease and relationships between clinical symptoms and biological markers [diagnostic, mechanistic]



Evolve classification system for categorical CNS conditions

Identify biological subtypes and/or predictive markers of treatment response for MDD & SCZ [diagnostic, mechanistic]

Align regulatory guidance with emerging state of the field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