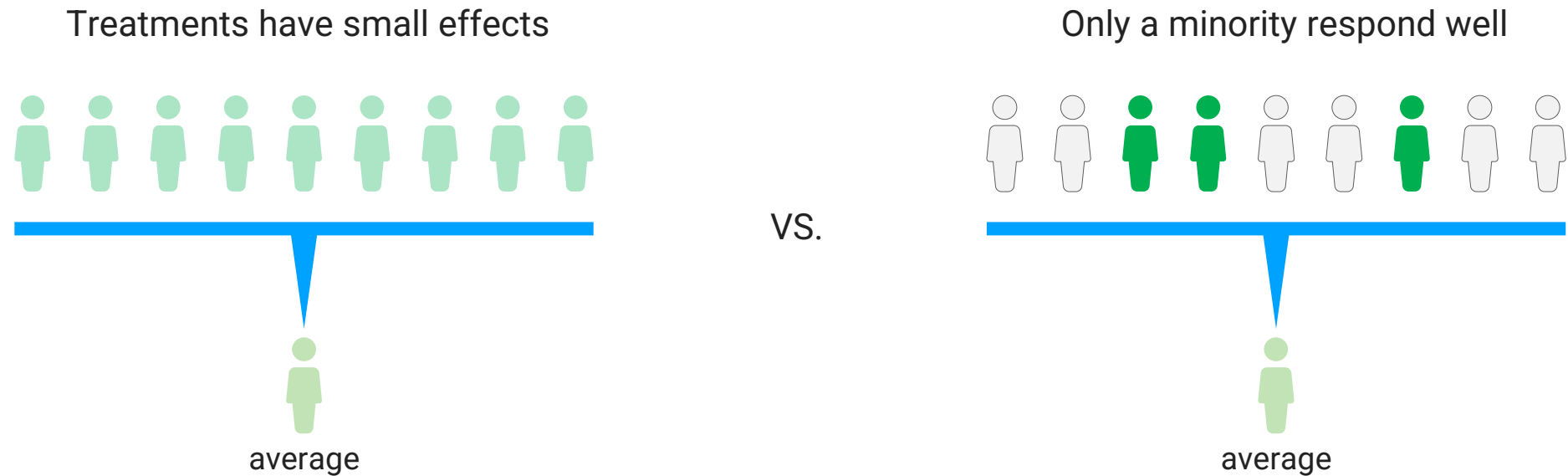# FINANCIAL DISCLOSURES

Equity:
Alto Neuroscience
Akili Interactive

Salary:
Alto Neuroscience

A PRECISION APPROACH REQUIRES REORIENTING OUR THINKING AND STUDIES

Two alternative perspectives on small average effects:

Treatments have small effects

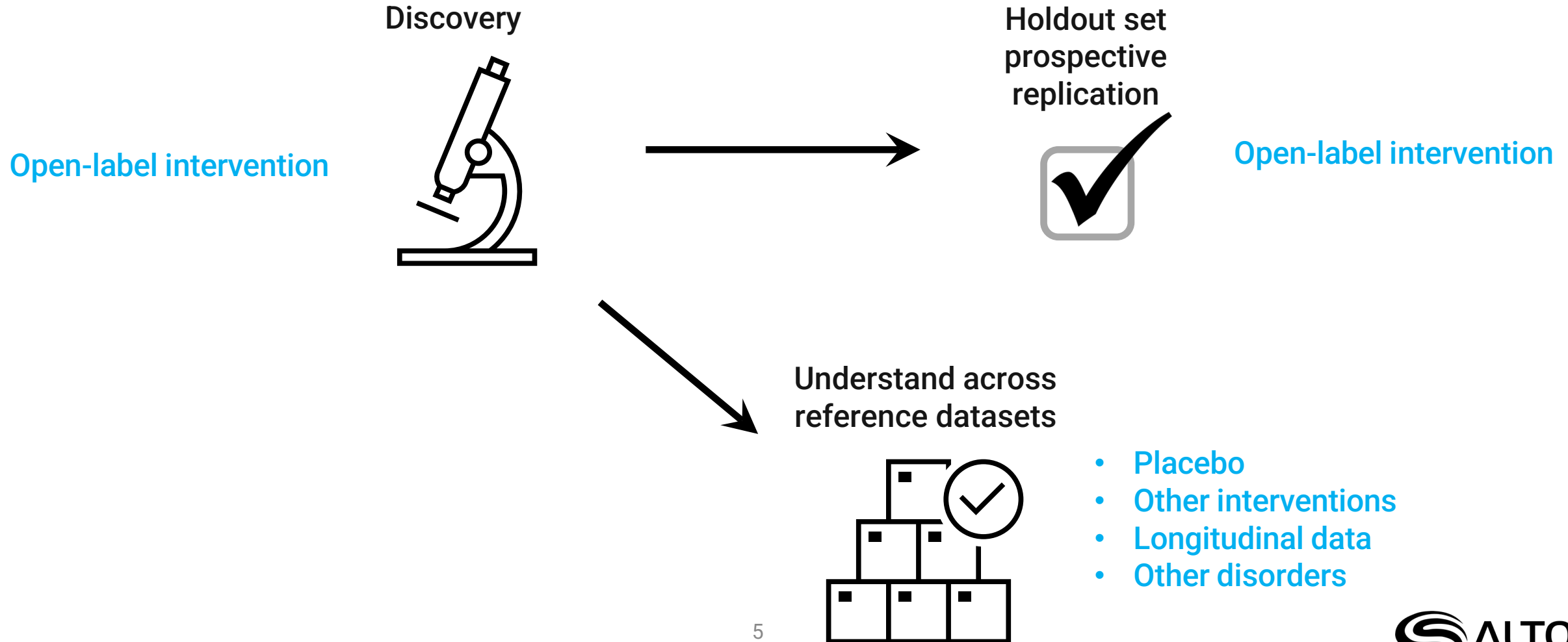Only a minority respond well

VS.

average

average

….but, for a precision approach to work, these differences cannot be due to random chance

A CENTRAL FOCUS ON BRAIN CIRCUITS – SCALABILITY MATTERS

EEG
(historically, fMRI)

Behavior

Wearables
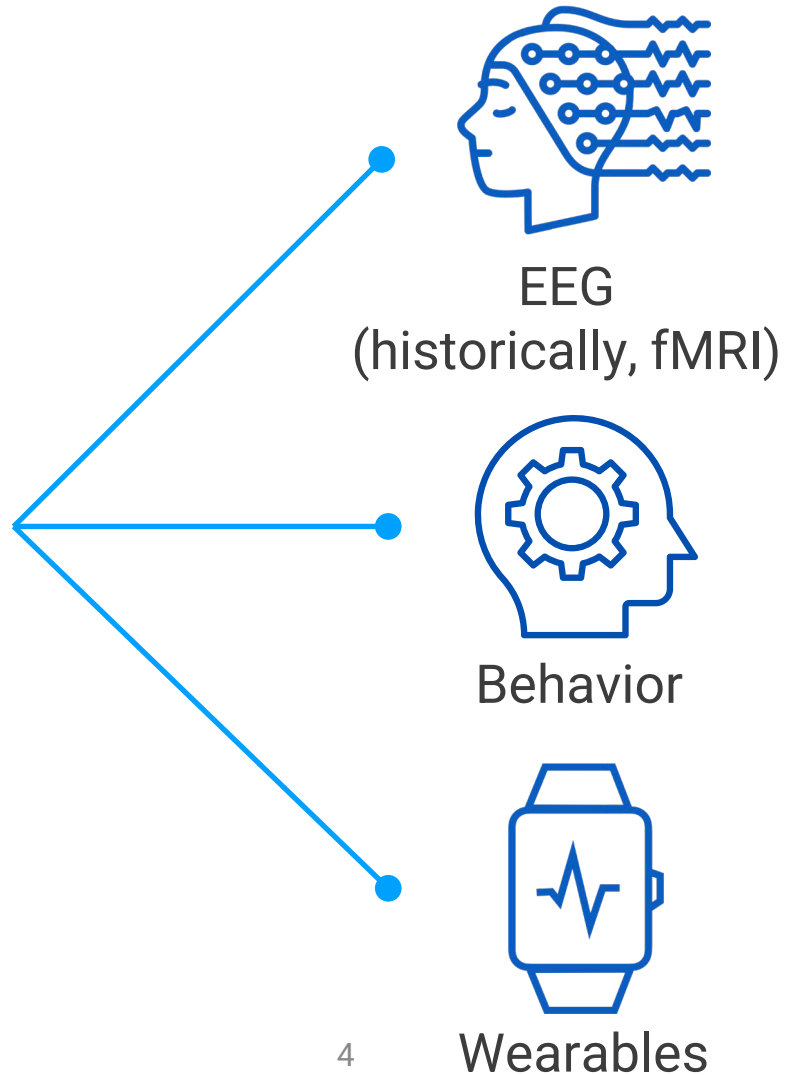
A biomarker can be as simple as reaction time, an EEG pattern, or how much a patient sleeps – or a combination of these factors.

4

ALTO NEUROSCIENCE

ALTO'S APPROACH TO BIOMARKER DISCOVERY

Discovery

Open-label intervention

Holdout set prospective replication

Open-label intervention

Understand across reference datasets
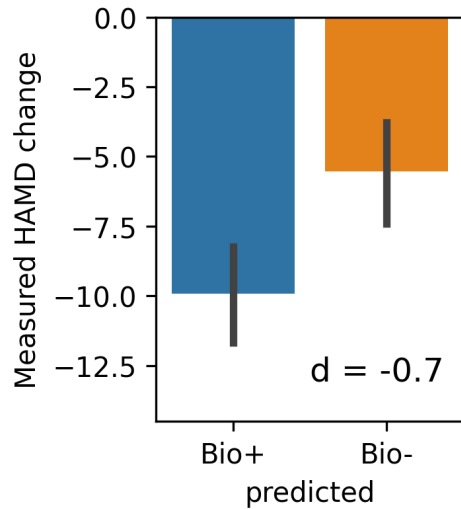
- Placebo
- Other interventions
- Longitudinal data
- Other disorders

DISCOVERY AND PROSPECTIVE REPLICATION OF AN SSRI BIOMARKER

Discovery
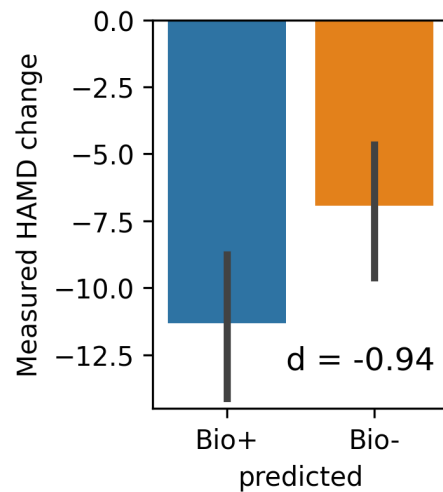### Biomarker + vs − (median split)

(MMRM analysis)

- N=93 open label SSRI
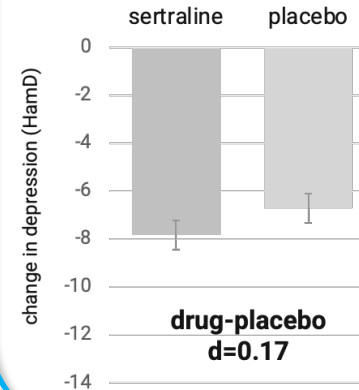- 8 weeks treatment
- 19-channel EEG

Replication
Biomarker + vs − (median split)

- N=42 open label SSRI
- Generalizes across specific SSRIs

All-comer

drug-placebo
d=0.17

Biomarker-stratified

sertraline   placebo

biomarker positive drug-placebo
d=0.61
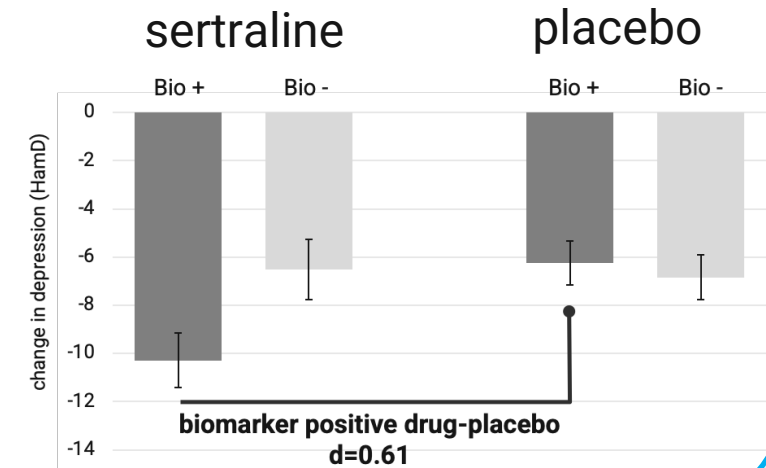
Reliability
(MDD patients in-clinic)

2 weeks gap

ccc = 0.66
rho = 0.66

8 weeks gap

ccc = 0.61
rho = 0.59

ALTO NEUROSCIENCE
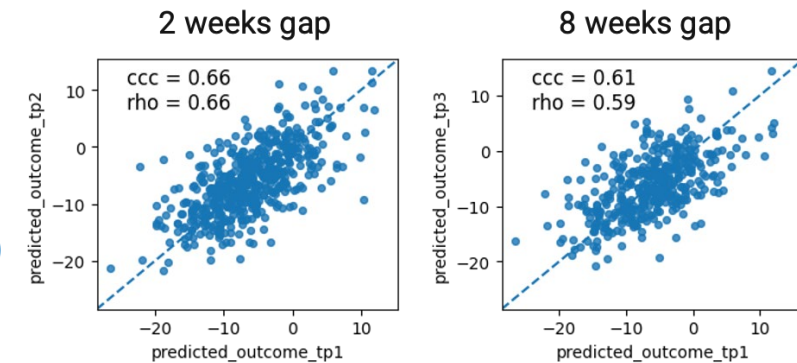
ALTO'S SUITE OF BIOMARKERS SEGMENTS PATIENTS TO DRIVE IMPROVED OUTCOMES

Heterogeneous Clinical populations

Alto Biomarker Platform
- EEG
- Behavior
- Wearable

Example Alto Biomarker
- EEG Signature
- Cognitive Profile
- Sleep/activity pattern

Activity throughout the day:

Biomarker Defined Sub-Population

Likely Responder to Alto Drug
- Drug 1
- Drug 2
- Drug 3
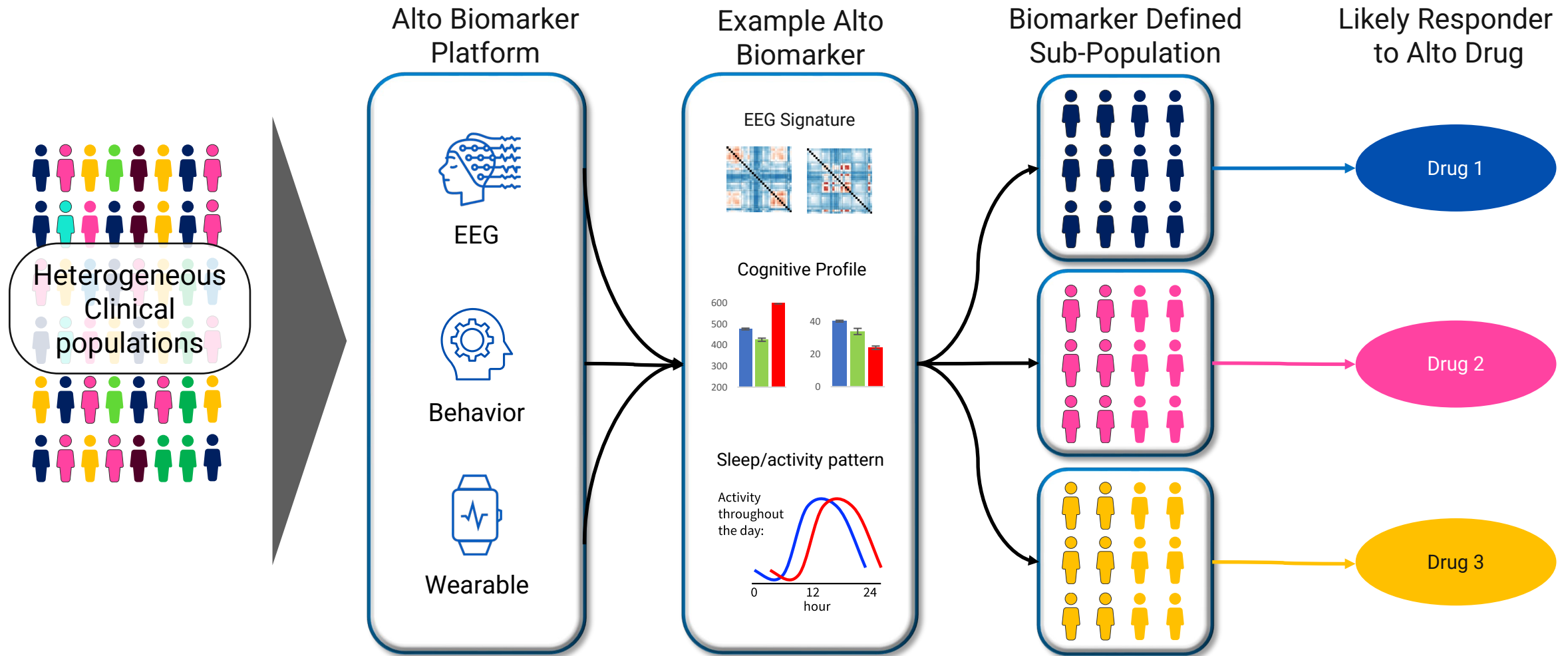
25-50% of patients likely to be biomarker positive
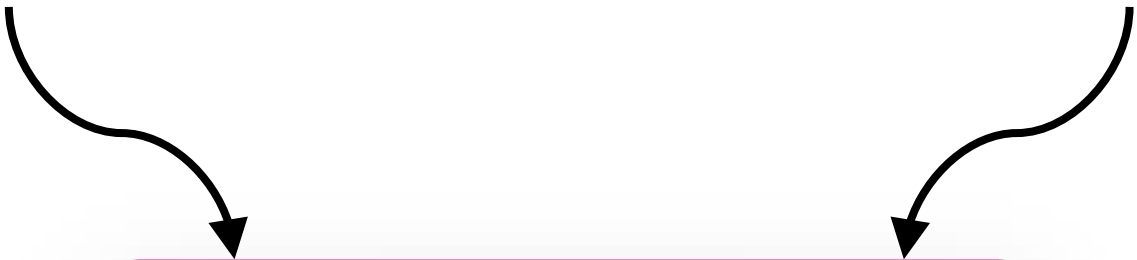
DEPRESSED PATIENTS WITH POOR COGNITION ARE A KEY TARGET FOR NOVEL DRUG DEVELOPMENT

Cognition in MDD – impaired in a subset:
- Includes executive function and memory
- Evident across ages, ~1SD below healthy
- Worse treatment response

Hippocampal plasticity and neurogenesis:
- Reduced in MDD and animal models of stress
- ↓ hippocampal volume → treatment resistance
- Plasticity role in cognition and mood

Alto's hypothesis:
Increasing neuroplasticity may benefit states of low mood and cognitive impairment

ALTO NEUROSCIENCE

DEVELOPING A NOVEL TREATMENT OPTION FOR MDD PATIENTS WITH POOR COGNITION

Aimed to discover NOVEL pro-plasticity compound

ALTO-100 identified ✓
Orally active lead discovered from 10k screened

Increases Plasticity ✓
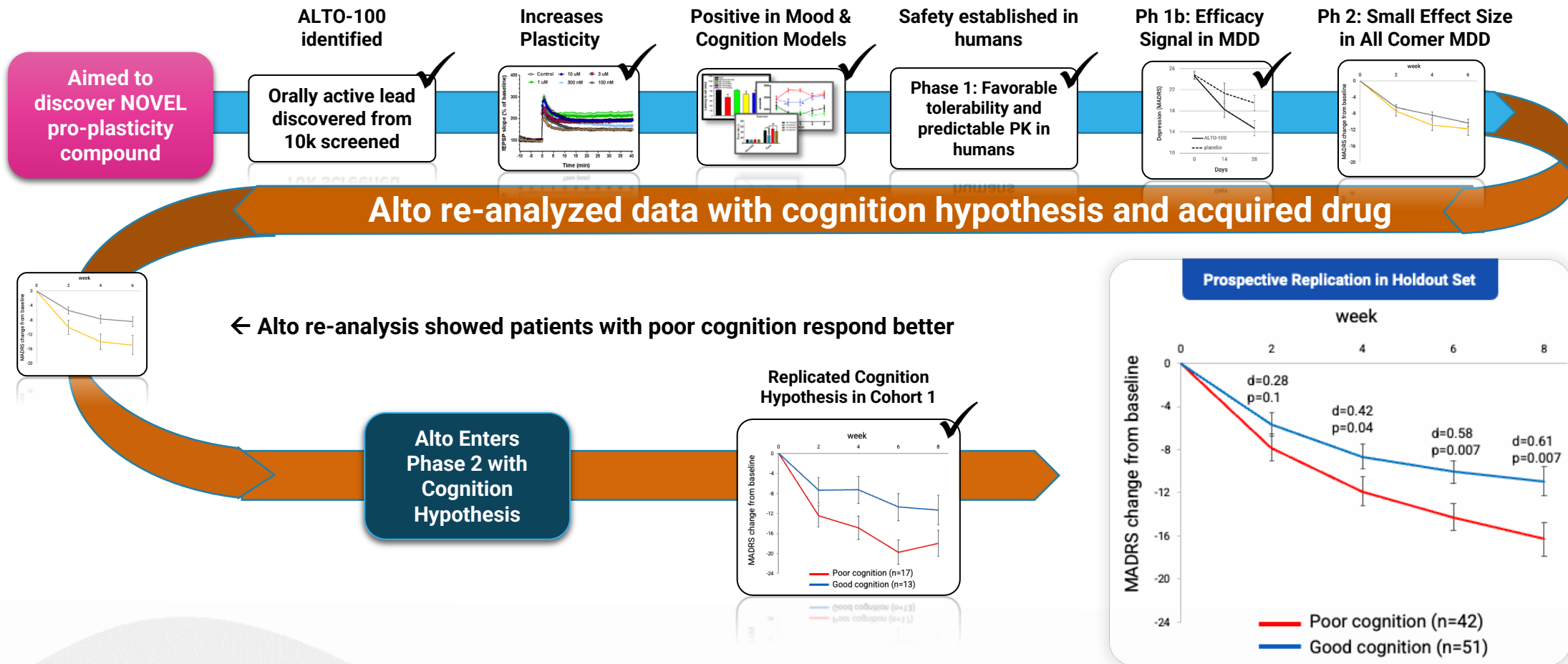
Positive in Mood & Cognition Models ✓

Safety established in humans ✓
Phase 1: Favorable tolerability and predictable PK in humans

Ph 1b: Efficacy Signal in MDD ✓

Ph 2: Small Effect Size in All Comer MDD

Alto re-analyzed data with cognition hypothesis and acquired drug

← Alto re-analysis showed patients with poor cognition respond better

Alto Enters Phase 2 with Cognition Hypothesis

Replicated Cognition Hypothesis in Cohort 1 ✓

Poor cognition (n=17)
Good cognition (n=13)

Prospective Replication in Holdout Set

week

d=0.28
p=0.1

d=0.42
p=0.04

d=0.58
p=0.007

d=0.61
p=0.007

Poor cognition (n=42)
Good cognition (n=51)

Phase 2b study will read out mid-2024

ALTO NEUROSCIENCE

THE PRECISION PSYCHIATRY FLYWHEEL

Novel paths for data collection

Scalable/at-home biomarkers

Biomarker-based clinical data

Drug brain effects drive indications

Value of aggregated data

AI algorithms

Novel drug targets

Drug approvals

Stratification & phenotypes
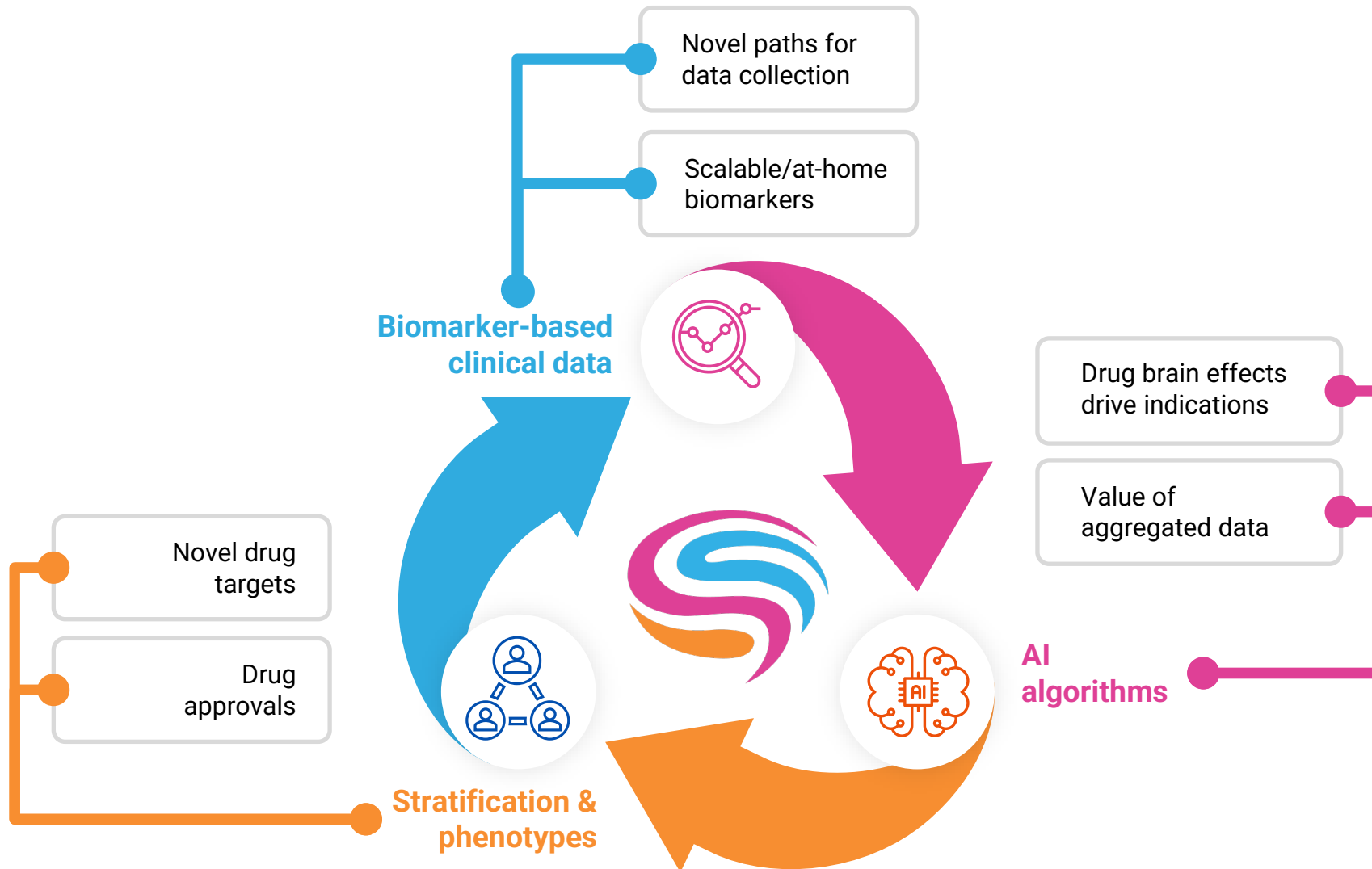
ROBUST PIPELINE OF ALL CLINICAL-STAGE CANDIDATES

	Product Candidate	MoA/Target	Discovery	Phase 1		Phase 2		Phase 3
				Safety	Brain Effects	Responder Biomarker Identification	Efficacy in Biomarker Positive	Registration Studies
COGNITION TARGETING	ALTO-100	BDNF				MDD/PTSD	MDD	
	ALTO-101	PDE4						
EMOTION TARGETING	ALTO-202	NMDA NR2B				MDD		
	ALTO-203	UNDISCLOSED						
SLEEP TARGETING	ALTO-300	UNDISCLOSED				MDD	MDD	
COMBINATION PHARMACOLOGY	100 Series	cAMP SIGNALING						
	200 Series	DOPAMINE SIGNALING						