

Bringing Precision to Psychiatry

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Disclosures

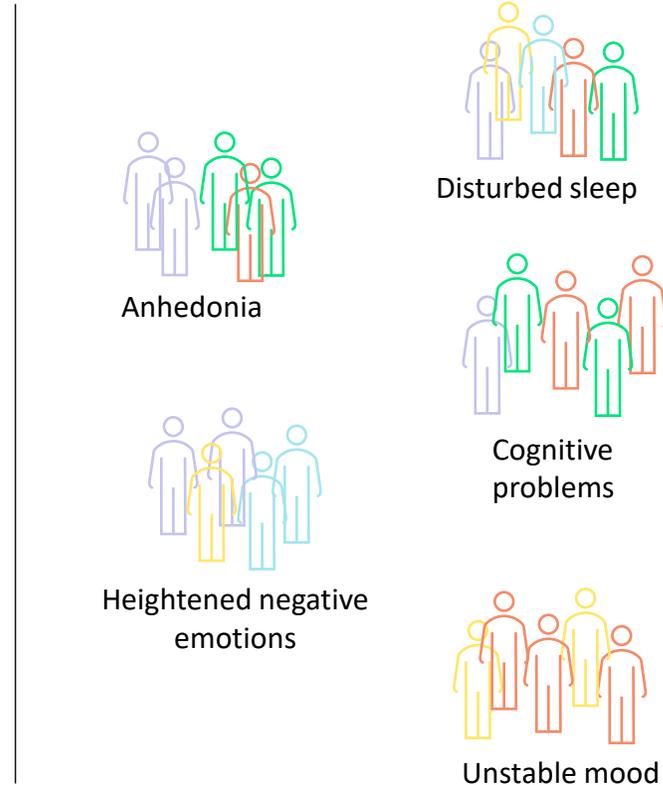
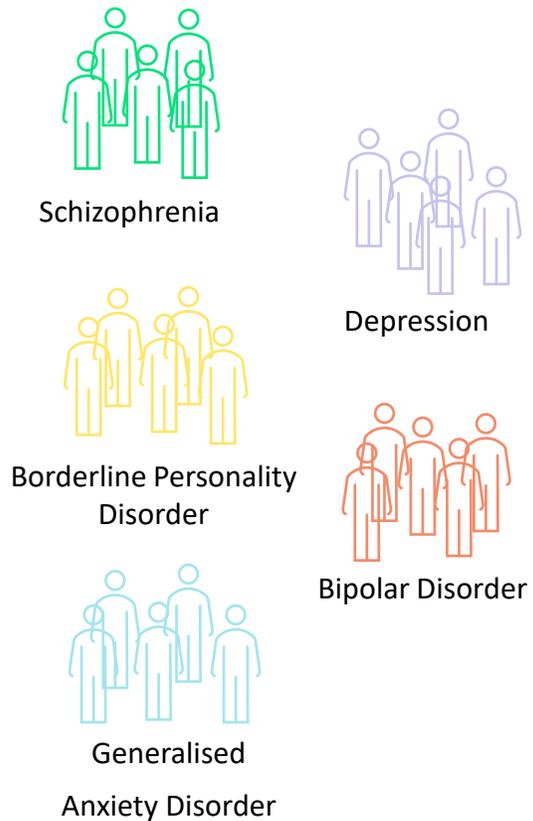
I am a full-time employee of Boehringer Ingelheim.

The views represented in this talk are my own and do not represent the position of Boehringer Ingelheim as a company.

Diagnosis is based on Syndromic Descriptions rather than Causal Neurobiology

'DSM' diagnosis looks "homogeneous" but...

..in reality symptoms overlap between diagnoses



As "DSM" Diagnoses don't map directly to neurobiology patient groups are biologically heterogeneous

This...

- Depowers clinical studies designed to test more "precise" hypotheses
- Hinders new understanding of patient biology and clinical endpoints

Resulting in...

- Fewer strong biological hypotheses against which to test novel drug targets
- Treatment regimens are based on trial and error

Depression: Analysis NESDA patient cohort provides biological insight and opportunity to improve annotation

	“TYPICAL” DEPRESSION	IMMUNO-METABOLIC DEPRESSION
Symptoms	less appetite/weight, insomnia, suicidal ideation	more appetite/weight, leaden paralysis, fatigue, hypersomnia
Correlates	smoking, negative life events, childhood trauma	female gender, early onset
Course	more persistent anxiety & suicidality	obesity, persistent poor metabolic syndrome profile
Pathophysiology	Hyperactivity of the HPA-axis (higher cortisol)	inflammation, dyslipidemia, leptin & insulin resistance
Genetic basis	stronger overlap with schizophrenia genes	Stronger overlap with weight & immuno-metabolic genes

Based on Lamers et al. J Clin Psych 2010; Mol Psych 2012; Mol Psych 2013; Br J Psych 2016; Penninx et al. BMC Med 2013; Milaneschi et al. Mol Psych 2015; Biol Psych 2016; Biol Psych 2020. Figure in Penninx, Neurosci Biobehav Rev 2016. **Slide courtesy of Prof. Brenda Penninx**

Many of the endpoints and assessment measures available to us today were....

Therefore, most clinical trial endpoints are not optimized:

- To reflect underlying neurobiology
- Address specific symptom domains
- Reflect the temporal dynamics of the patient and/or a treatment

So, Phase II proof of concept may be achieved but Phase III is becoming the challenge

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

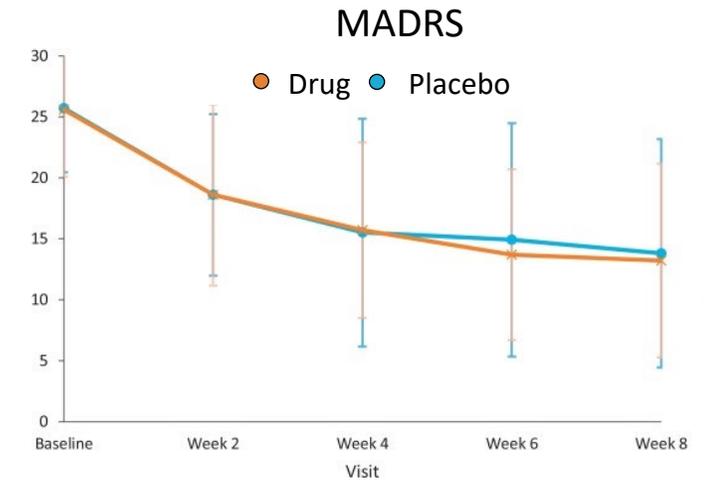
HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

... not designed to measure clinical change...

or

... designed to measure clinical change with specific, validated classes of mechanism...



...and have often proved ineffective at measuring clinical change

MADRS

Montgomery and Åsberg Depression Rating Scale

Drug

We need innovation to bridge the unmet needs of patients to our increasing knowledge of brain biology

High unmet need in psychiatry; assessed by DSM-5-based tools

Increasingly robust understanding of circuit biology

Bridging
requires ensuring that assessment measures, selection criteria, and endpoints:

Reflect circuit function

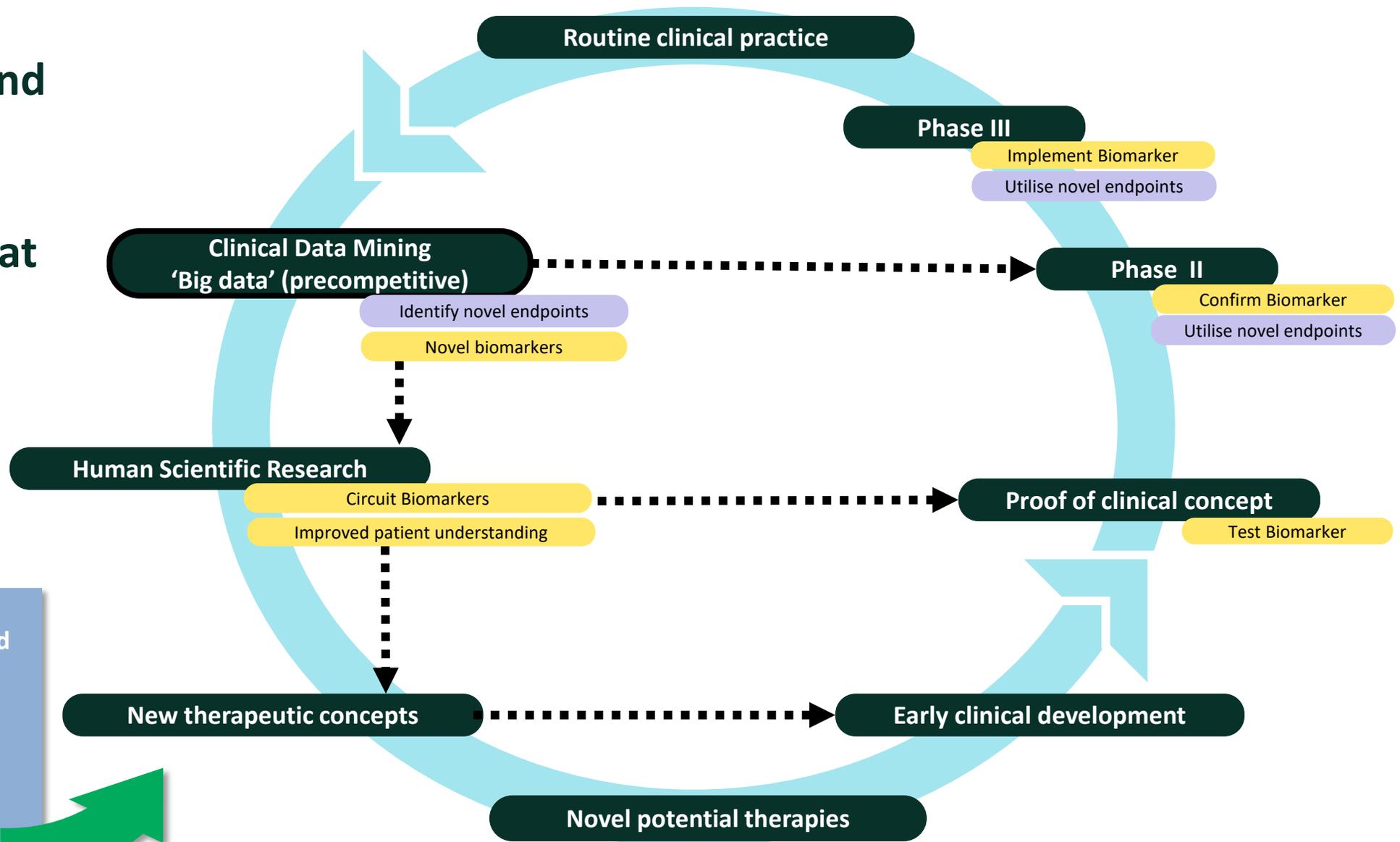
Are scalable in clinical contexts

Are patient-centric (i.e. measure things that matter to patients)

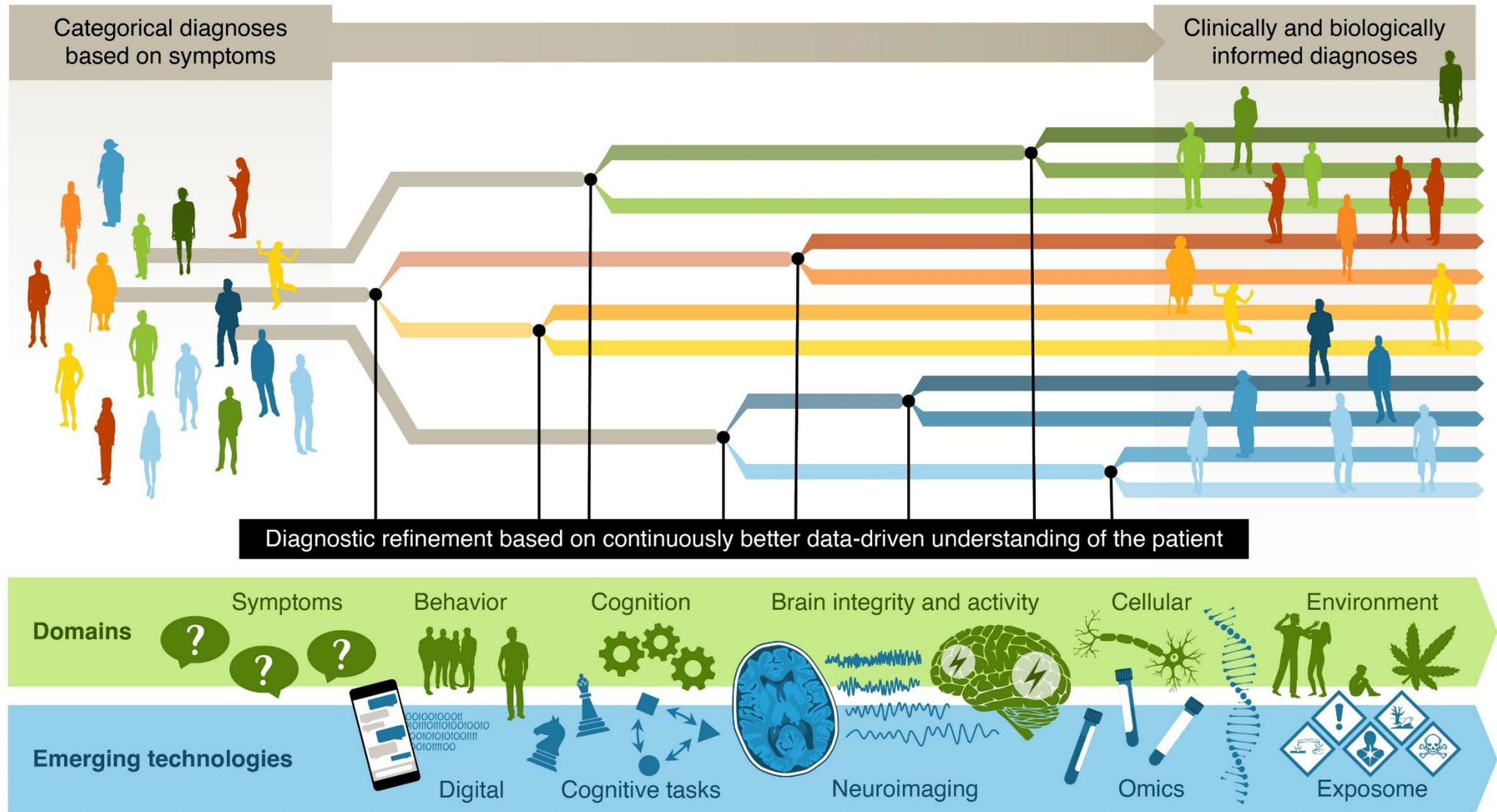


Better patient understanding and data integration will allow us to test hypotheses at scale in the real-world and in clinical trials

Driven by a new and improved understanding of the patient



A continuously evolving diagnostic framework leading to mechanistic-based treatments





fMRI images: © 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



Neuropsych 2014
 PRISM 2016-19
 PRISM2 2021-24

- Established that Social Dysfunction is Transdiagnostic
- Identified that Default Mode Network structure and function are key
- Suggested new guideline for Clinical outcome use
- Evidenced the benefit for a new digital endpoint

SZ: Schizophrenia AD: Alzheimer's disease MD: Major depressive disorder HC: Healthy control

Analysis of patient experience in PTSD led to the suggestion of two separate patient subgroups who are likely need different treatment approaches

Yale University and Boehringer Ingelheim have successfully identified a subset of PTSD patients with a distinct behavioral/symptomatic profile

This finding

- Informs neurobiological basis and offers new therapeutic hypotheses
- Predefines potentially improved patient stratification biomarkers & proof mechanism measures
- Offers starting point for new clinical outcome measures

Two Faces of PTSD: Fear vs. Emotional Pain

The Fear Profile ("Threat Reactivity")

The Emotional Pain Profile ("Internalized Distress")



Flashbacks



Nightmares



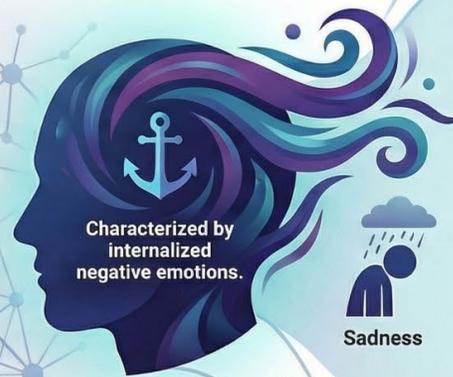
Exaggerated startle



Avoiding external reminders



Characterized by classic threat responses.



Characterized by internalized negative emotions.



Loss of interest



Negative beliefs



Sadness



Guilt



Shame



Has a predictable neural signature.

Early brain connectivity patterns can predict the long-term severity of symptoms.



Lacks a clear predictive neural signature.

The same early brain patterns did not predict long-term symptom severity.

31%

31%

of patients. Identified Fear as the most central and interfering emotion in their daily life.

69%

69%

of patients. Rated Emotional Pain as the more central and impairing part of their experience.

NotebookLM

In conclusion



A **better understanding of the patient and their biology**, gained through more exploratory experiments, will enable us to more **successfully develop new treatments**, and design **more effective clinical trials** to test those treatments



Strong biological hypotheses will allow us to more accurately trace the path from brain biology through to the individual patient, so we can give the **right treatment to the right patient at the right time**.



To achieve this, we need:

- Validated **mechanistic biomarkers** aligned with therapeutic hypothesis
- More **accurate and precise stratification** of patients into homogeneous biologies
- Clinical trial **endpoints** that more closely reflect the patient's therapeutic needs and are tuned to detect the change.

Thank you for your attention

Notes slide

- Short Outline
- Precision strategies addressing psychiatric and mental health conditions face additional challenges. Understanding these challenges and addressing them is key to improving our ability to get the right drug to the right patient and measuring the right outcome.
- Areas where we have strong biological hypotheses (understanding of biological hypotheses might be a bit weaker compared to other areas). If you have a strong biological hypothesis, one would assume that the mechanism is clear therefore the translation into early clinical studies should be comparatively straightforward.
- Then we need the tools to stratify, which then should reduce heterogeneity and increase homogeneity which should make the clinical trials more robust, but need to make sure we are picking the right clinical endpoints to match the hypothesis
- Acknowledge that in these better understood biological areas, the real weakness between preclinical and clinical work – need to ensure you are moving from a demonstration of proof of concept in Phase 2 to real world clinical benefit in Phase 3 – need to ensure the right clinical endpoints are aligned is something that we need to do
- Concept of biological hypothesis - ensuring that when we're designing clinical trials, that the biological hypotheses are not just testing the academic hypothesis – tools exist to turn them into operational and truly testable
- In the mental health space, beginning to move into new biological areas – can share 2-3 studies to illustrate that point
- Importance of thinking about the clinical stage at the research stage early on (way before lead optimization starts)
- Importance of having the patient in the center at the early stage