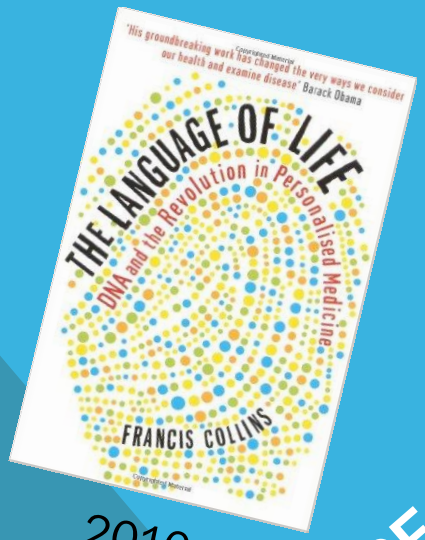
# CAN PSYCHIATRY BE PRECISE?

## PSYCHIATRIC NOSOLOGY AND 21ST-CENTURY MEDICINE

Kathryn Tabb
Columbia University

# OUTLINE OF THE TALK

1. The Precision Medicine Initiative
2. The turn to precision in psychiatric research
3. The virtues of precision medicine
   - ① Reductionism
   - ② Big Data
   - ③ Nosological Revisionism
4. Are these three virtues necessary and sufficient for progress in psychiatry?
5. Can these three virtues be disaggregated?



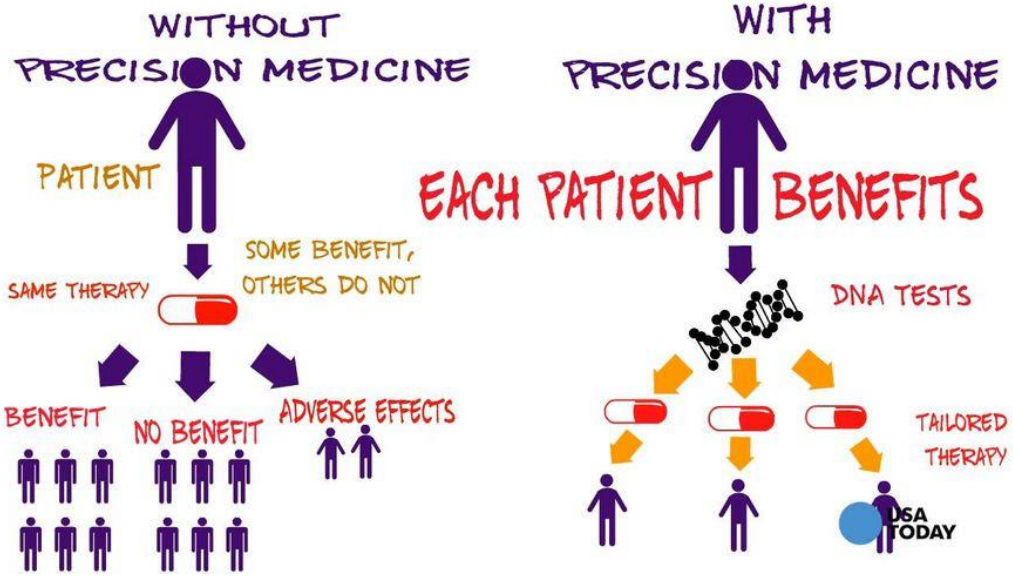

2010

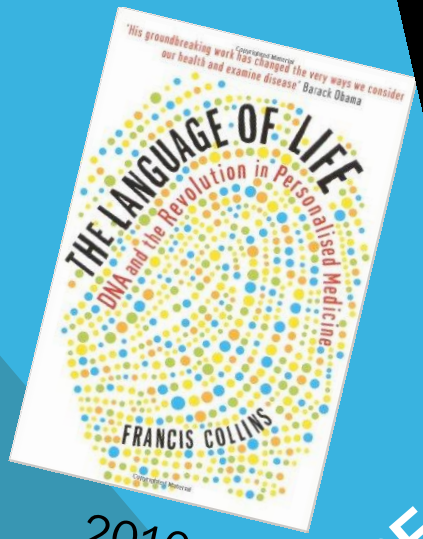
# PRECISION MEDICINE

A new paradigm?

The goal of precision medicine is to "ensure that the right treatment is delivered to the right patient at the right time"

-- (National Academies of Sciences, Engineering, and Medicine: *Biomarker Tests For Molecularly Targeted Therapies: Key to Unlocking Precision Medicine*)



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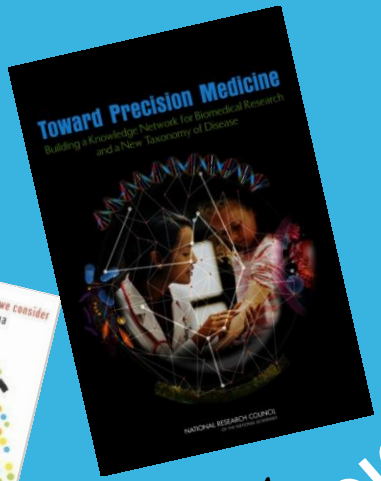


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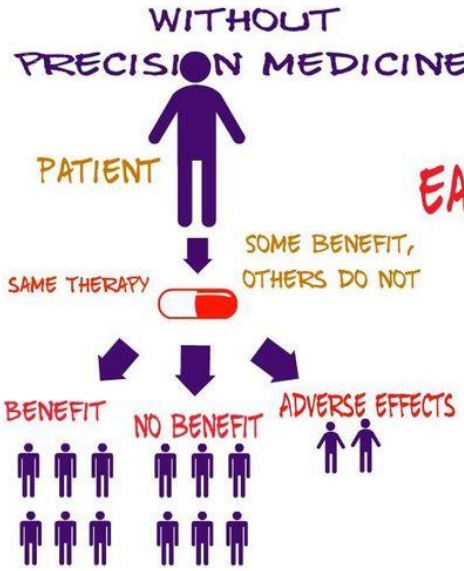
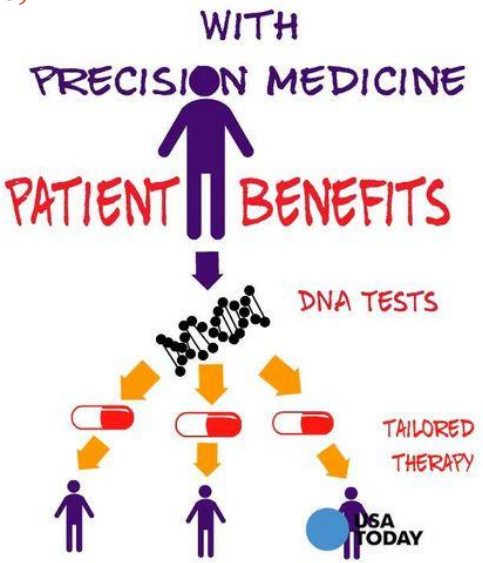


# THE PRECISION MEDICINE INITIATIVE

*“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”*

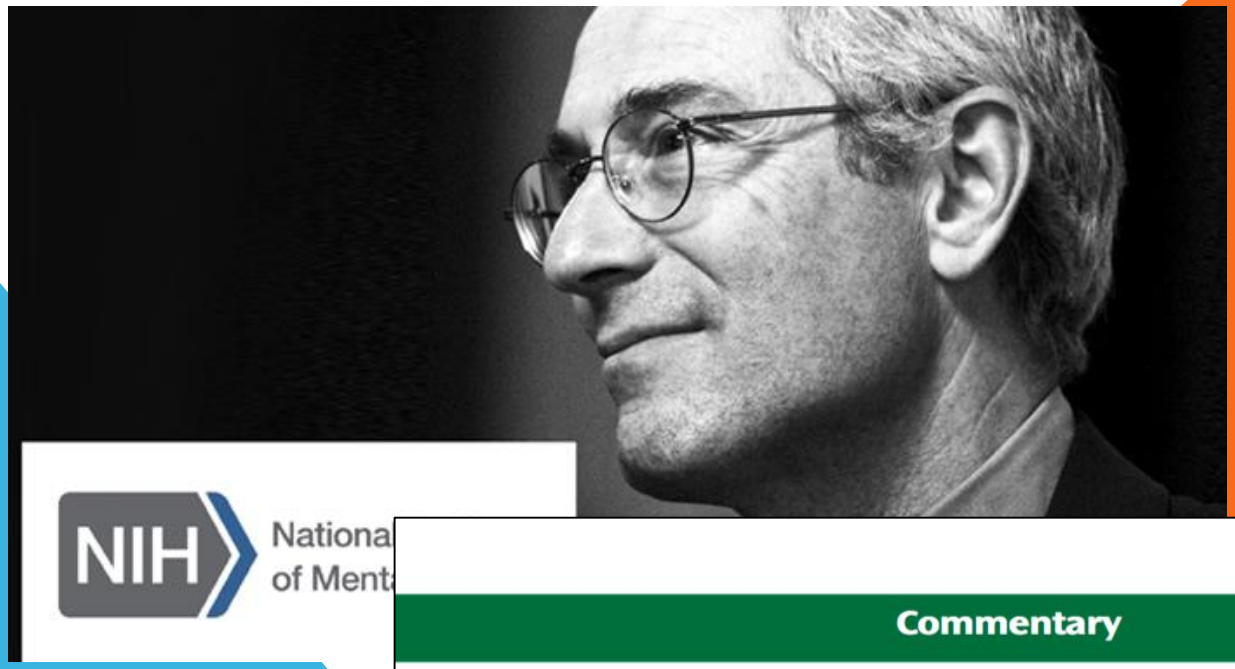
*- President Obama, January 30, 2015*

“We’ve applied the new powers of technology…. to strike an enemy force with speed and incredible precision. By a combination of creative strategies and advanced technologies, we are redefining war on our terms. In this new era of warfare, we can target a regime, not a nation.”

# PRECISION MEDICINE

## A new paradigm?

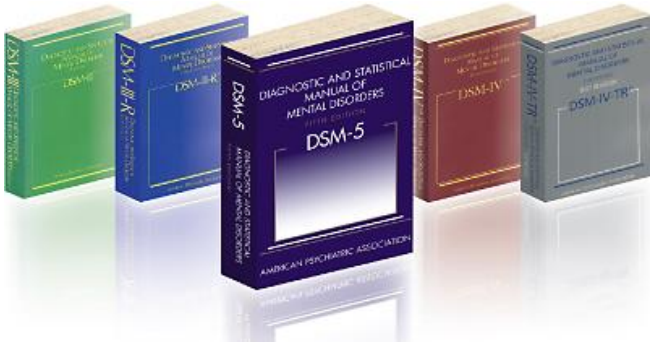
# Insel in 2014:




Commentary

## The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry

*"How small, of all that human hearts endure, That part which laws or kings can cause or cure."*—Samuel Johnson




# PRECISION PSYCHIATRY

In 2012 over 90% of articles in three of the top psychiatric research journals — the American Journal of Psychiatry, Biological Psychiatry, and the Archives of General Psychiatry (now JAMA Psychiatry) examined a single DSM disorder, comparing patients diagnosed with the condition to healthy controls (Bruce Cuthbert, personal communication)

Clinician complaints:

diagnosis bloat

bracket creep

neglect of phenomenology

neglect of social factors

and the list goes on....

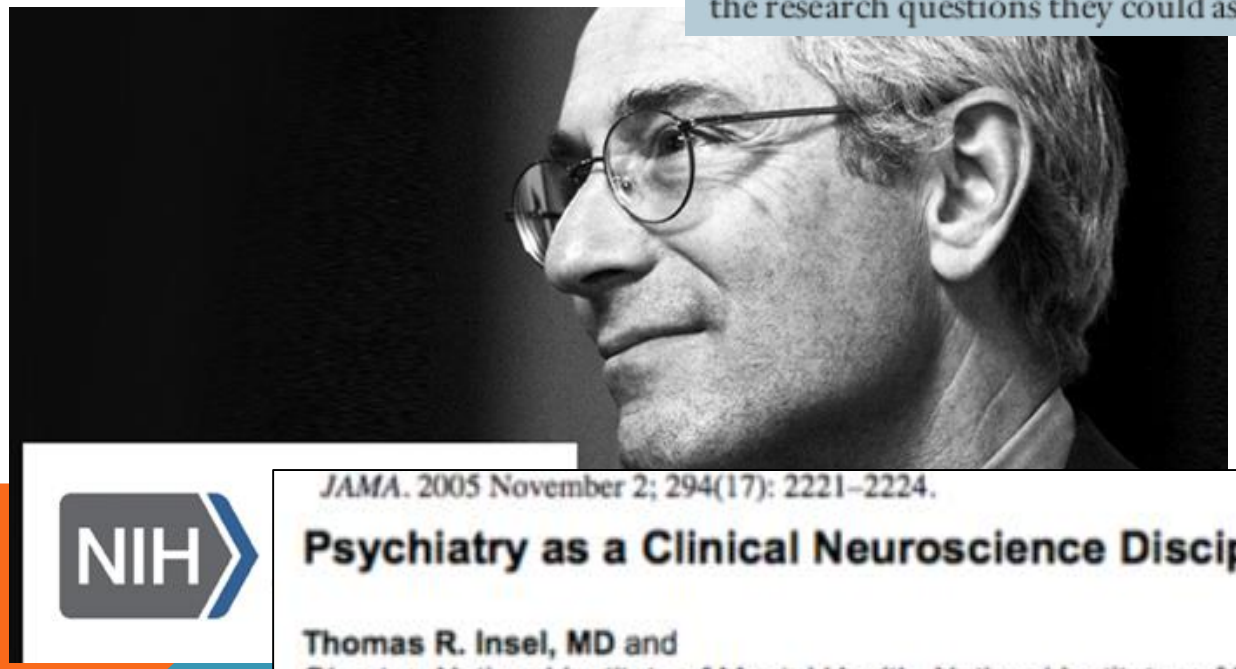
# PRECISION PSYCHIATRY

"Categorical mental disorders do not "line up" one-to-one with variations in the functioning of neural circuits. Rather, neural circuits align with narrower neurobehavioral constructs that are themselves related to psychopathology in cross-cutting fashion: Dysfunction in each construct is related to multiple forms of psychopathology and most forms of psychopathology are related to dysfunction in more than one construct."

(Lahey and Zald 2013)

# THE DSM AS AN "EPISTEMIC PRISON"

The DSM system was a critical platform for research that made possible shared understandings of disease models or affected populations under study. At the same time, it created an unintended epistemic prison that was palpably impeding scientific progress. Outside of their ongoing research projects, most investigators understood that the DSM-IV was a heuristic, pending the advance of science. In practice, however, DSM-IV diagnoses controlled the research questions they could ask, and perhaps, even imagine.



NIH

*JAMA*. 2005 November 2; 294(17): 2221–2224.

## Psychiatry as a Clinical Neuroscience Discipline

**Thomas R. Insel, MD** and
*Director, National Institute of Mental Health, National Institutes of Health, tinsel@mail.nih.gov*

**Remi Quirion, Ph.D, FRSC, CQ**
*Director, Institute of Neurosciences, Mental Health and Addiction, Canadian Institutes of Health Research, remi.quirion@douglas.mcgill.ca*

# THE RESEARCH DOMAIN CRITERIA MATRIX

- The National Institute of Mental Health decided to develop an alternative classification, not of mental disorders but of targets for research: the Research Domain Criteria project

- RDoC is a classification protocol for researchers that aims to encourage a profound shift in the way research samples are conceived of and assembled

- RDoC changes the targets of validation from diagnoses to any sort of phenomenon relevant to psychopathology that may be viewed either as an extreme on a spectrum of human variation or as a dysfunctional structure or process.

## Cognitive Systems

| Construct/Subconstruct | | Genes | Molecules | Cells | Circuits | Physiology | Behavior | Self-Report | Paradigms |
|---|---|---|---|---|---|---|---|---|---|
| Attention | | Elements | Elements | Elements | Elements | Elements | Elements | | Elements |
| Perception | Visual Perception | Elements | Elements | Elements | Elements | Elements | Elements | Elements | Elements |
| | Auditory Perception | Elements | Elements | Elements | Elements | Elements | Elements | Elements | Elements |
| | Olfactory/Somatosensory/Multimodal/Perception | | | | | | | | Elements |
| Declarative Memory | | Elements | Elements | Elements | Elements | Elements | Elements | Elements | Elements |
| Language | | Elements | | | Elements | Elements | Elements | Elements | Elements |
| Cognitive Control | Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 1 of 2 ⇒ Goal Selection | | | | Elements | | | Elements | Elements |
| | Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 2 of 2 ⇒ Updating, Representation, and Maintenance | Elements | Elements | Elements | Elements | Elements | Elements | Elements | Elements |
| | Response Selection; Inhibition/Suppression ⇒ Focus 1 of 2 ⇒ Response Selection | Elements | Elements | Elements | Elements | Elements | Elements | Elements | Elements |
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| | Performance Monitoring | Elements | Elements | | Elements | Elements | Elements | Elements | Elements |
| Working Memory | Active Maintenance | Elements | Elements | Elements | Elements | Elements | | | Elements |
| | Flexible Updating | Elements | Elements | Elements | Elements | Elements | | | Elements |
| | Limited Capacity | Elements | Elements | | Elements | Elements | | | Elements |
| | Interference Control | Elements | Elements | Elements | Elements | Elements | | | Elements |

# Cognitive Systems

## Circuits

### Subcortical

Koniocellular | Magnocellular | Parvocellular

### Cortical

Cortico-cortical connections into supra- and infra-granular layers | Dorsal/ventral streams

### Non-retinogeniculate

Superior colliculus | Suprachiasmatic nucleus

### Local circuitry

Lateral interactions | Top-down interactions

Implicated in contextual fields and association fields (responsible for the influence of spatial context on target processing)

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### Dorsal/ventral streams (RDoC Element)

Type of Element: Circuit

The following construct(s)/subconstruct(s) refer to this element...

- Domain: Cognitive Systems
  - Construct: Perception
    - **Subconstruct: Visual Perception**
    - **Subconstruct: Auditory Perception**

# RDoC'S VIRTUES

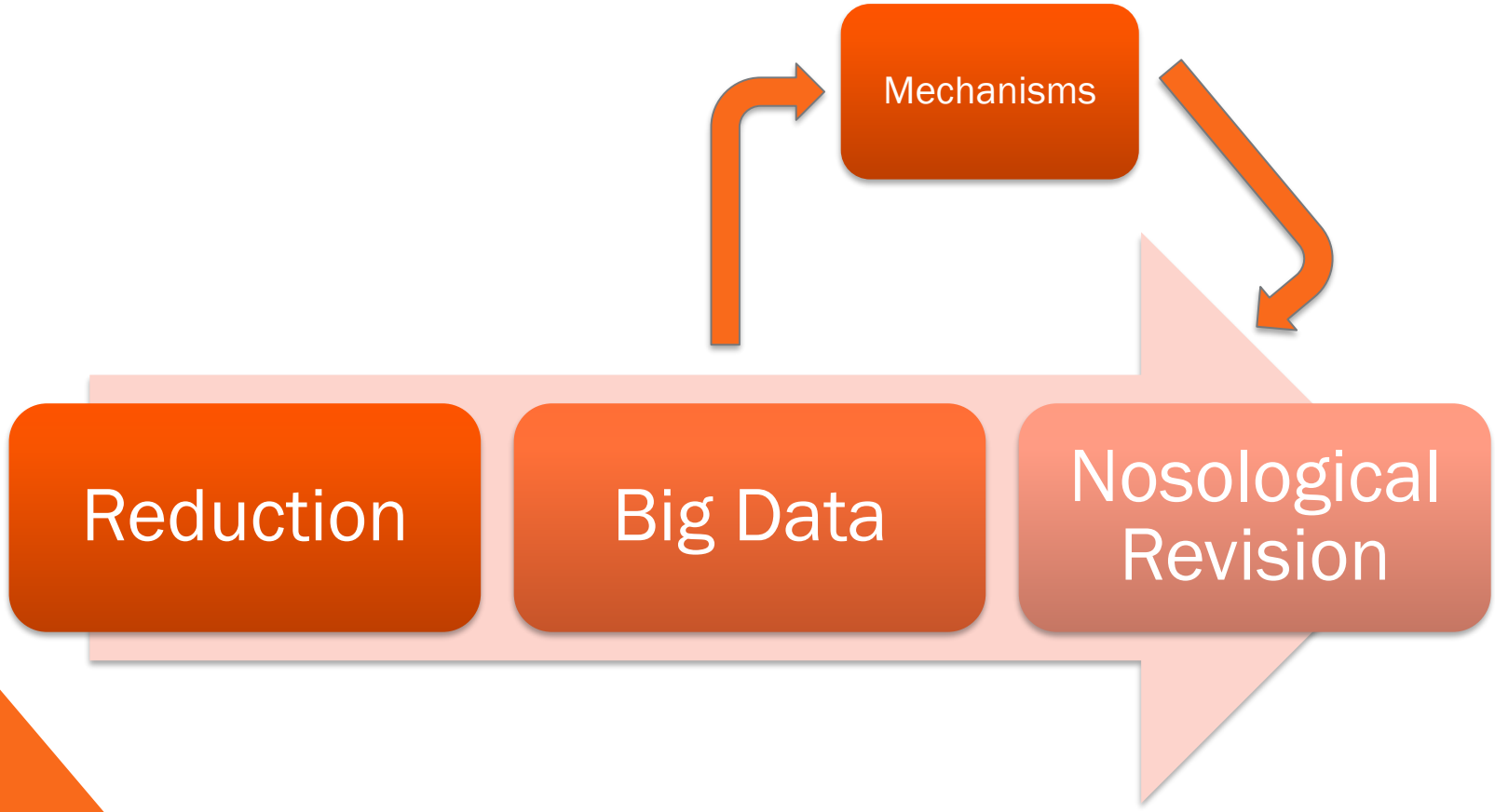
"First, mental illnesses are presumed to be disorders of brain circuits. Secondly, it is assumed that the tools of clinical neuroscience, including functional neuroimaging, electrophysiology, and new methods for measuring neural connections can be used to identify dysfunction in neural circuits. Third, the RDoC approach presumes that data from genetics research and clinical neuroscience will yield biosignatures that will augment clinical signs and symptoms for the purposes of clinical intervention and management."

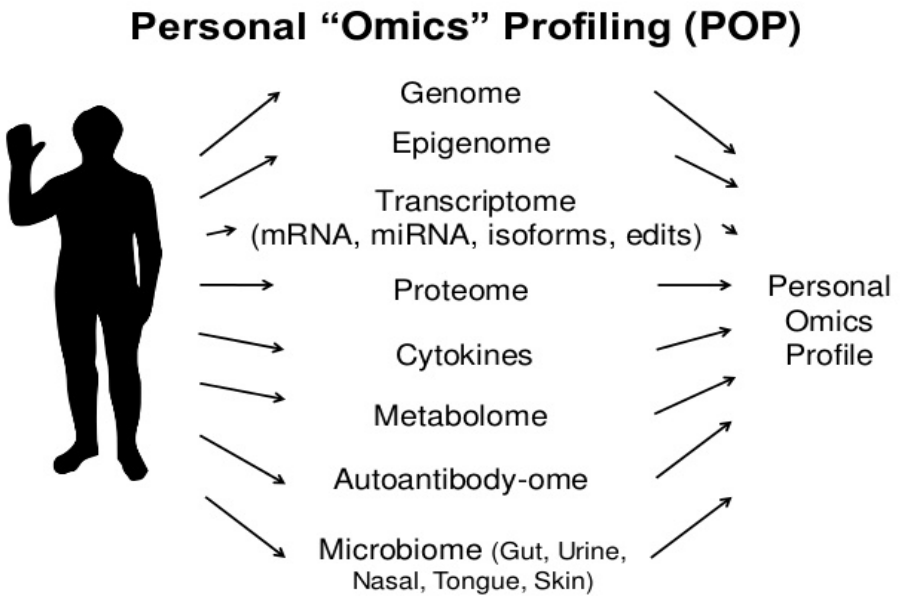
(Morris and Cuthbert 2012).

Reductionism

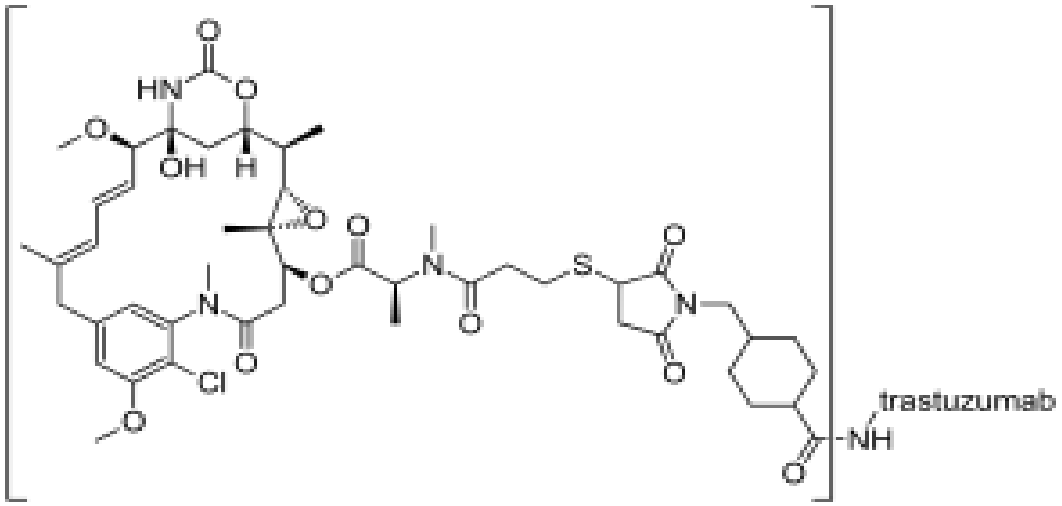
Nosological Revisionism

Big Data


Mechanisms
Reduction
Big Data
Nosological Revision




# REDUCTIONISM IN PRECISION MEDICINE





# REDUCTIONISM IN PRECISION MEDICINE

# REDUCTIONISM IN PSYCHIATRY

- In comparison to oncology, psychiatry lacks what Bechtel and Richardson (1993) have referred to as loci of control: those parts of a system whose functions contribute to the effect of interest and which can be manipulated to ultimately allow for the discovery of "precise" targets for intervention within the parts themselves.
- We have reasons to be doubtful that genetic loci of control will be identified:
  - Evidence from GWAS have revealed only genes implicated in psychopathology that have very small effect-sizes, suggesting that phenotypes associated with mental illness are polygenetic
  - Genes implicated in psychopathology are biomarkers of susceptibility to disease, rather than biomarkers of disease

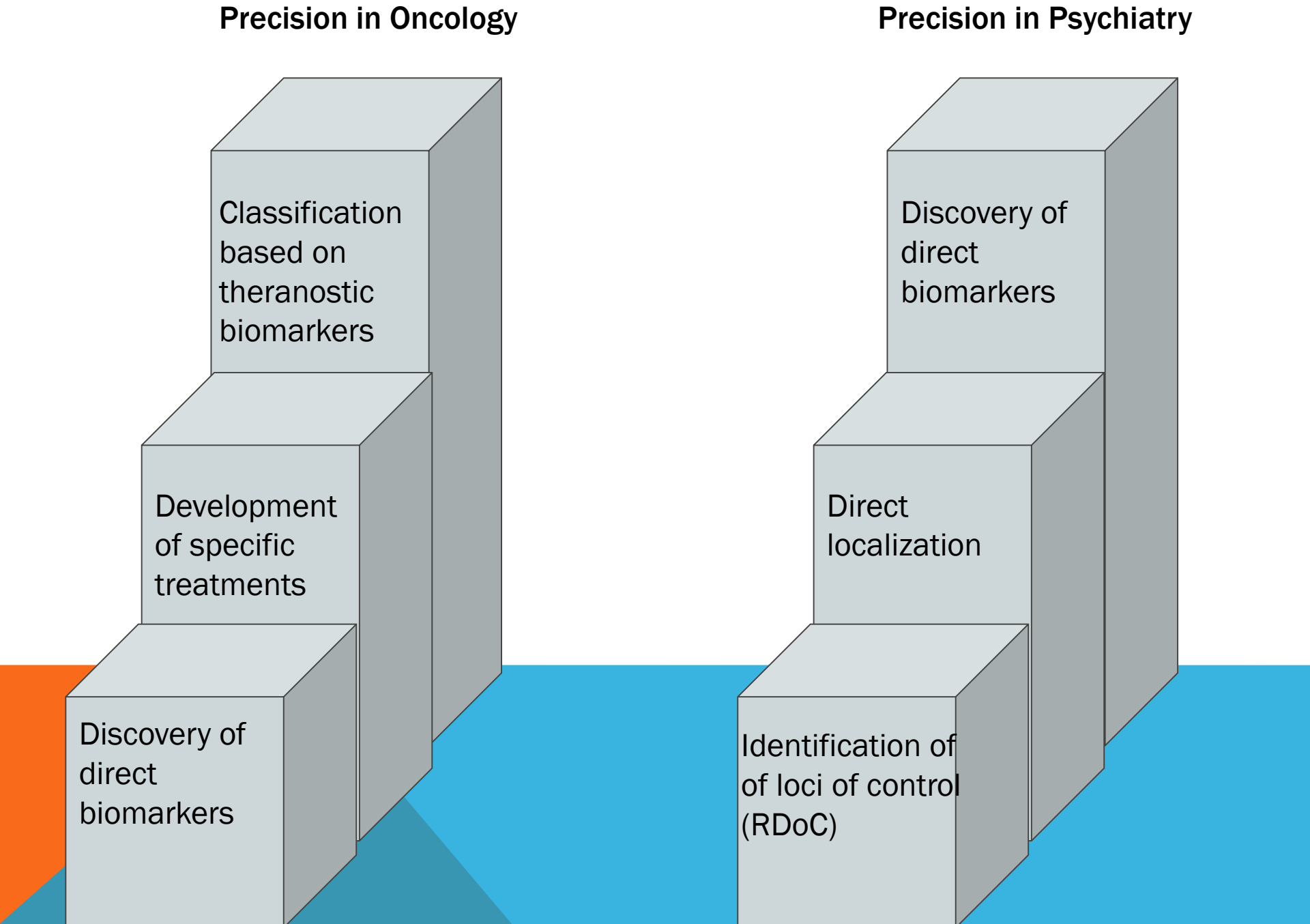
Maël Lemoine (Tours)

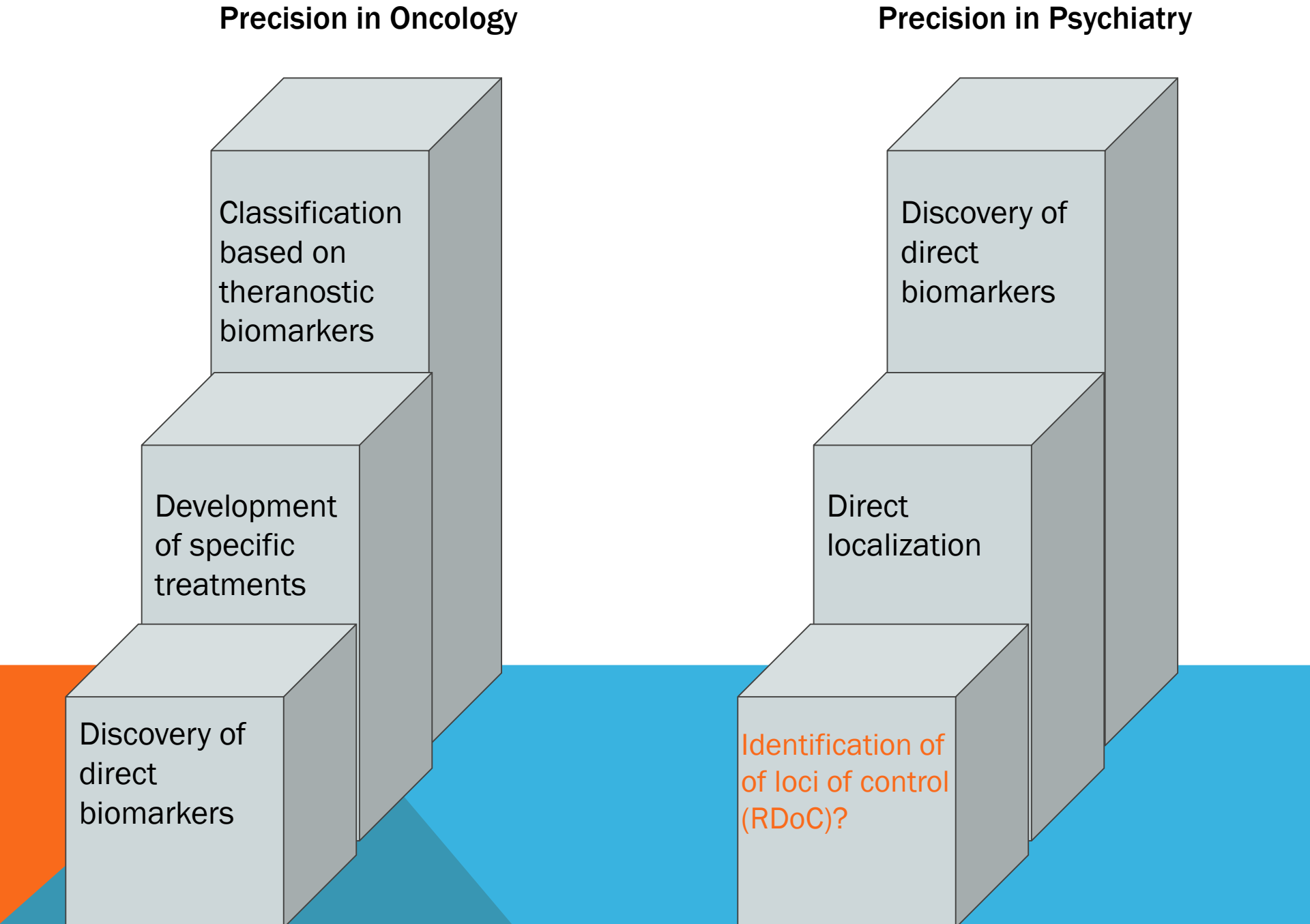
# REDUCTIONISM IN PSYCHIATRY

What about neurological loci of control?

RDoC-funded projects focus on discovering the neural circuitry underlying domains implicated in psychopathology, not correlating biomarkers at this level with therapeutic targets in order to develop new treatment protocols

Maël Lemoine (Tours)


Precision in Oncology
Classification based on theranostic biomarkers
Development of specific treatments
Discovery of direct biomarkers
Precision in Psychiatry
Discovery of direct biomarkers
Direct localization
Identification of of loci of control (RDoC)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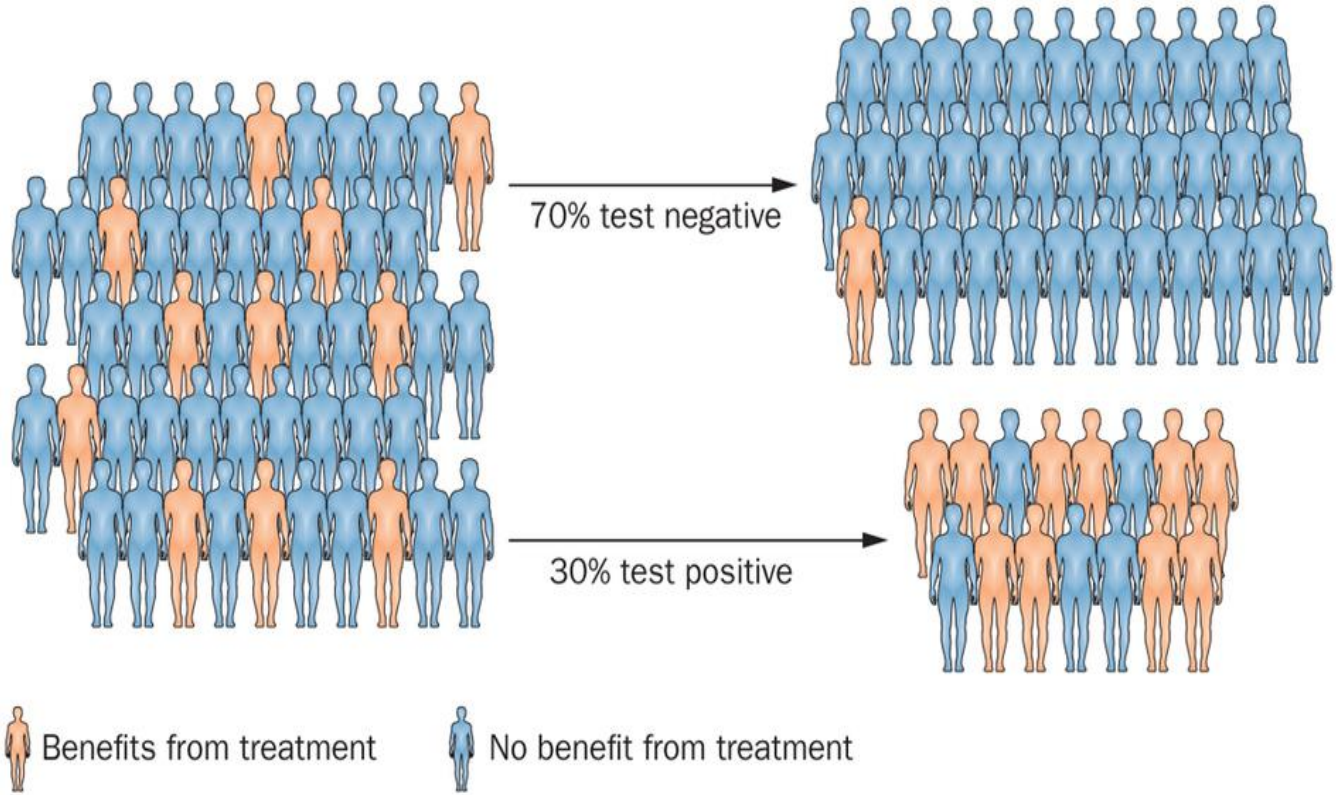
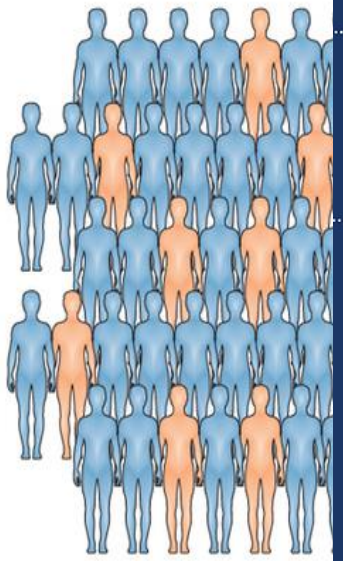
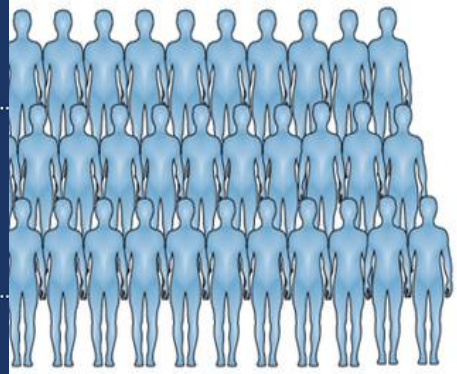
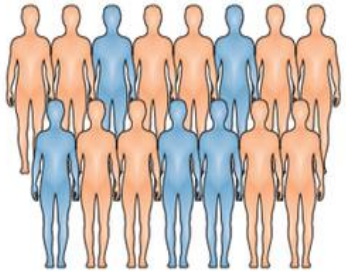



# BIG DATA IN PRECISION MEDICINE

# PRECISION MEDICINE INITIATIVE®
# COHORT PROGRAM







Benefits from treatme

## WHAT IS IT?

**Precision medicine** is a groundbreaking approach to disease prevention and treatment based on people's individual differences in environment, genes and lifestyle.

The Precision Medicine Initiative® Cohort Program will lay the foundation for using this approach in **clinical practice.**

## WHAT ARE THE GOALS?

Engage a group of **1 million or more U.S. research participants** who will share biological samples, genetic data and diet/lifestyle information, all linked to their electronic health records. This data will allow researchers to develop more precise treatments for **many diseases and conditions**.

Pioneer a new model of research that emphasizes **engaged research participants, responsible data sharing and privacy protection.**

Research based on the cohort data will:

- Lay **scientific foundation** for precision medicine
- Help identify new ways to **treat and prevent disease**
- Test whether **mobile devices**, such as phones and tablets, can encourage healthy behaviors
- Help develop the **right drug** for the **right person** at the **right dose**

## WHY NOW?

The **time is right** because:

We have a greater understanding of human genes

People are more engaged in healthcare and research

We have the tools to track health information and use large databases

Research technologies have improved

Follow the Initiative's progress and be one of the first to join this landmark effort.

**www.nih.gov/precision-medicine-initiative-cohort-program**

MEDICAL DISPATCH | JULY 21, 2014 ISSUE

# ONE OF A KIND

*What do you do if your child has a condition that is new to science?*

**BY SETH MNOOKIN**

*Until recently, Bertrand Might was the only known patient with a certain genetic disorder. His parents began searching for others.*

# BIG DATA IN PRECISION MEDICINE

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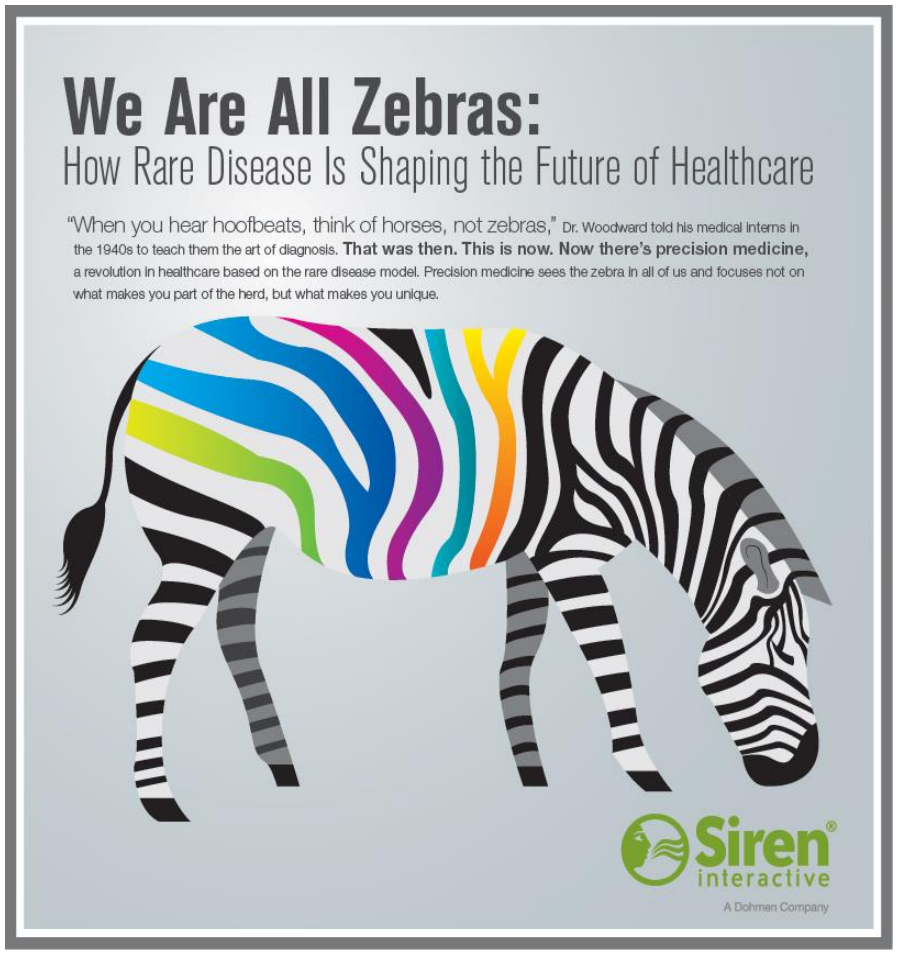


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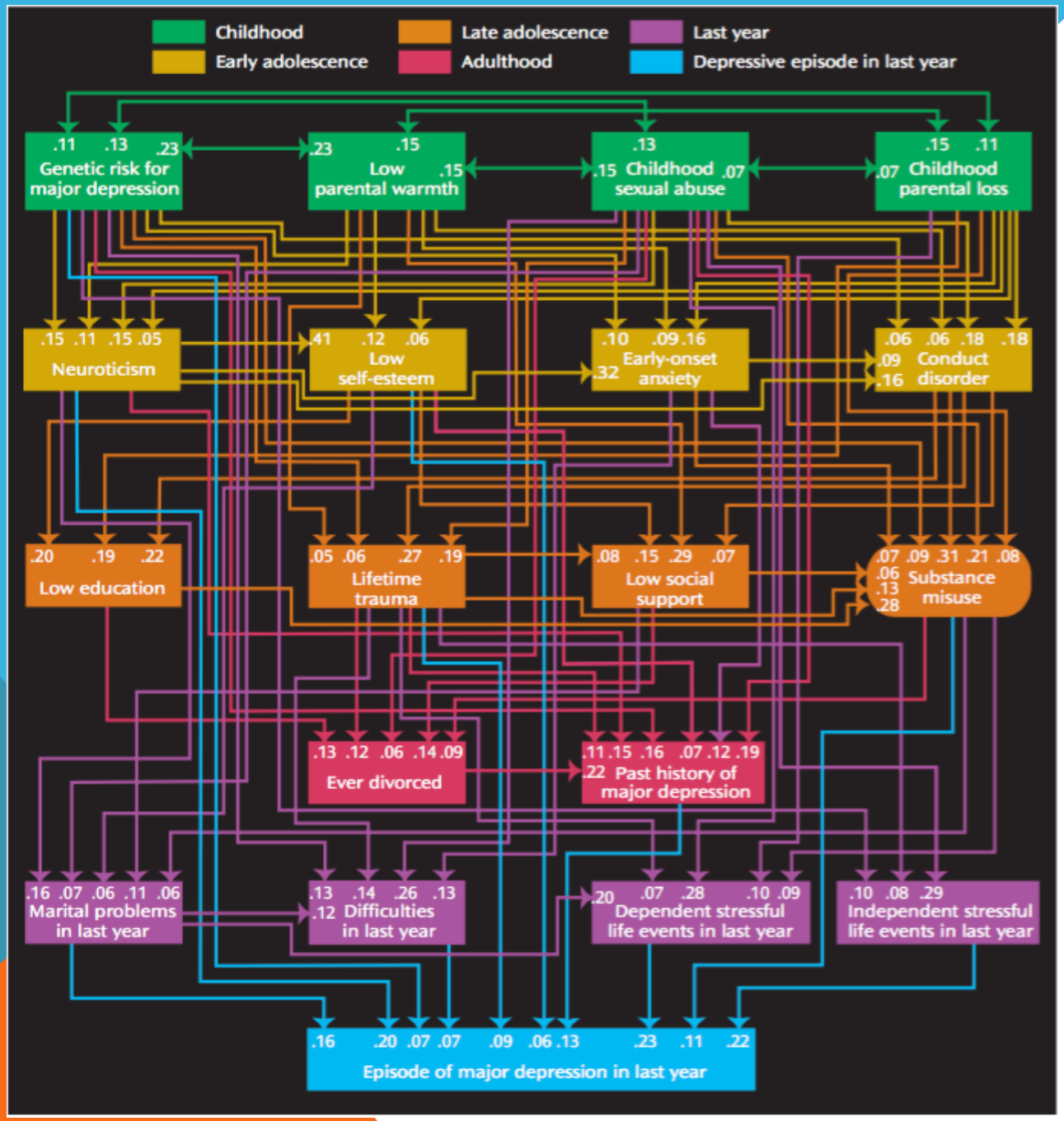
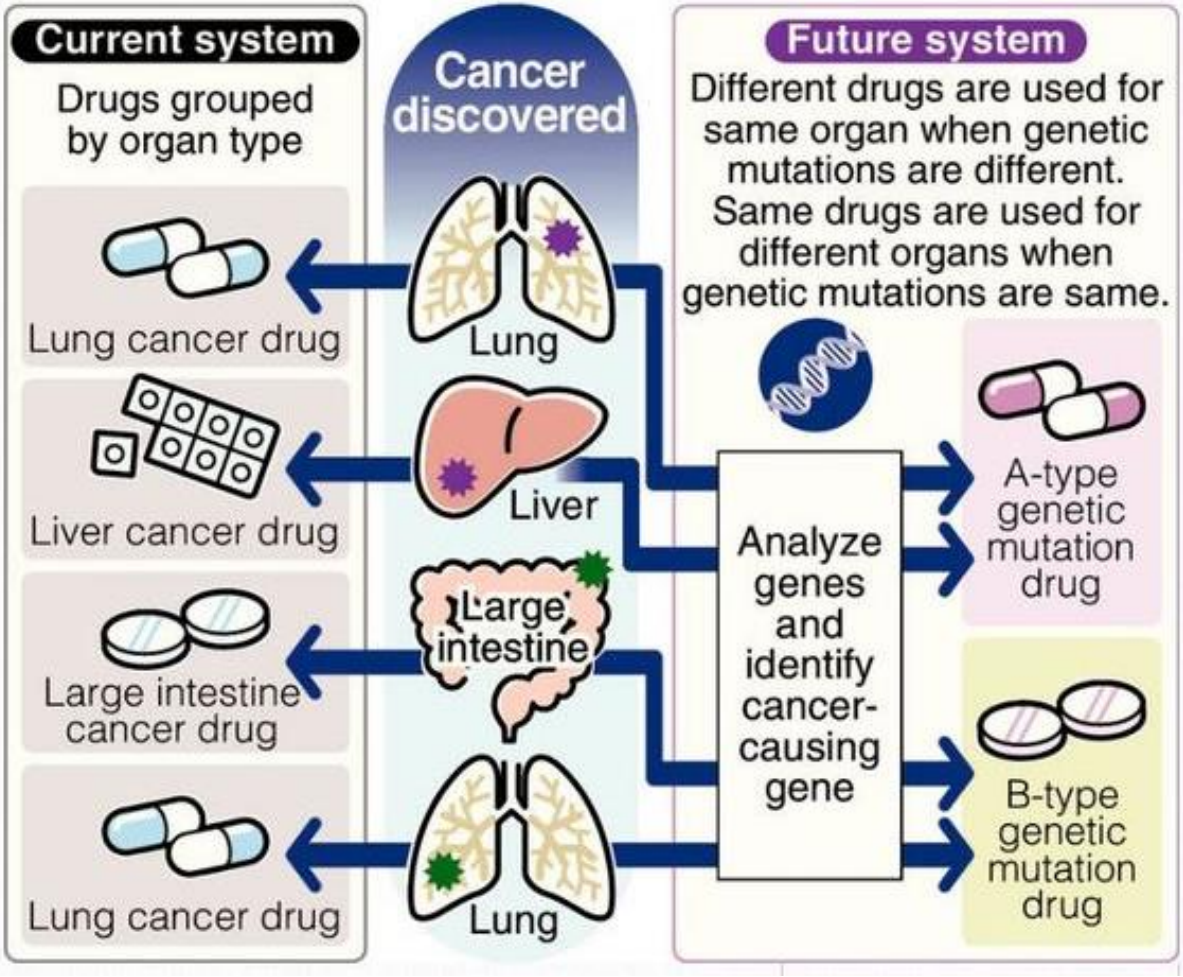



Kendler, Kenneth S., Gardner, Charles O., and Prescott, Carol A. 2006. "Toward a Comprehensive Developmental Model for Major Depression in Men." *American Journal of Psychiatry* 163 (1): 115–24.




# NOSOLOGICAL REVISIONISM IN PRECISION MEDICINE

# NOSOLOGICAL REVISIONISM IN PSYCHIATRY

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NIH

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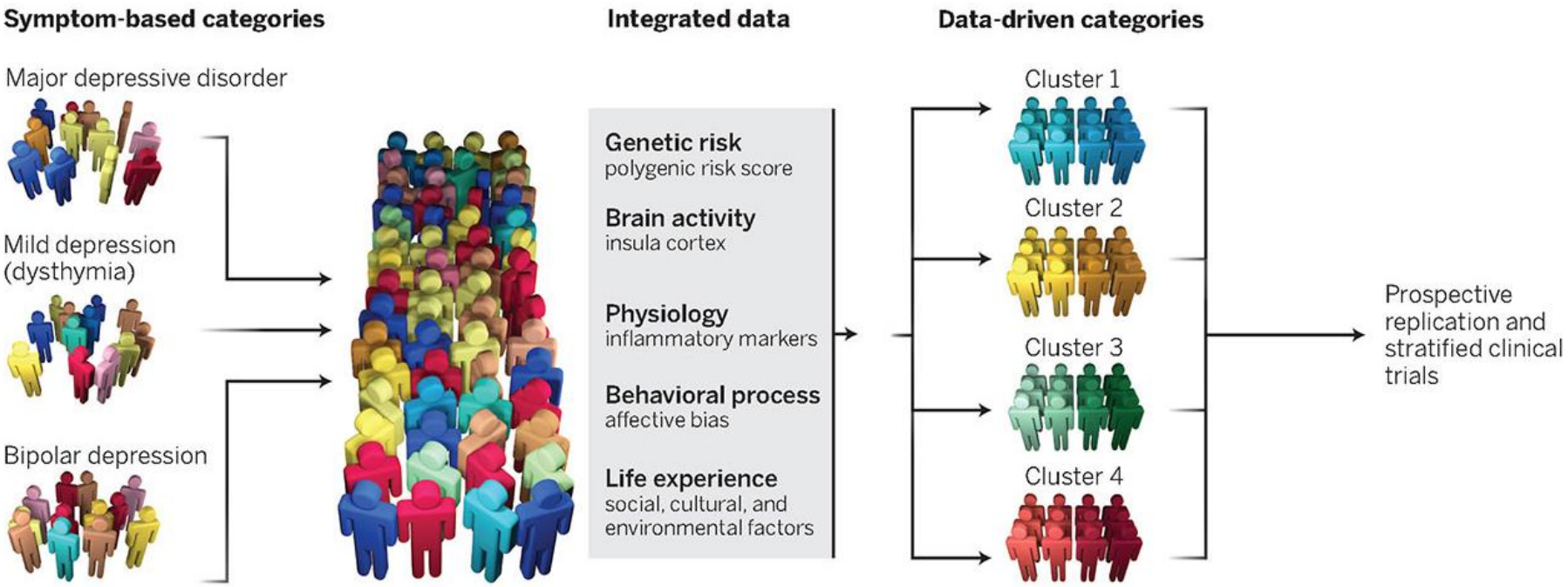
## Psychiatry as a Clinical Neuroscience Discipline

**Thomas R. Insel, MD** and
*Director, National Institute of Mental Health, National Institutes of Health, tinsel@mail.nih.gov*

**Remi Quirion, Ph.D, FRSC, CQ**
*Director, Institute of Neurosciences, Mental Health and Addiction, Canadian Institutes of Health Research, remi.quirion@douglas.mcgill.ca*

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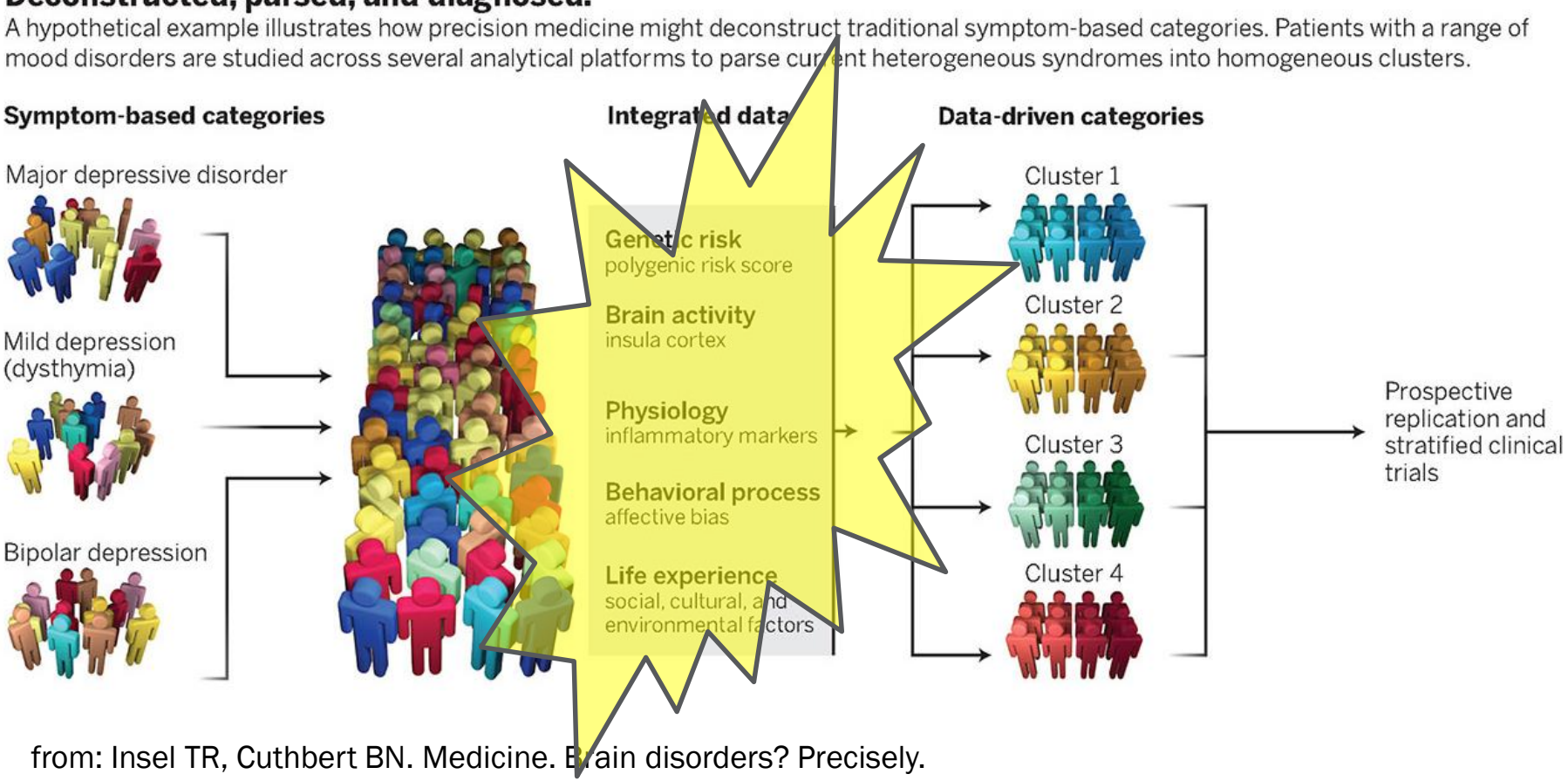
# NOSOLOGICAL REVISIONISM IN PSYCHIATRY

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# NOSOLOGICAL REVISIONISM IN PSYCHIATRY

## Cognitive Systems

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| | Limited Capacity | Elements | Elements | | Elements | Elements | | | Elements |
| | Interference Control | Elements | Elements | Elements | Elements | Elements | | | Elements |

"Although RDoC is labeled as an experimental classification approach, it is actually not a classification system in the formal sense. It might better be termed "an experiment toward classification." Notably, RDoC does not have any a priori specifications for defining disorders—that is, it does not involve criteria by which any given individual will be given a diagnosis. This omission is intentional. Another of the steps called for by aim 1.4 is to "develop reliable and valid measures of these fundamental components . . . for use in basic studies and in more clinical settings"; development of appropriate measurement is obviously necessary for a quantitatively based system to be instantiated in the future."

(Cuthbert and Kozak 2013)

THE SOLUTION TO THE PROBLEM THE NIMH DIAGNOSED IS NOSOLOGICAL REVISIONISM, NOT REDUCTIONISM

IRONICALLY, RDoC FOCUSES ON REDUCTION AT THE EXPENSE OF NOSOLOGICAL REVISION

## A NEW PARADIGM?

# NOSOLOGICAL REVISIONISM IN PSYCHIATRY

Since Insel's strategic plan was implemented, the NIMH's spending on basic science has gone up by 28%, while the budget for research into epidemiology, treatment, and health services has gone down by 16.7%, bringing the overall budget to around a 50/50 split between basic science research and clinical/translation research

This is in line with a broader shift in spending priorities…

Reduction

Big Data

Nosological Revision

# A NEW PARADIGM?


Reduction
Big Data
Nosological Revision


Reduction
Big Data
Nosological Revision


Nosological Revision
Big Data?
Reduction??

# A NEW PARADIGM?

There are reasons to think the scientific virtues reductionism, nosological revisionism, and big data will all be harder to pursue in psychiatry than in the branches of medicine where the precision medicine approach has been successful, like oncology. There is little reason to think, therefore, that they will together produce the kind of progress that has been seen elsewhere. The current vogue for precision begs the question of whether reductionism, big data, and nosological revisionism are all in fact necessary and sufficient for medical progress

In other words, we should not be confident that in psychiatry

Reduction + nosological revision + big data

= "the vindication project" OR progress through basic science research

# ARE THESE THREE VIRTUES NECESSARY?

There are reasons to think the scientific virtues reductionism, nosological revisionism, and big data will all be harder to pursue in psychiatry than in the branches of medicine where the precision medicine approach has been successful, like oncology. There is little reason to think, therefore, that they will together produce the kind of progress that has been seen elsewhere.

**But what if they were disaggregated?**

Reduction - Nosological revision + big data
= basic science research

# ARE THESE THREE VIRTUES NECESSARY?

There are reasons to think the scientific virtues reductionism, nosological revisionism, and big data will all be harder to pursue in psychiatry than in the branches of medicine where the precision medicine approach has been successful, like oncology. There is little reason to think, therefore, that they will together produce the kind of progress that has been seen elsewhere.

**But what if they were disaggregated?**

Reduction + Nosological revision - big data
= business as usual

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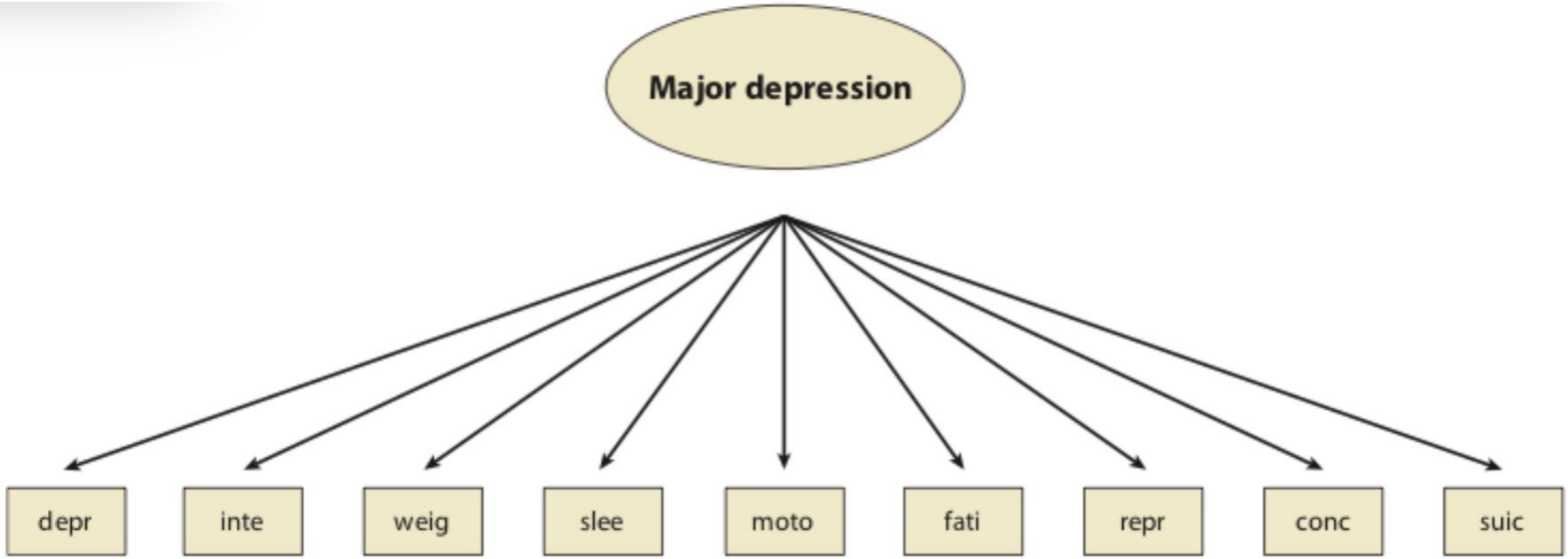
**But what if they were disaggregated?**

Nosological revision – reduction + big data
= psychopathology

# NOSOLOGICAL REVISIONISM WITHOUT REDUCTIONISM




(Borsboom and Kramer 2013)

# NOSOLOGICAL REVISIONISM WITHOUT REDUCTIONISM

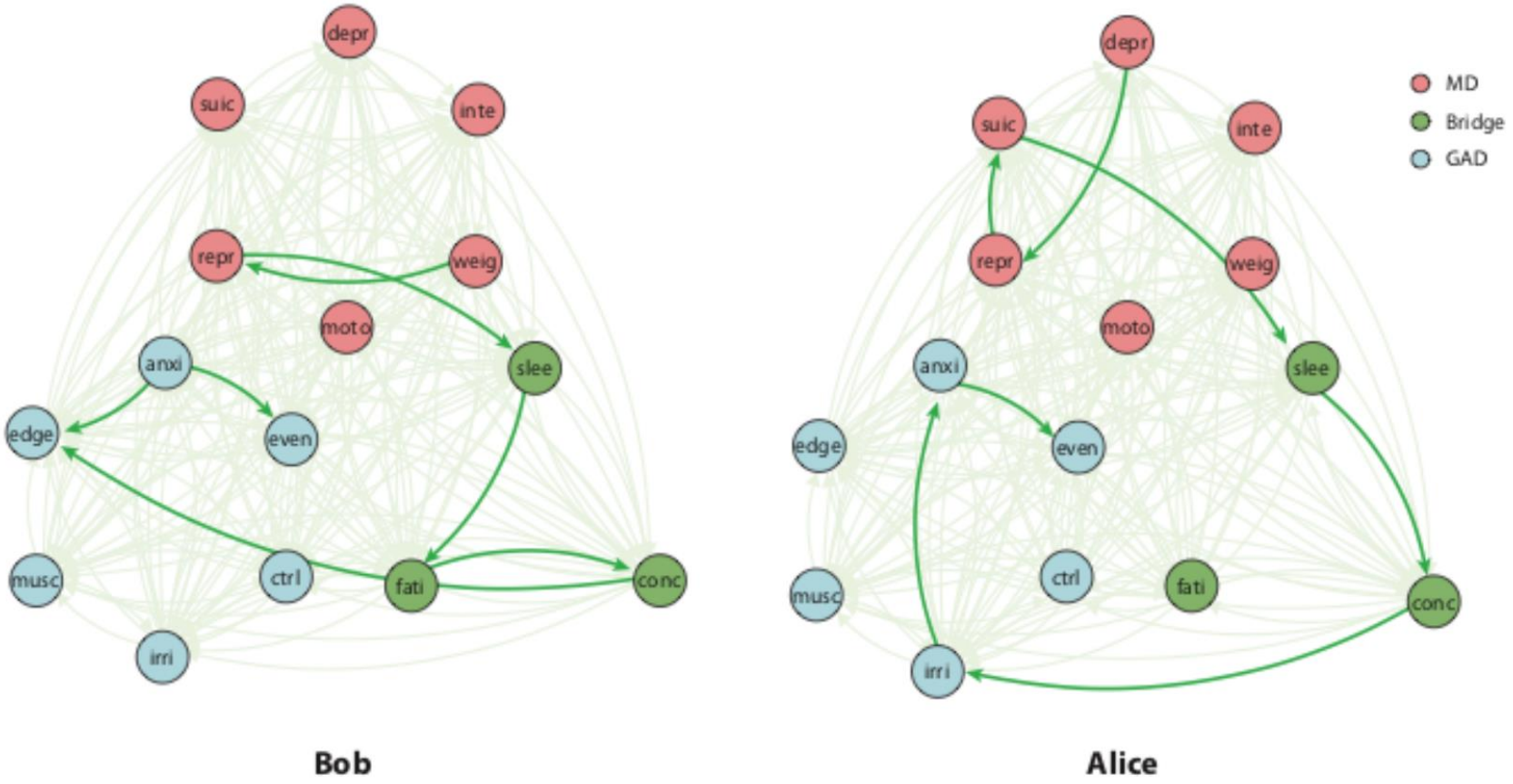



**Figure 8**

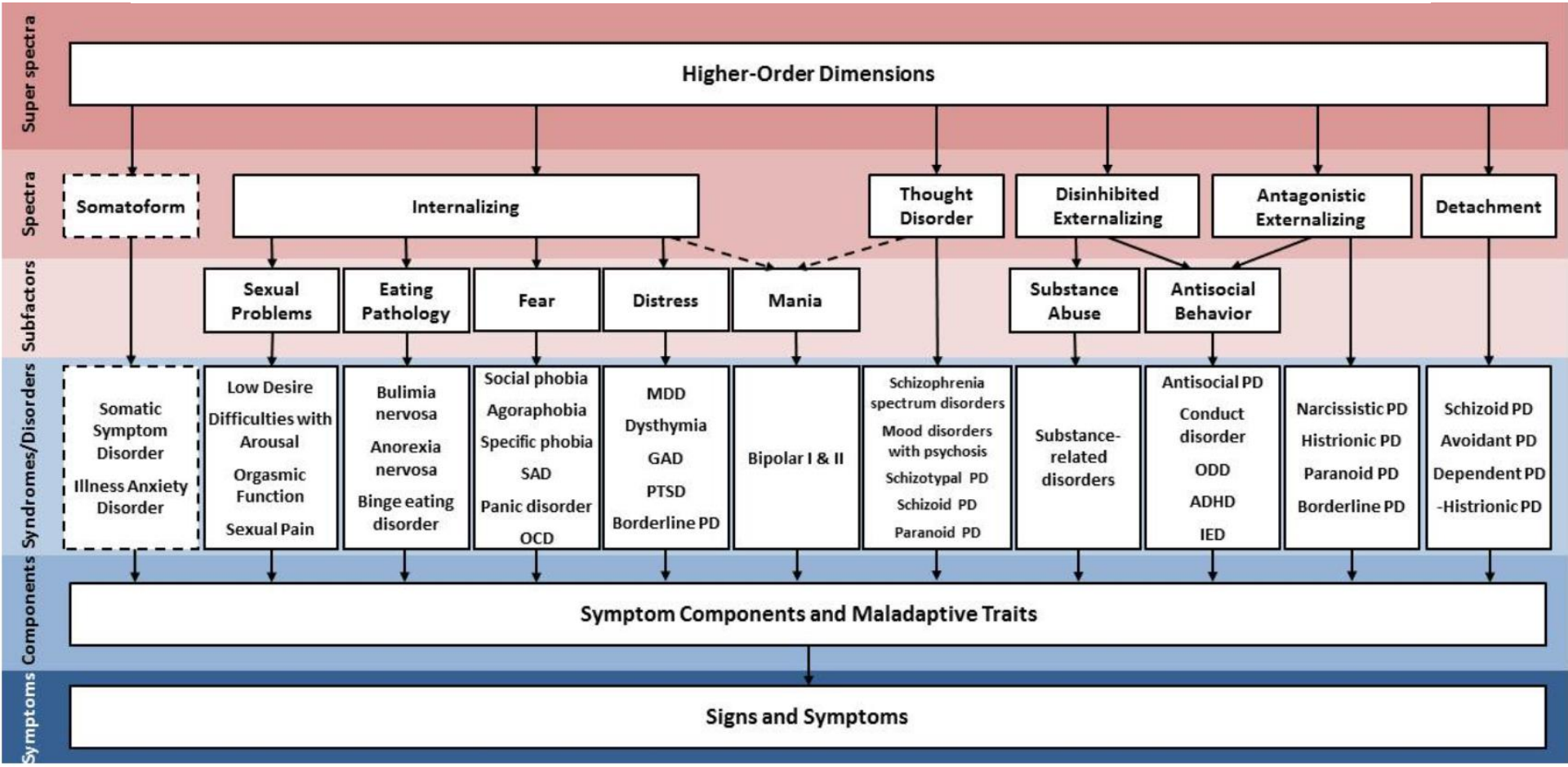
Hypothetical major depression (MD) networks for two fictitious people, Bob and Alice. Thicker green edges represent stronger causal relations between the symptoms of MD. These networks show that there are many ways to develop both MD and GAD

(Borsboom and Cramer 2013)

# About HiTOP

Objectives of the Hierarchical Taxonomy of Psychopathology (HiTOP) are to advance the classification of psychopathology to maximize its usefulness for research and clinical practice. The HiTOP aims to address limitations of traditional nosologies, such as the DSM-5 and ICD-10, including arbitrary boundaries between psychopathology and normality, often unclear boundaries between disorders, frequent disorder co-occurrence, heterogeneity within disorders, and diagnostic instability.

The HiTOP approaches these problems by conducting an empirical search for psychopathology structures starting from the most basic building blocks and proceeding to the highest level of generality: combining individual signs and symptoms into homogeneous components or traits, assembling them into empirically-derived syndromes, and finally grouping them into psychopathology spectra (e.g., internalizing and externalizing).



# A NEW PARADIGM? OR CLEVER PACKAGING?

Nosological revision +/– reduction +/- big data

# ARE THESE THREE VIRTUES SUFFICIENT?

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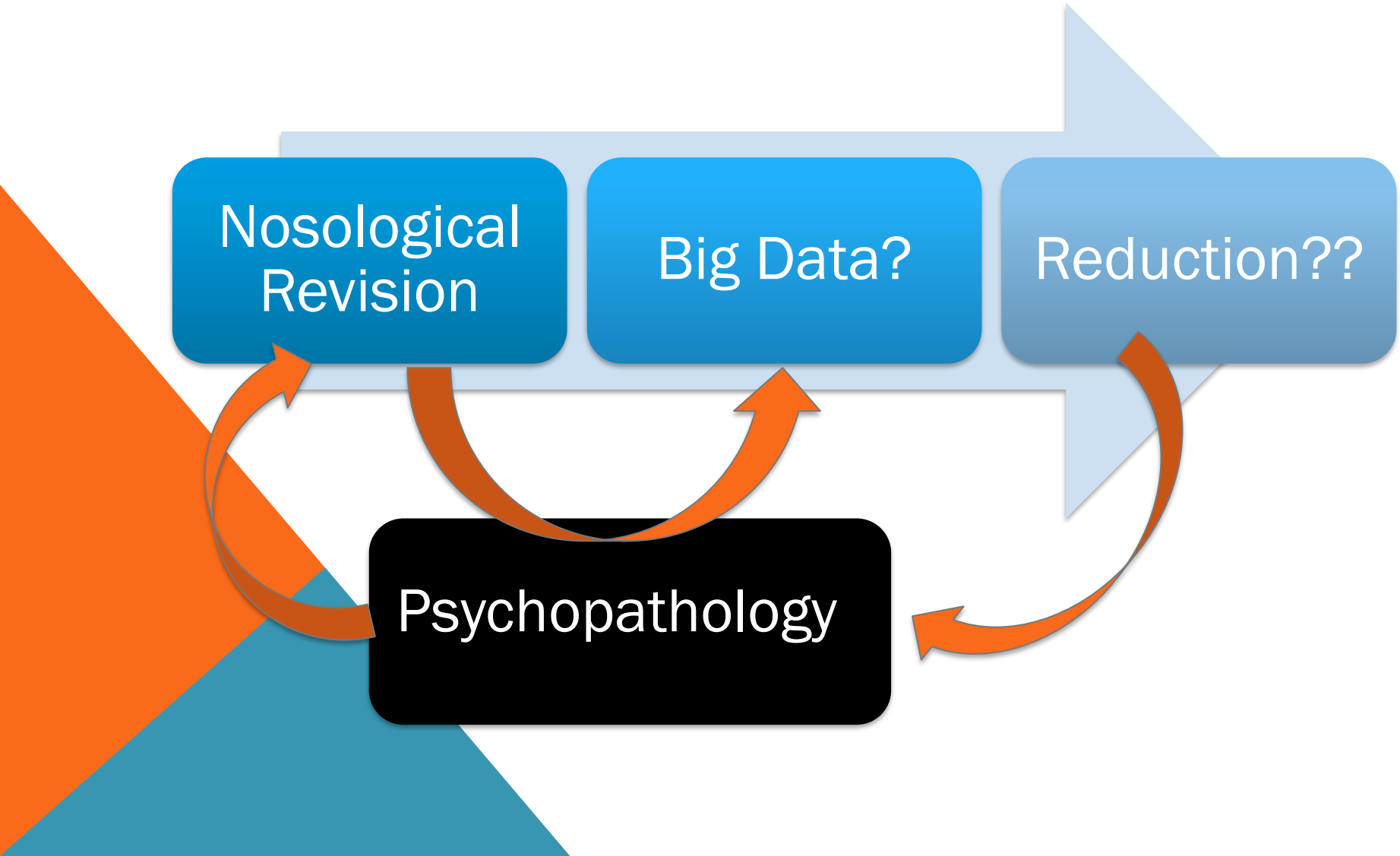

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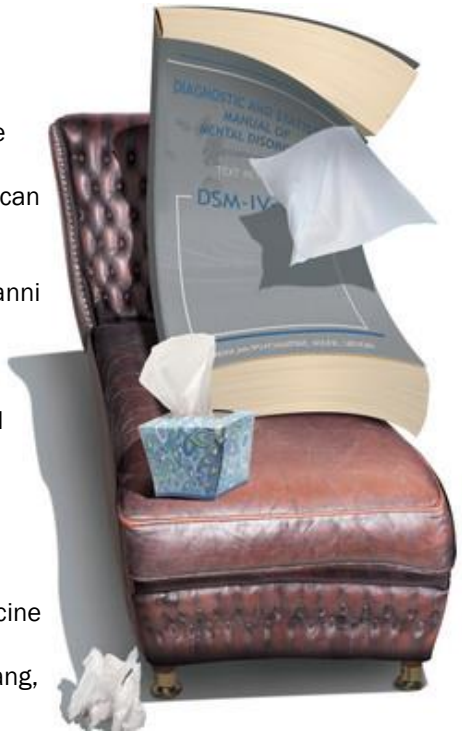


Thank you


I can be reached at
kct2121@columbia.edu