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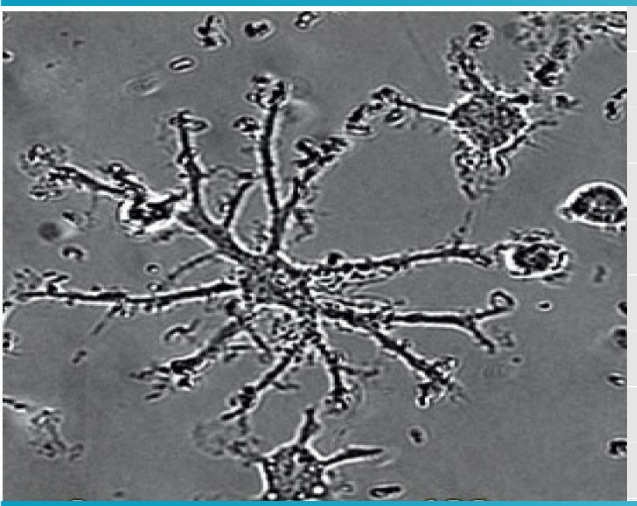
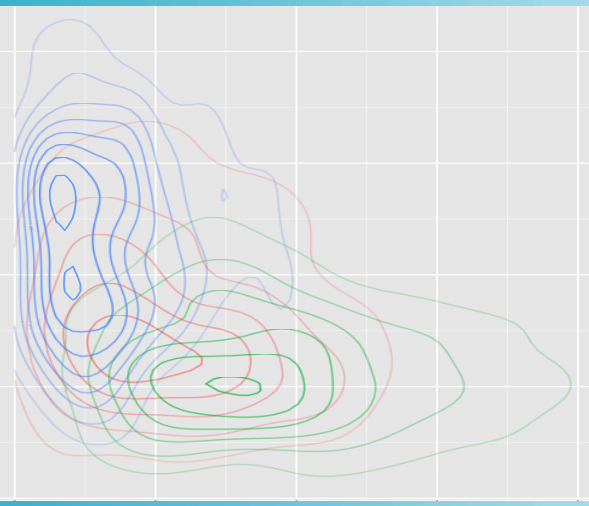
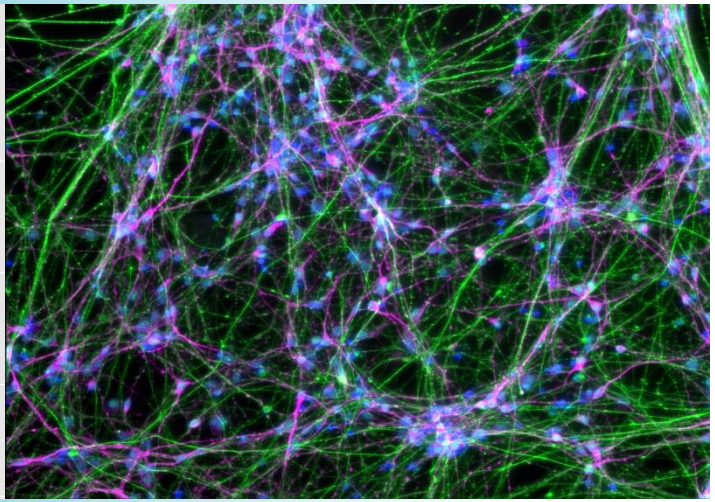
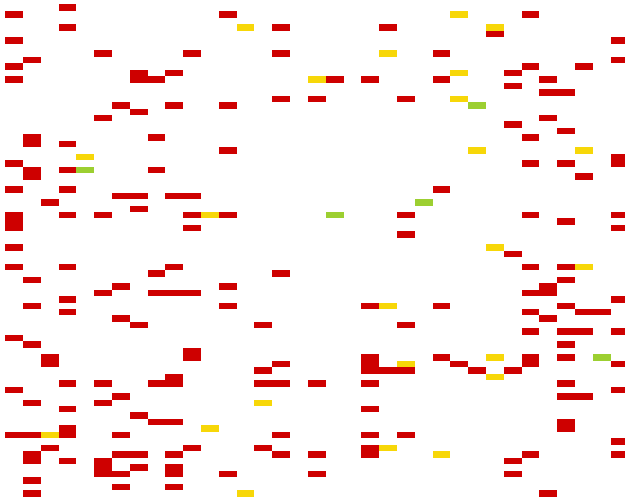
PSYCHIATRY ACADEMY

Implications of Psychiatric Genetics for Psychopharmacology

Roy Perlis, MD MSc
MGH Center for Quantitative Health
rperlis@mgh.harvard.edu

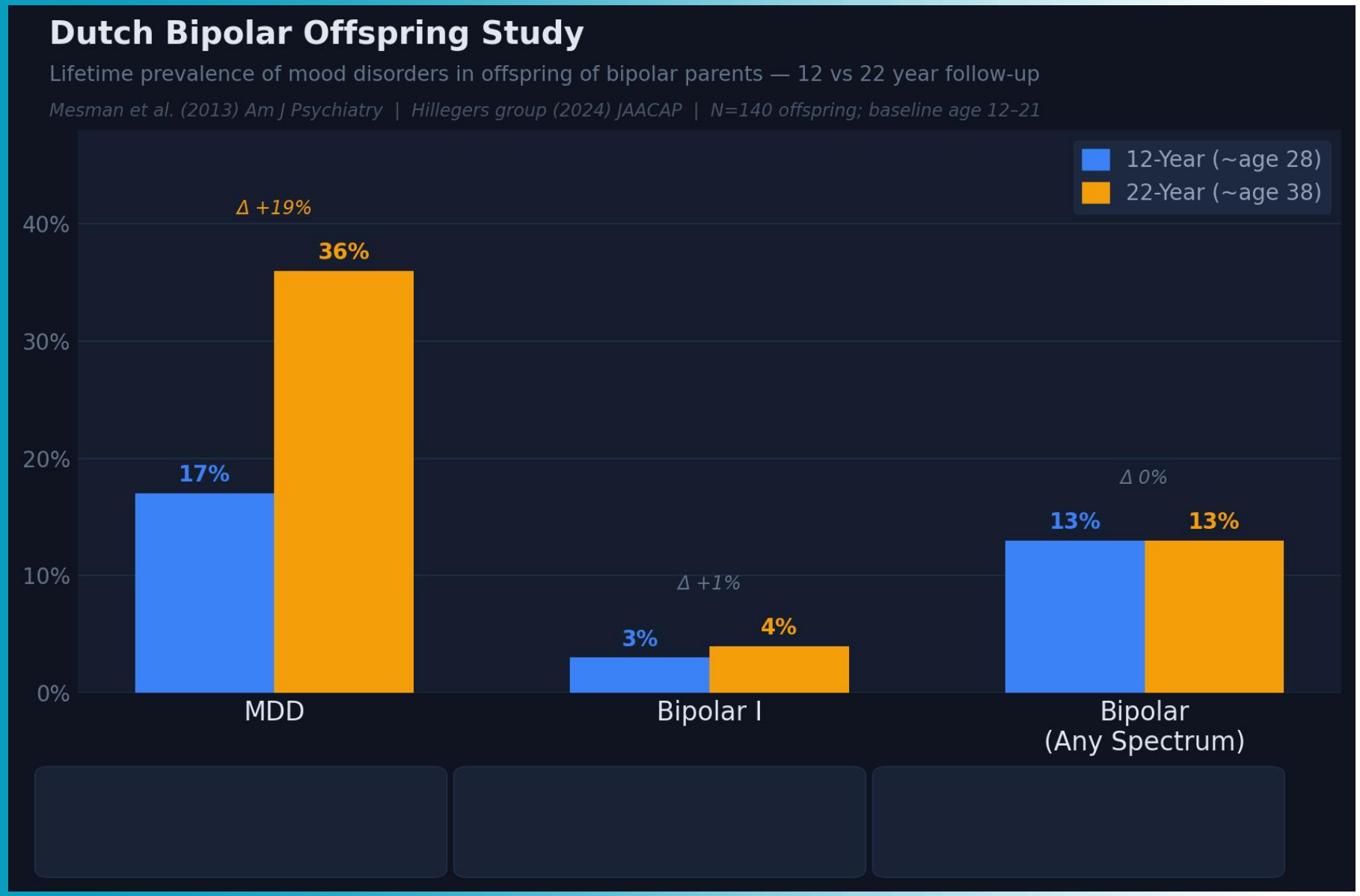
CEDD CENTER FOR EXPERIMENTAL DRUGS & DIAGNOSTICS
CENTER FOR GENOMIC MEDICINE
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

Disclosure

- Dr. Perlis has received payment for service on scientific advisory boards of Genomind, Circular Genomics, Atella, and Alkermes
- He has received payment (and a really cool fleece) for service as Editor in Chief of JAMA+ AI, and as AI Editor at JAMA Network Open

Case BZ: All in the Family

- Mr. Z. is a 51 y.o. accountant with bipolar 1 disorder, stable on lithium for >10 years.
- He refers his 18 y.o. son, a college student who 'seems down'.
- Without knowing anything else, son's most likely diagnosis is…?



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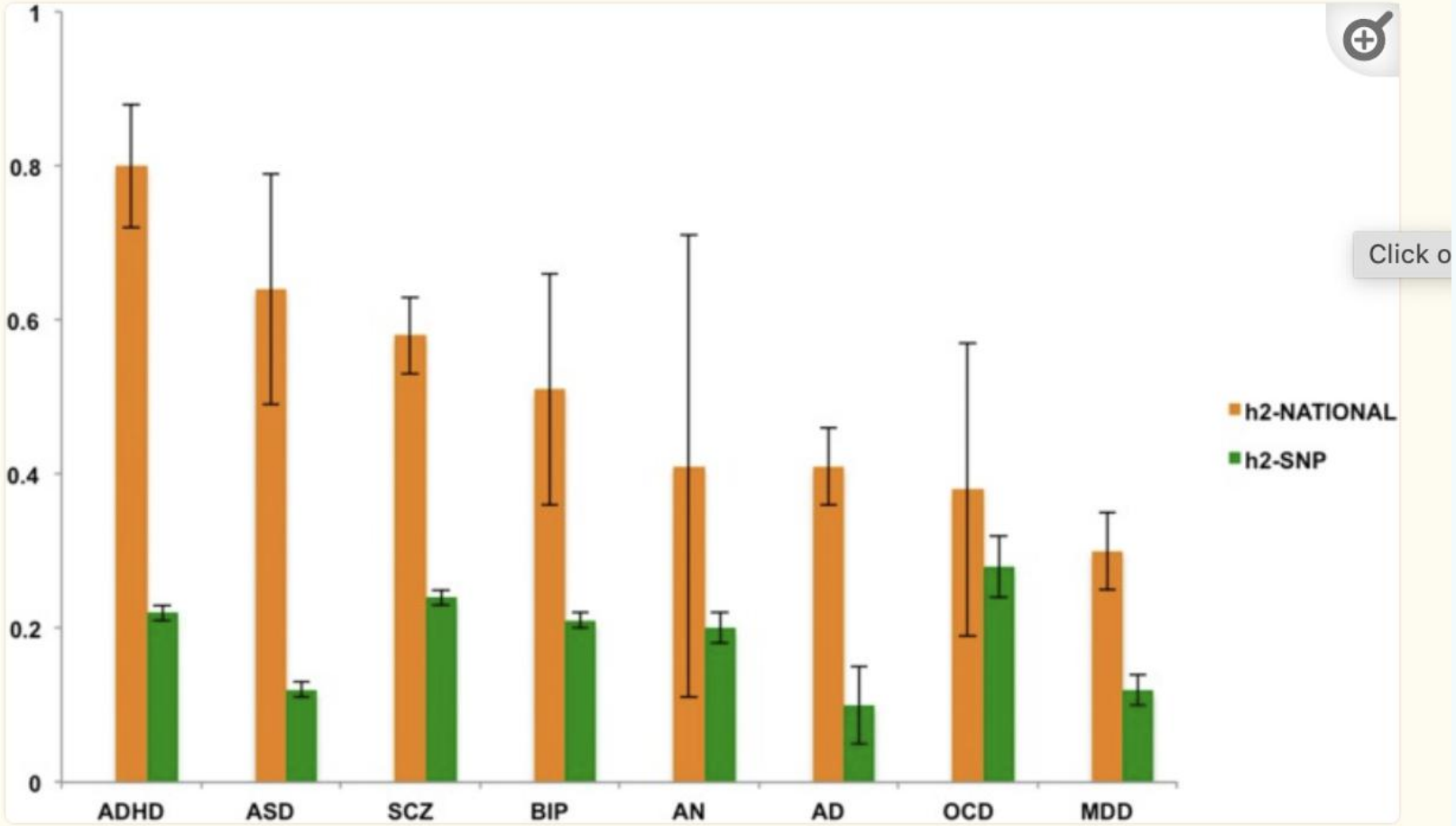
Mesman AJP 2013; JAACAP 2024

Key point

- Psychiatric disorders do run in families…
- BUT not everyone will manifest the same disorder – or even any disorder!

- SO **beware diagnosis-by-family-history**

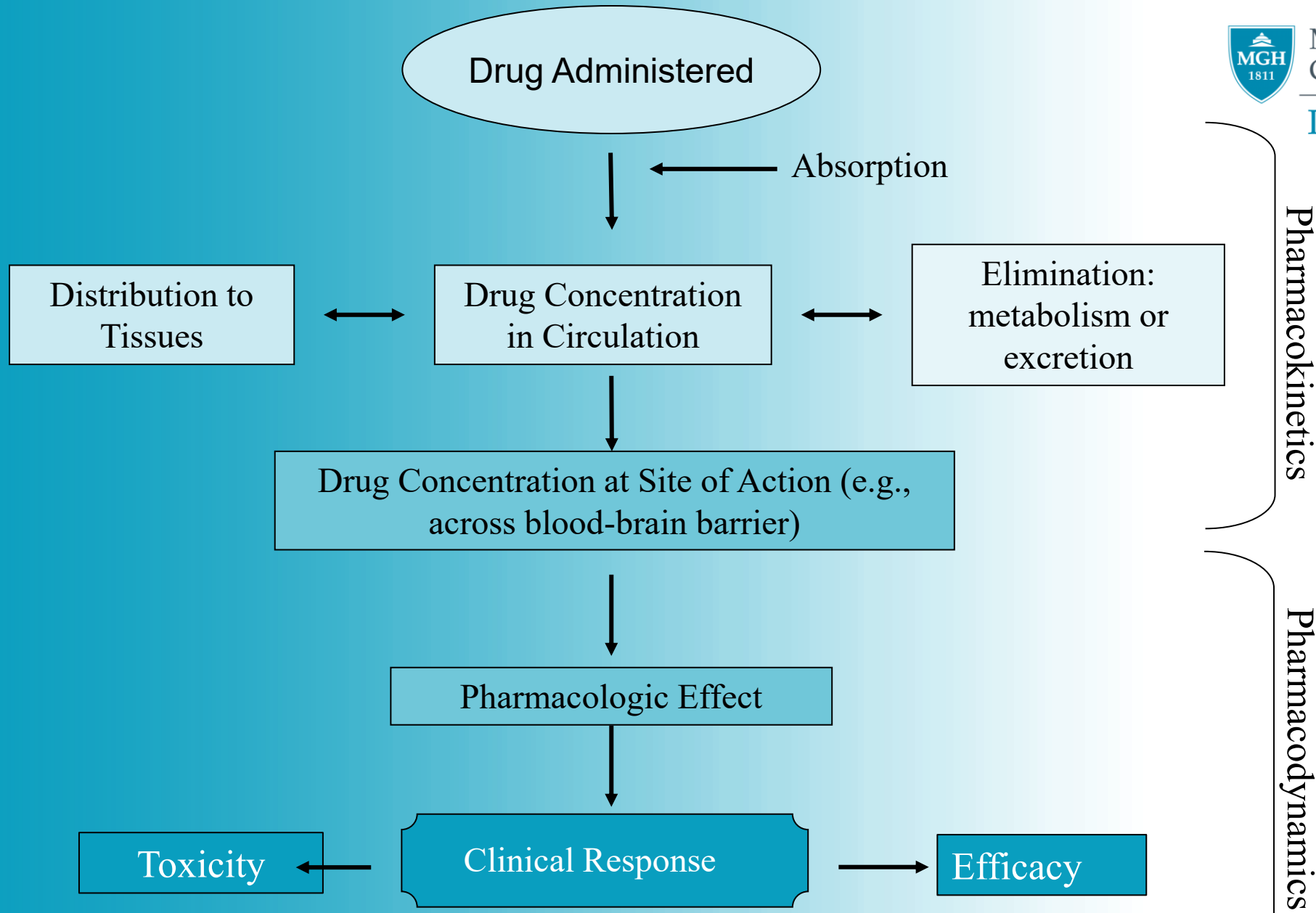
How much of the risk for psychiatric disorders is inherited?



Pettersson Psychol Med 2019

Pharmacogenomics: the effect of genetic variation on response to medications

Efficacy
Adverse effect
Drug level


Drug Administered
Absorption
Distribution to Tissues
Drug Concentration in Circulation
Elimination: metabolism or excretion
Drug Concentration at Site of Action (e.g., across blood-brain barrier)
Pharmacologic Effect
Clinical Response
Toxicity
Efficacy
Pharmacokinetics
Pharmacodynamics

Theoretical rationale for pharmacogenomics

- When FDA approves a medication, they approve a dose *range* that is believed to be safe and effective for an average patient
- There are many factors that can influence the effects of medications
  - Environment (smoking; diet; other medications)
  - Genetic variation
- Testing for these genetic variations helps to predict whether blood levels will be much higher, or much lower than usual
- For most medications there is not a 'target' blood level – but it makes sense that levels that are way too low are unlikely to work, and levels way too high are more likely to cause side effects

When might testing be helpful?

- There are often 'hints' of unusual metabolism when people haven't benefited from multiple medication trials
- For example:
  - Many side effects, or intolerable side effects, even at very low doses.
  - No improvement and minimal side effects despite high doses – 'it felt like I was just taking ibuprofen, or a sugar pill'

RESEARCH ARTICLE

WILEY ADAA

Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: A propensity-score matched study

Roy H. Perlis MD, MSc[1] | Rajesh Mehta RPh, MS[2] | Alison M. Edwards MStat[2] | Arun Tiwari MBA[2] | Guido W. Imbens PhD[3]

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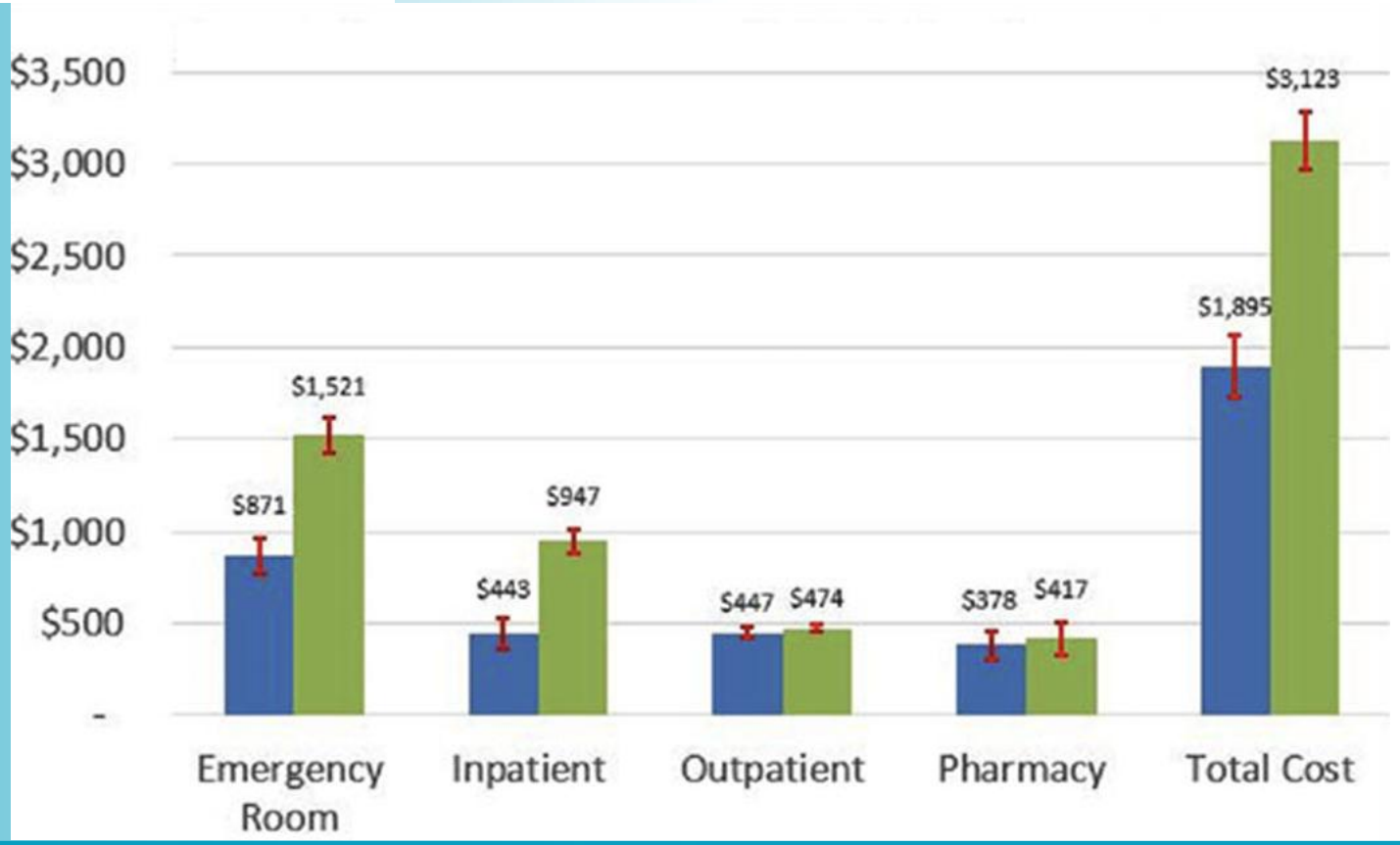
- Matched 875 tested patients to 2,745 untested patients
- Overall 6-month health care costs reduced by $1,948 (+/- $611) in tested group

[1] Perlis…Imbens, *Depression and Anxiety* 2018



Pharmacogenomics vs Treatment as Usual for Depressive Symptom Remission: Meta-analysis

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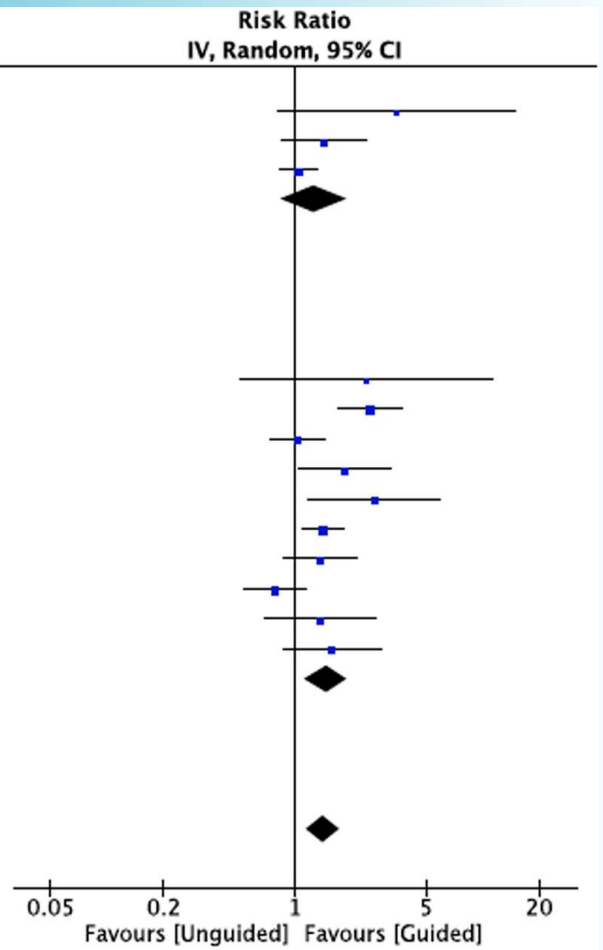
Study or Subgroup	Guided Events	Guided Total	Unguided Events	Unguided Total	Weight	Risk Ratio IV, Random, 95% CI	Year
1.1.1 Open Label Trials							
Hall-Flavin 2012	7	22	2	22	1.8%	3.50 [0.82, 15.01]	2012
Hall-Flavin 2013	22	72	20	93	7.7%	1.42 [0.84, 2.39]	2013
Oslin 2022	130	966	126	978	12.6%	1.04 [0.83, 1.31]	2022
Subtotal (95% CI)		**1060**		**1093**	**22.2%**	**1.26 [0.84, 1.88]**	
Total events	159		148				
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.51$, df = 2 (P = 0.17); $I^2 = 43\%$							
Test for overall effect: Z = 1.12 (P = 0.26)							
1.1.2 Randomized Controlled Trials							
Winner 2013	5	25	2	24	1.6%	2.40 [0.51, 11.21]	2013
Singh 2015	53	74	21	74	9.8%	2.52 [1.71, 3.73]	2015
Perez 2017	48	141	46	139	10.9%	1.03 [0.74, 1.43]	2017
Han 2018	24	52	12	48	7.1%	1.85 [1.04, 3.27]	2018
Bradley 2018	14	40	7	53	4.6%	2.65 [1.18, 5.95]	2018
Greden 2019	115	560	88	607	12.2%	1.42 [1.10, 1.82]	2019
Shan 2019	19	31	18	40	9.0%	1.36 [0.88, 2.12]	2019
Perlis 2020	35	146	46	150	10.1%	0.78 [0.54, 1.14]	2020
McCarthy 2021	16	55	10	47	5.7%	1.37 [0.69, 2.72]	2021
Tiwari 2022	41	211	12	97	6.7%	1.57 [0.86, 2.85]	2022
Subtotal (95% CI)		**1335**		**1279**	**77.8%**	**1.46 [1.13, 1.88]**	
Total events	370		262				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 25.28$, df = 9 (P = 0.003); $I^2 = 64\%$							
Test for overall effect: Z = 2.93 (P = 0.003)							
Total (95% CI)		**2395**		**2372**	**100.0%**	**1.41 [1.15, 1.74]**	
Total events	529		410				
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 31.46$, df = 12 (P = 0.002); $I^2 = 62\%$							
Test for overall effect: Z = 3.24 (P = 0.001)							
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$							



(Brown Clin Pharm Ther 2022)

Key study – Oslin, JAMA 2022

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JAMA | Original Investigation

Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder
The PRIME Care Randomized Clinical Trial

- N=1944 – largest pharmacogenomic study to date*
- Tested patients less likely to receive a medication with a drug-gene interaction
- Over 24 week follow-up, tested patients more likely to reach remission (risk difference 2.8%)

* Uses standard CYP450 panel plus pharmacodynamic variants

"New tool: Genotyping makes prescribing safer, more effective."

- *Current Psychiatry*

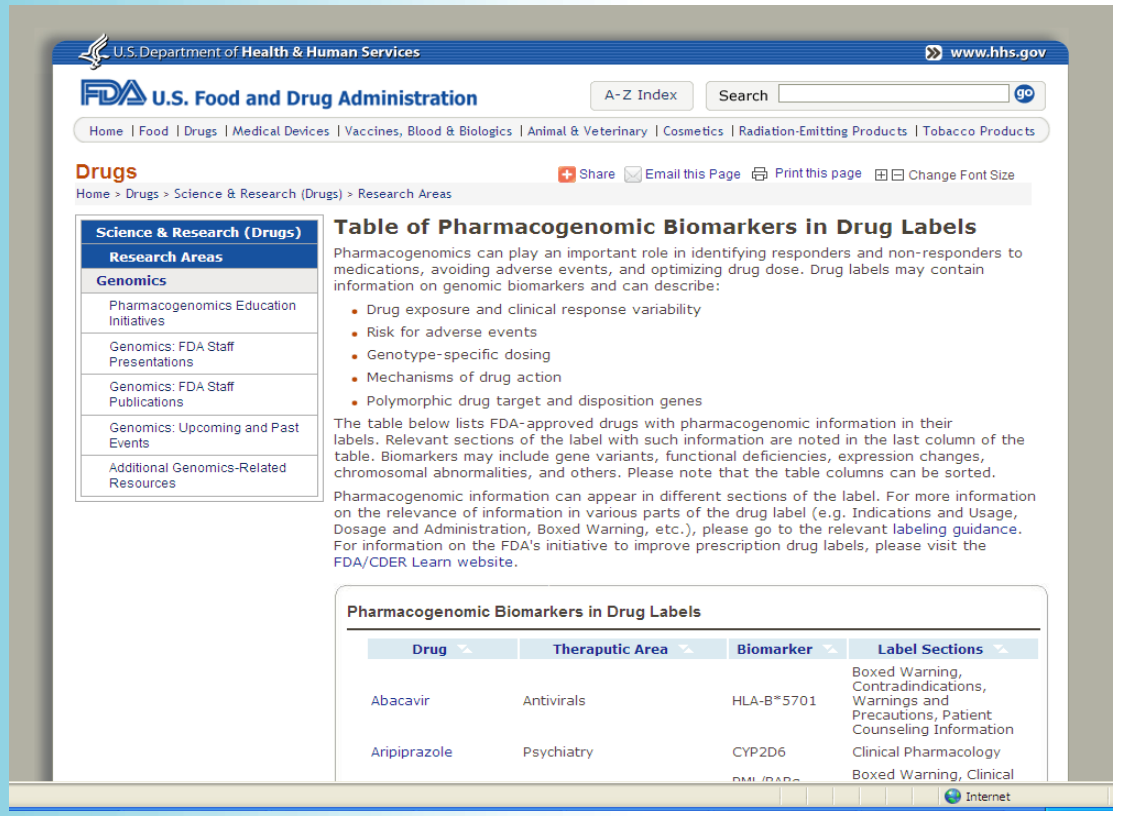
"New tool: Genotyping makes prescribing safer, more effective."

- *Current Psychiatry*, September 2004

Pharmacogenomics in medicine, 2026

- >100 labels reflect genetic data
- *Majority relate to safety or dosing, not efficacy*
- Nearly all derived from post-hoc analysis

- Psychotropic:
  - CYP450
  - HLA (carbamazepine)



https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Example: Carbamazepine

- Testing for carbamazepine toxicity
  - SJS/TEN seen in 1.6/10,000 Caucasians
    - but 5-30x more common in some Asian groups
  - HLA-B*1502:
    - Positive predictive value ~0.1
    - Negative predictive value ~1
  - Labeling: test for variant in Asian patients, use alternative drug if positive

Carbamazepine US package insert

The prototypical pharmacokinetic gene: *CYP450 2D6*

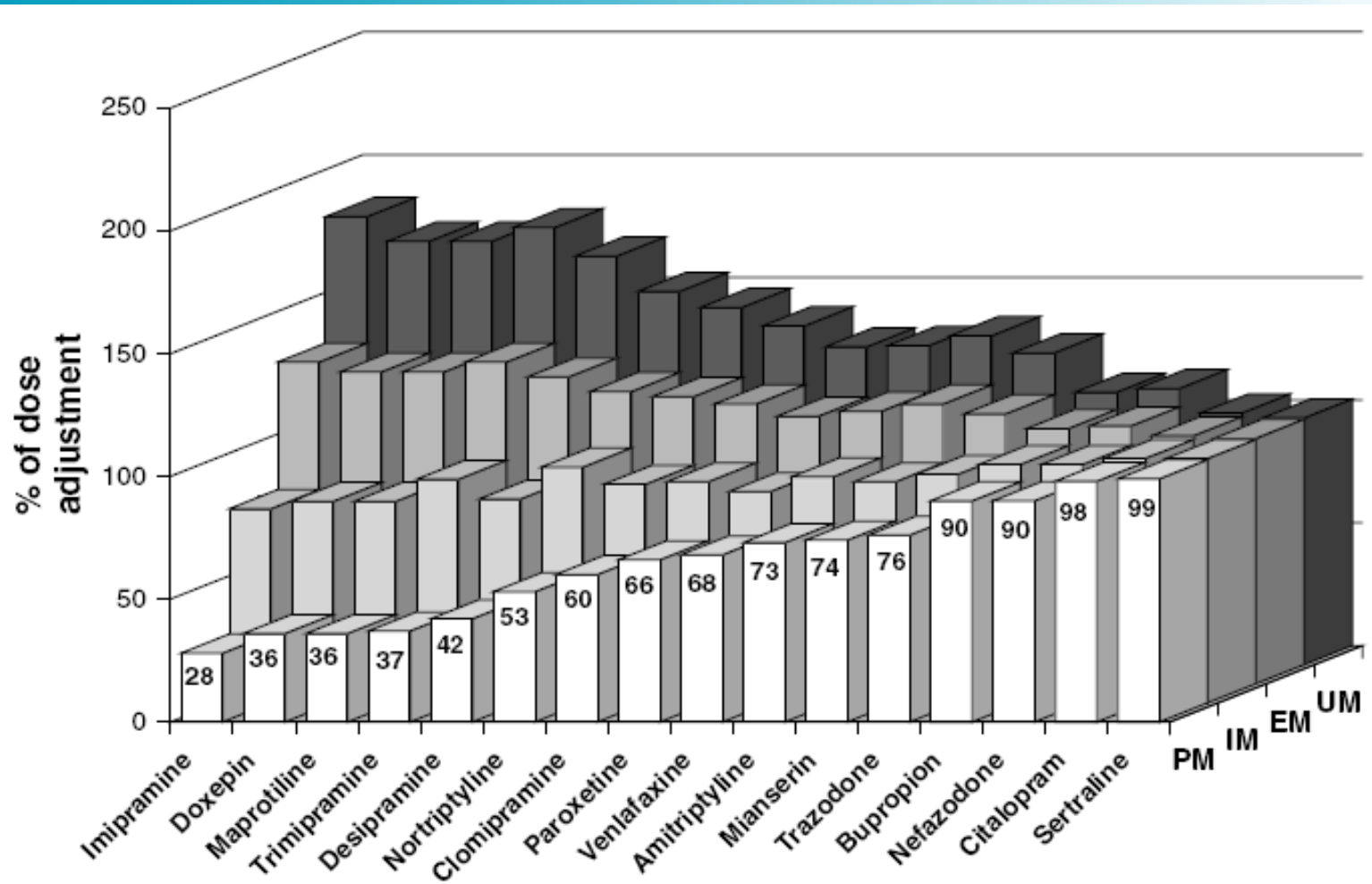
- Most important member of palette of hepatic drug/toxin-metabolizing enzymes ("phase I")
- Relevant effects on 25%+ of pharmacopeia (for all CYP450, up to 80%)

De Gregori Curr Drug Metab 2010; Ingelman Pharm Ther 2007

Naming variations

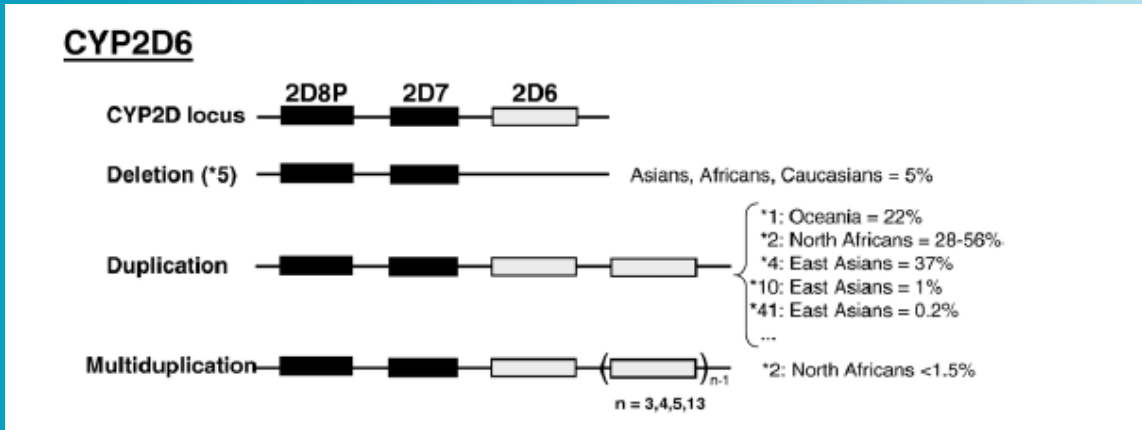
- Variants in the CYP450 genes are named according to their effect on metabolism:
  - **Poor metabolizer:** Little or no ability to metabolize drugs through this pathway
  - **Intermediate metabolizer:** Reduced ability to metabolize drugs through this pathway (may not be clinically meaningful)
  - **Wildtype/extensive/normal metabolizer:** Normal (for general population) metabolism
  - **Ultrarapid metabolizer:** Increased ability to metabolize drugs through this pathway

Dose Adjustments for Antidepressants by CYP2D6 Genotype



Kirchheiner et al, Mol Psych 2004)

The prototypical pharmacokinetic gene: *CYP450 2D6*



- Small deletions/polymorphisms
  - Poor metabolizer
- Deletion of entire locus
  - Poor metabolizer
- One functional copy, one deletion
  - Intermediate metabolizer
- Two functional copies
  - Extensive or wildtype (or normal) metabolizer
- Duplication
  - Ultrarapid metabolizer

De Gregori Curr Drug Metab 2010; Ingelman Pharm Ther 2007

But… blood levels do not necessarily predict response (except at the extremes)

Example

Drug 1-> poor metabolizer->

= higher than expected blood levels

= ?greater risk for adverse effects

In most pgx reports, drugs that are metabolized through that pathway are labelled in red…

Example

Drug 1 - > poor metabolizer - >

= higher than expected blood levels

= greater risk for adverse effects?

In most pgx reports, drugs that are metabolized through that pathway are labelled in red…

Solution

Drug 1- > poor metabolizer - >

= higher than expected blood levels

= ?greater risk for adverse effects

So – avoid this drug if there are other good choices, but…

If required, simply start low(er) and go slow(er) – generally aim for low end of therapeutic range

Example 2

Drug 2 - > ultrarapid metabolizer - >

= lower than expected blood levels

= greater risk for nonresponse?

Solution

Drug 2 - > ultrarapid metabolizer - >

= lower than expected blood levels

= greater risk for nonresponse?

So – avoid this drug if there are other good choices, but…

If required, titrate cautiously but consistently to response – may require high end of therapeutic range, or even supratherapeutic doses

Managing non-wildtype patients who require CYP450 substrate medications

- *monitor adverse effects*
- *consider checking a blood level (trough)*

Do not memorize cyp450 interactions…

- Good current resource:

http://medicine.iupui.edu/clinpharm/ddis/main-table/

- Consider using software for automated interaction checking

  - Drug interaction checking
  - Sequence2script.com (free)

But what about all the other information on the reports?

The bad news…


Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

- "It can be proven that most claimed research findings are false."
- Small samples, small effects, multiple hypotheses, varying definitions, and…
- "chase for statistical significance"

Ioannidis PLOS One
2005

You mean I should ignore the other genes?

- For non-CYP450 assays, extent of support for individual variants varies widely
- Most are probably false-positives – but even the true-positives have very, very small effects

- Ignore them. Really.

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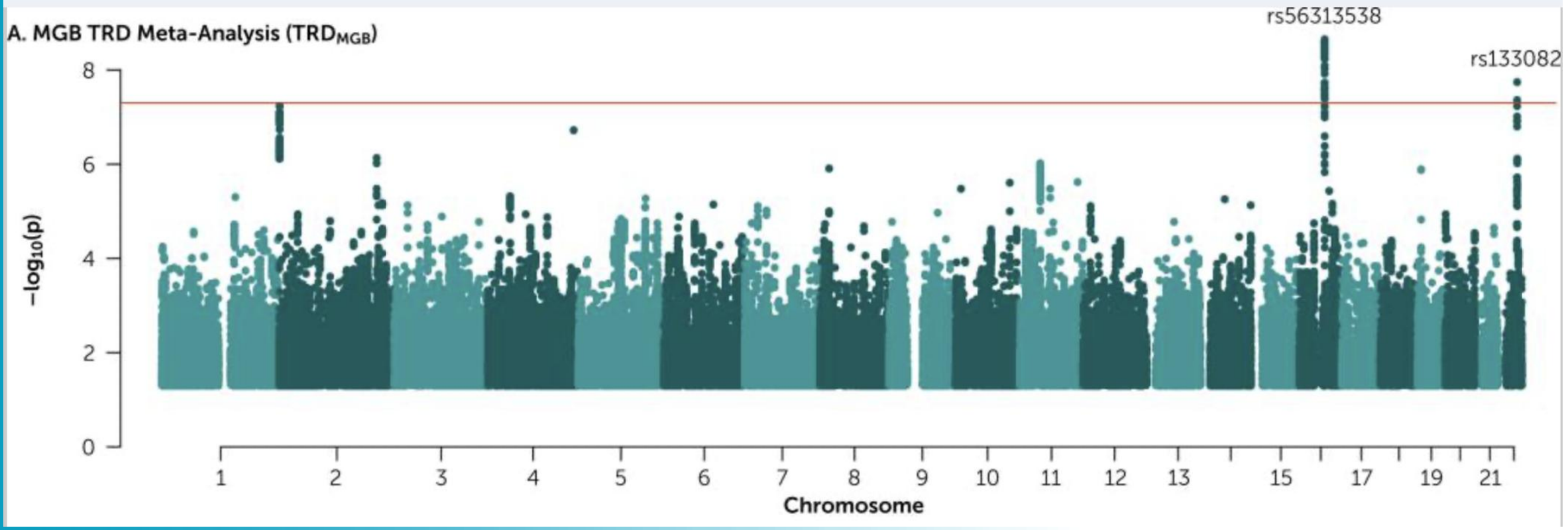
What about GWAS?



- Heritability ~4.2%

Kang AJP 2024

Thank you!

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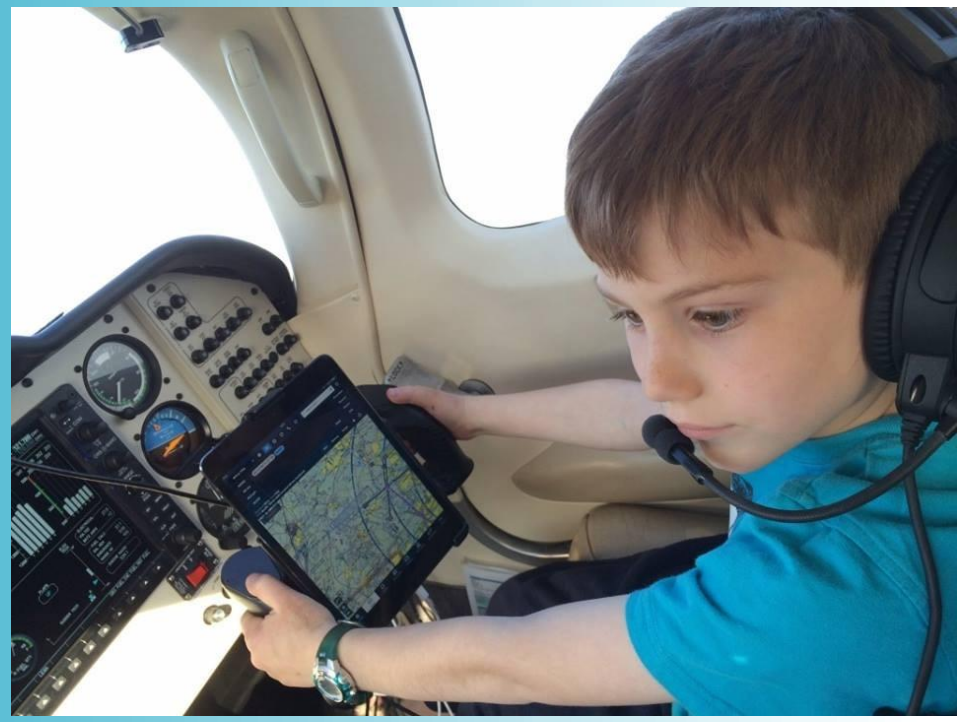

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