MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Implications of Psychiatric Genetics for Psychopharmacology

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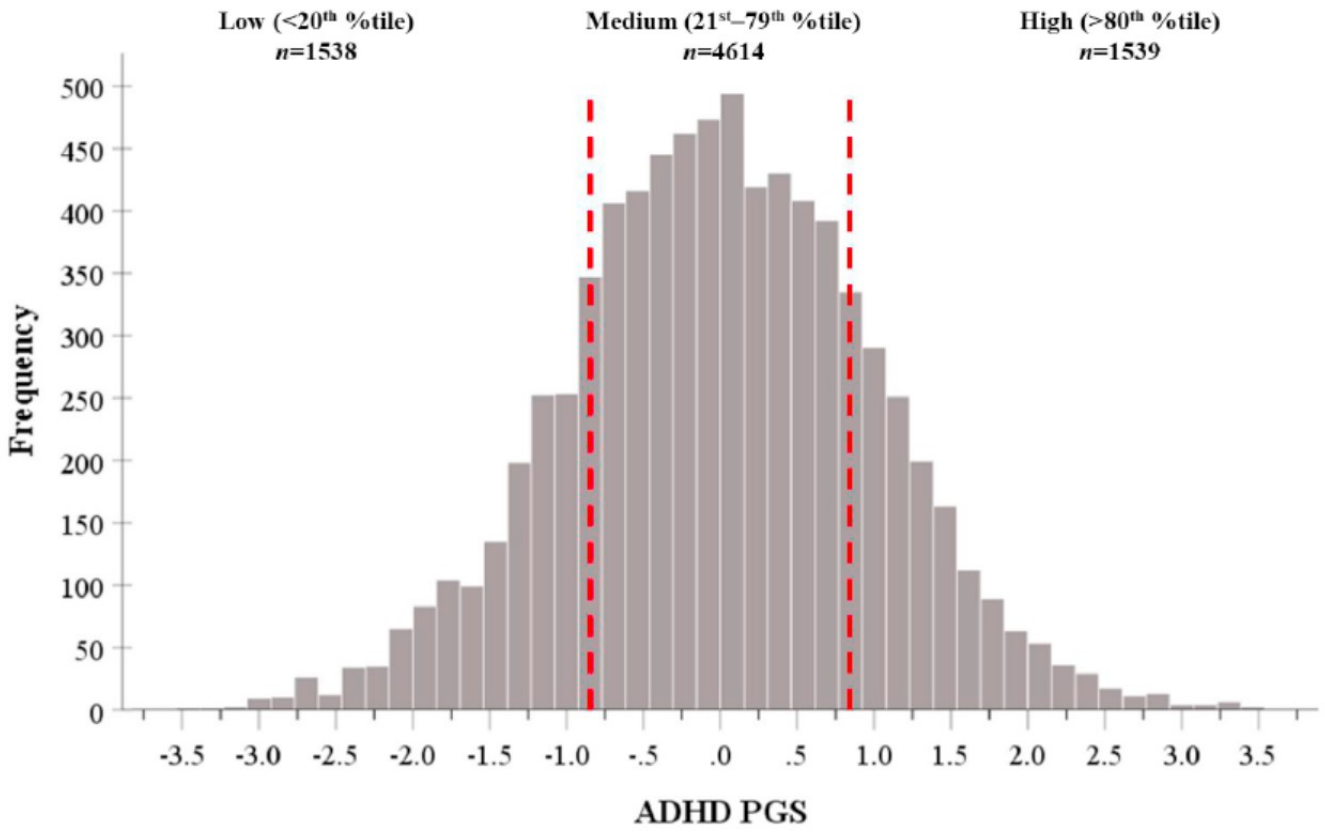
Source	Research or CME Funding	Consult Fees	Speakers Bureau	Royalties or IP	In Kind Services	Stock / Equity	Honorarium or expenses for this meeting
NHE Inhibitor Patent				X			
Shire/Takeda	X				X		
Rhodes		X					
Akili		X				X	
Vallon		X					
Tris		X					
Otsuka	X						
IronShore		X			X	X	
Supernus		X					
Sunovion	X	X					
Genomind		X			X	X	
Arbor	X				X		
OnDosis		X					

Genomic Discoveries Suggest we Rethink Diagnostic Practices

Polygenic Risk Scores

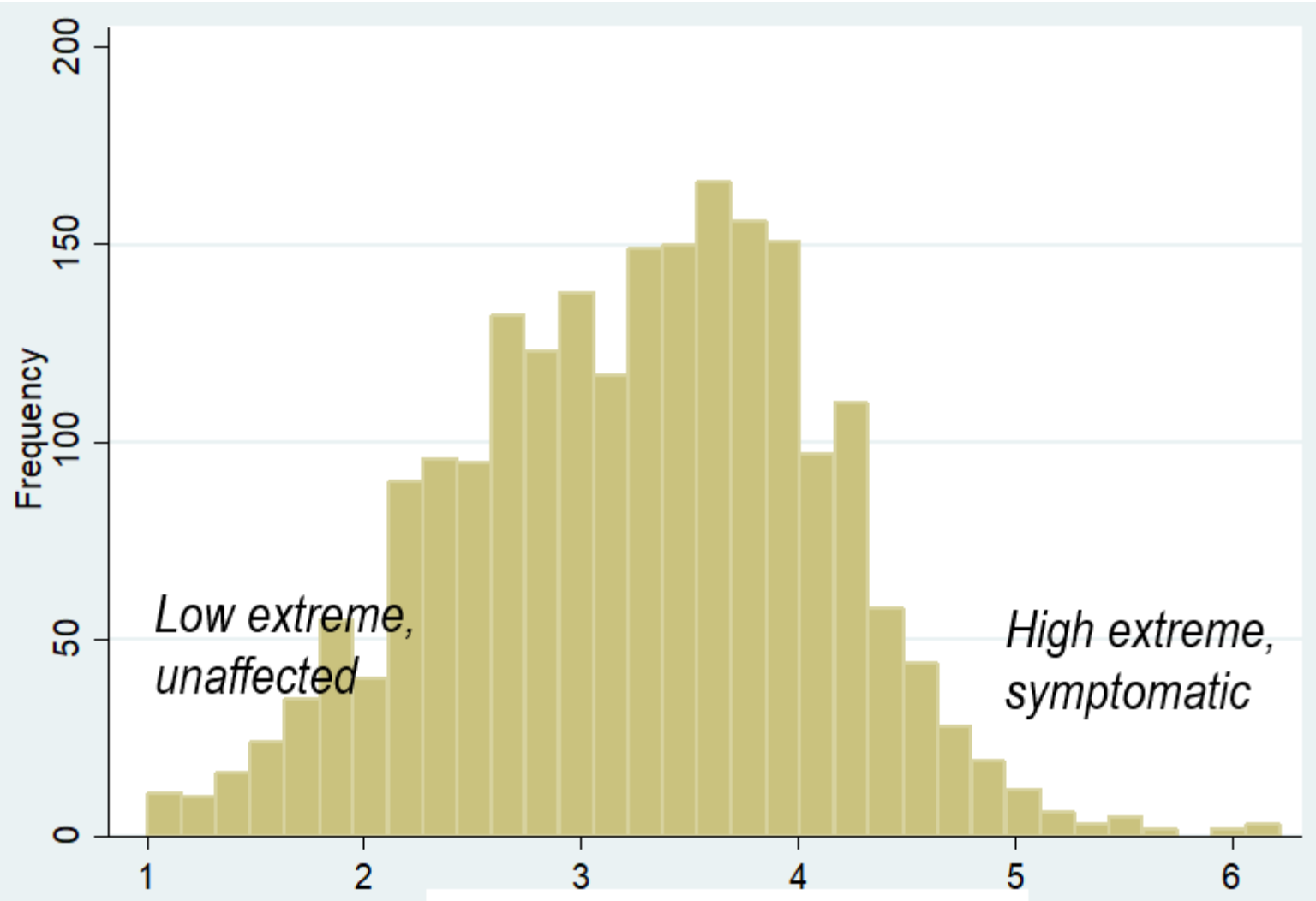
(Faraone, Biol Psychiat, 2014; Li, BioRxiv; http://dx.doi.org/10.1101/611897)

- ADHD Polygenic Risk in 7,000 Adolescents



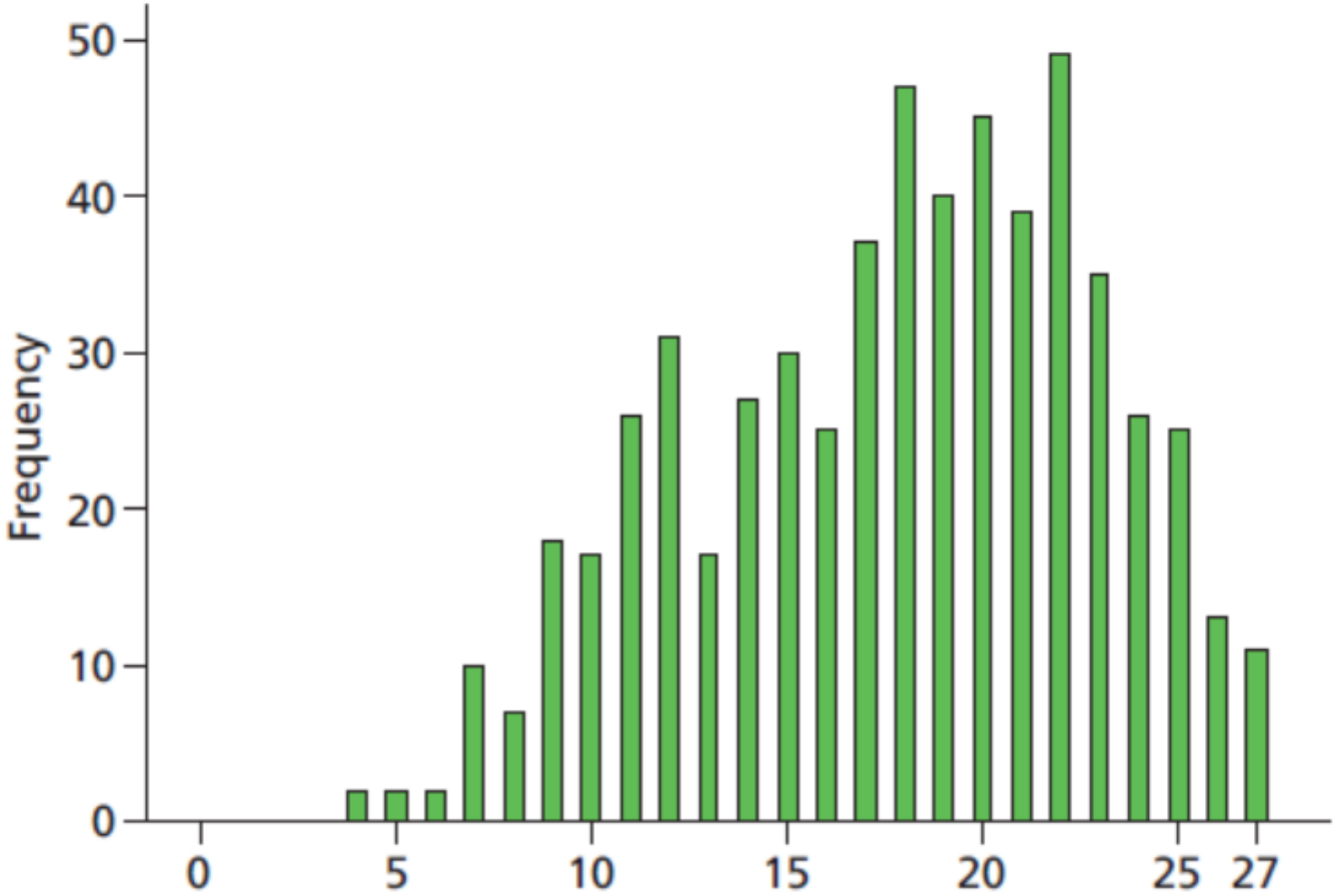
ADHD Symptom Scores in the Population

(Greven et al., JCPP, 2016)



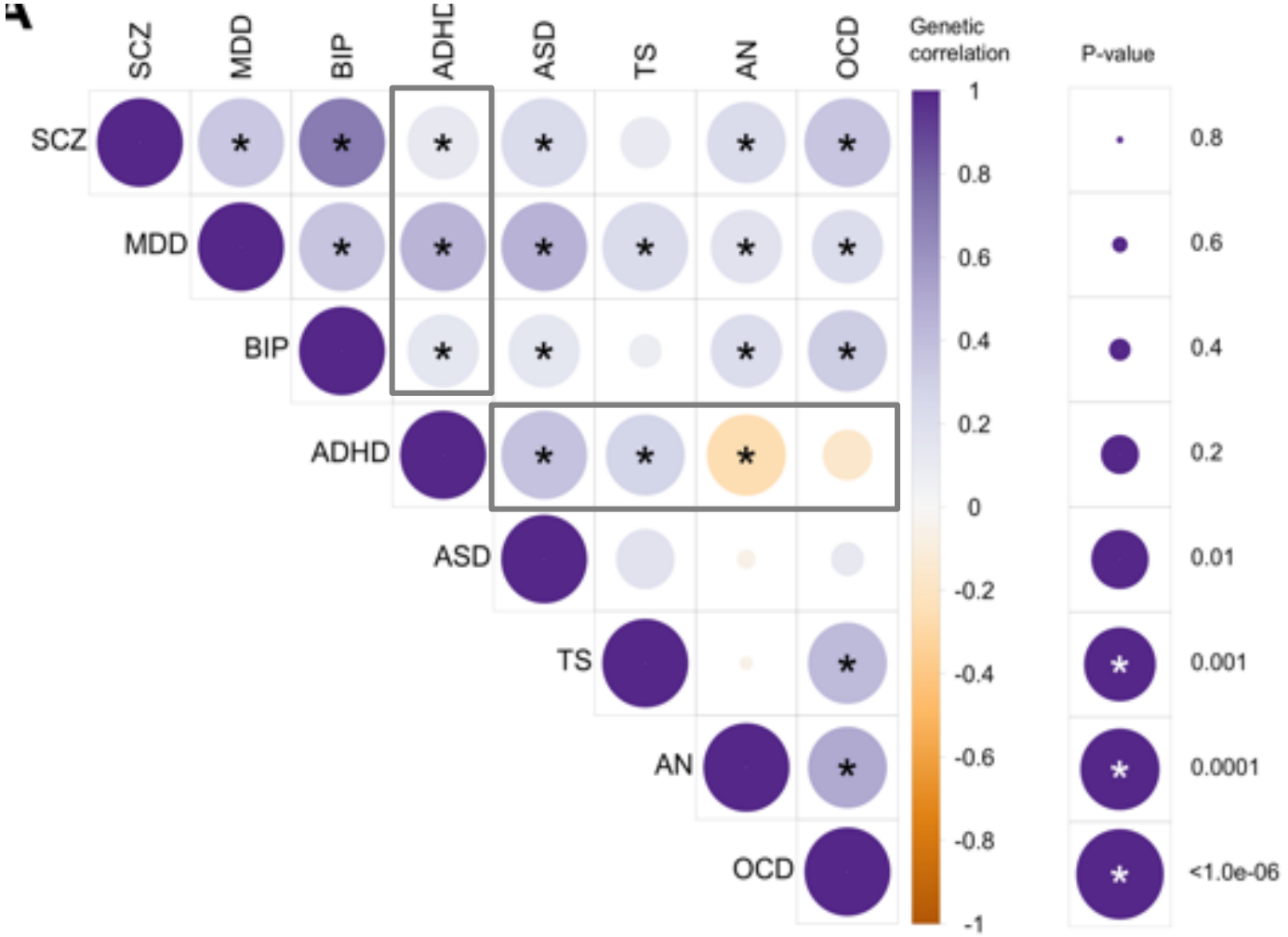
Depression Symptoms in the Population

(Richards et al., Health Tech Assess., 2016)



Genetic Correlations among Psychiatric Disorders

(PGC Cross Disorder Group, Cell, 2019)



Can We Use DNA to Make Psychiatric Diagnoses?

- No
- Current polygenic risk scores are not sufficiently accurate for use in the clinic
- Accuracy may improve as samples get larger, more sophisticated algorithms are applied and other data sources (transcriptome, epigenome imaging) are combined

How Should we Think about Psychiatric Comorbidity in ADHD?

- The new molecular genetic data will, hopefully, put an end to debates about psychiatric comorbidity.
- We now know that most psychiatric disorders are correlated with one another at the level of DNA.
- Diagnosticians should expect "pervasive comorbidity"
  - ADHD can co-occur with many disorders
  - Multiple comorbidities are to be expected in some patients

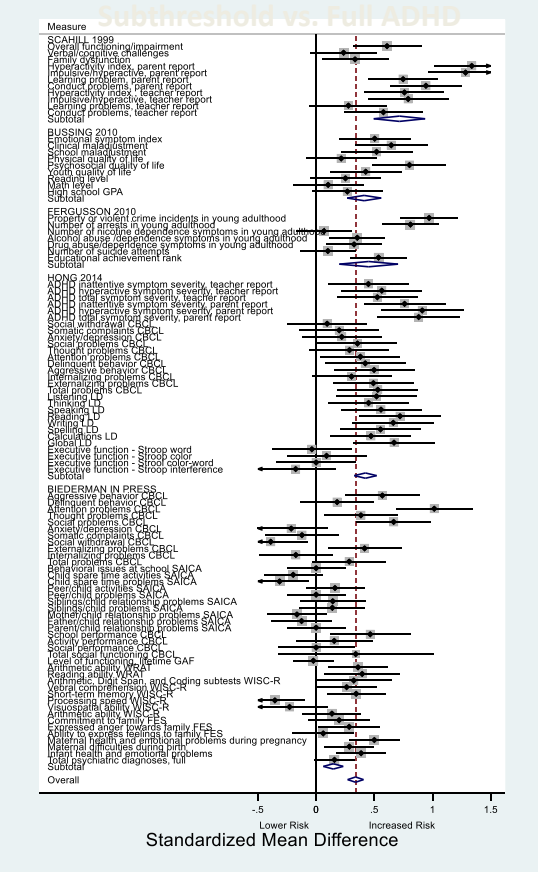
How Should We Think About Subthreshold Disorders?

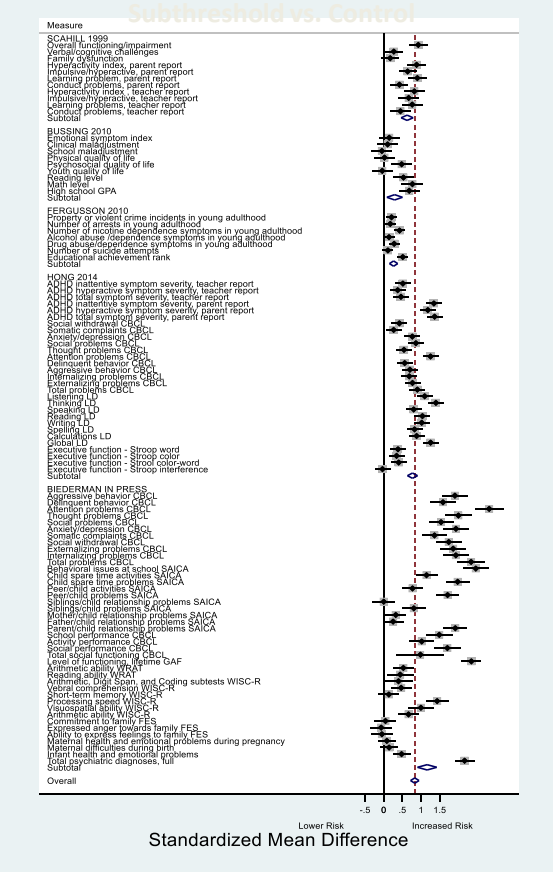
- The existence of subthreshold disorders makes sense from a genetic perspective
- Subthreshold ADHD is analogous to borderline hypertension

Meta-Analysis of Subthreshold ADHD

(Kirova et al., Psychiatry Res., 2019)

- Subthreshold cases milder than Full ADHD Cases but, compared with controls show more:
  - Psychopathology
  - School Failure
  - Neuropsychological Impairment
  - Substance Use
  - Psychosocial Impairment





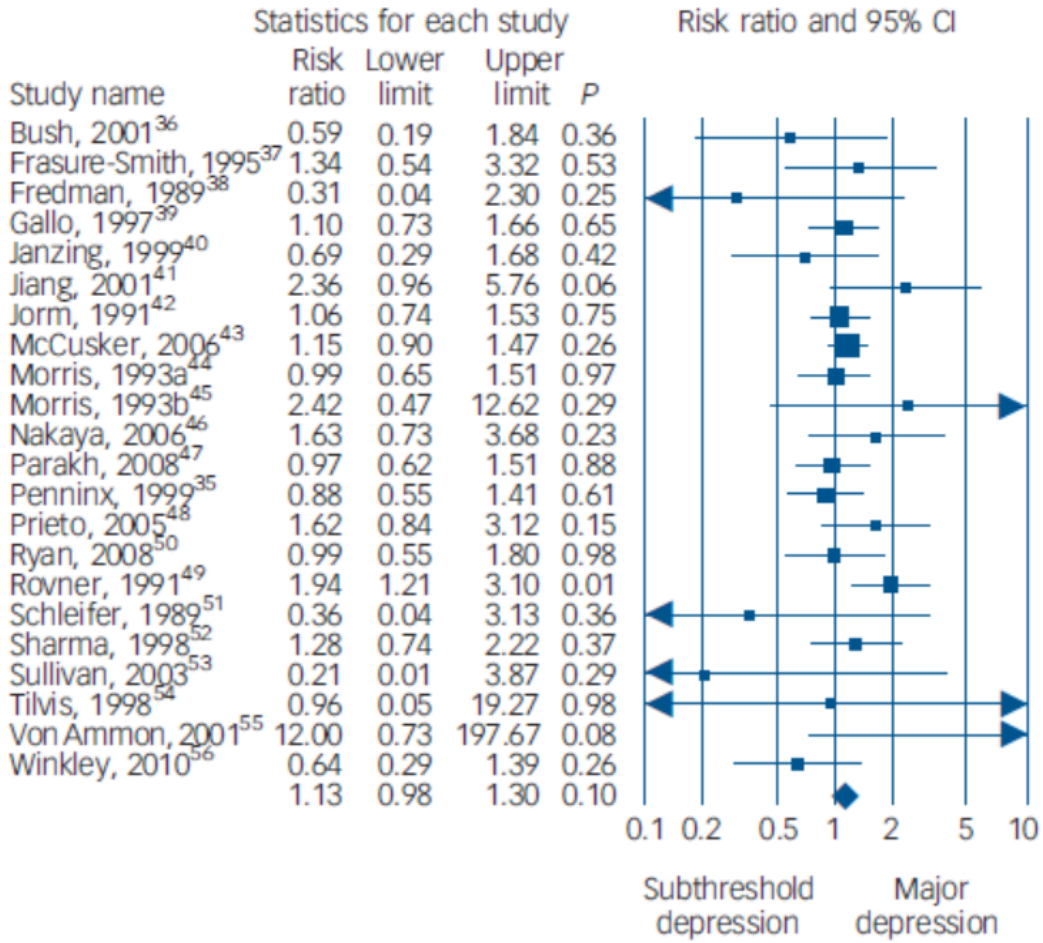
Subthreshold Pediatric Bipolar Disorder: A Systematic Literature Review and Meta-Analysis

(Vaudreuil, Faraone & Biederman, Bipolar Disorders, 2019)

Subthreshold pediatric BP was associated with greater functional impairment, greater severity of manic and depressed mood symptoms, higher rates of disruptive behavior and substance use disorders, and higher rates of suicidal ideation and attempts

No Difference in Mortality between Full and Subthreshold Depression: A Meta-Analysis

(Cuijpers et al., BJP, 2013)

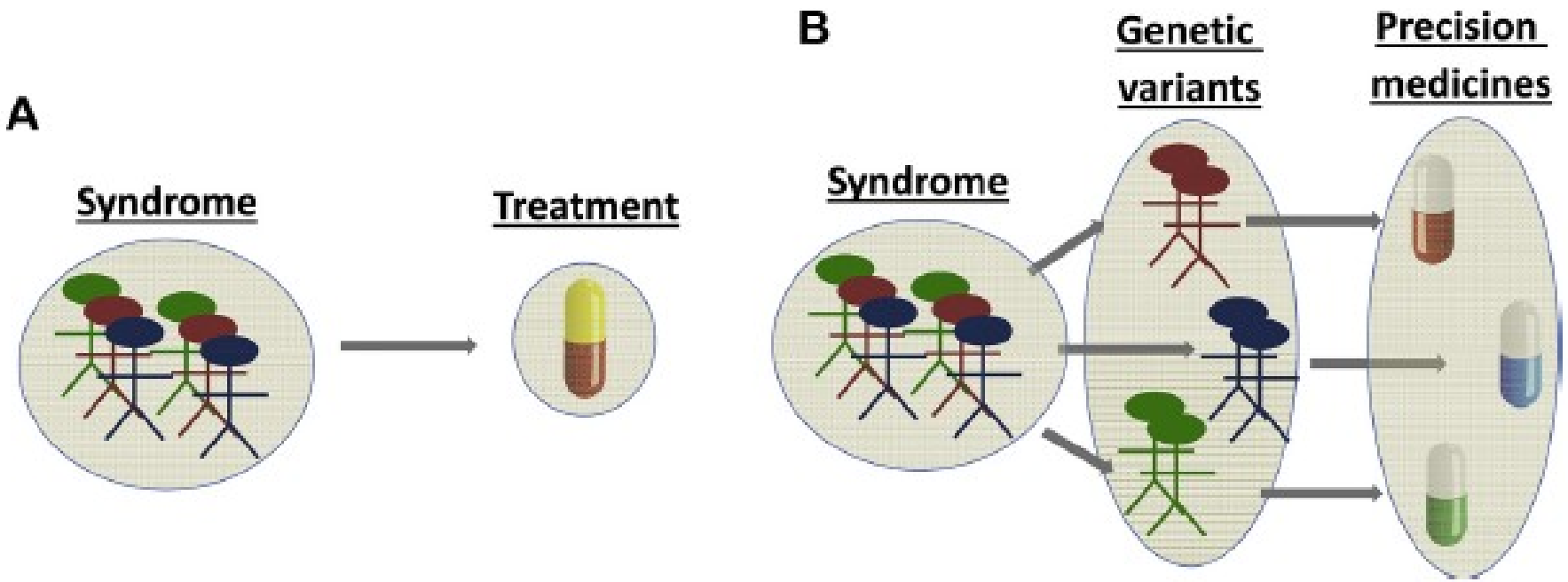


People with major depression had a somewhat increased chance of dying earlier than people with subthreshold depression but this difference was not significant ($p = 0.1$)

The Genome and Drug Response: Are we Ready for Personalized Medicine?

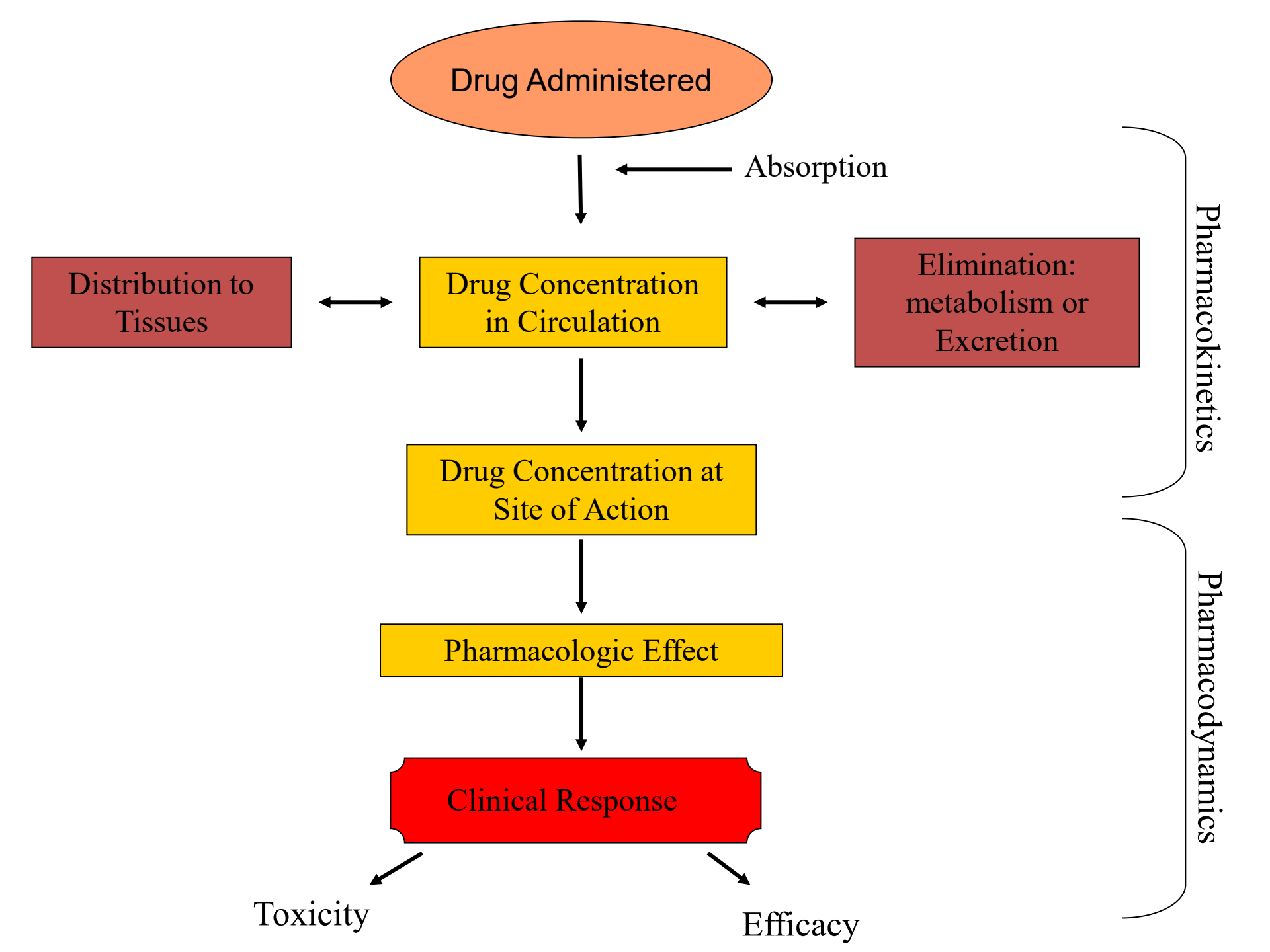
Pharmacogenetics: Theory

(Posner, JAACAP, 2018)



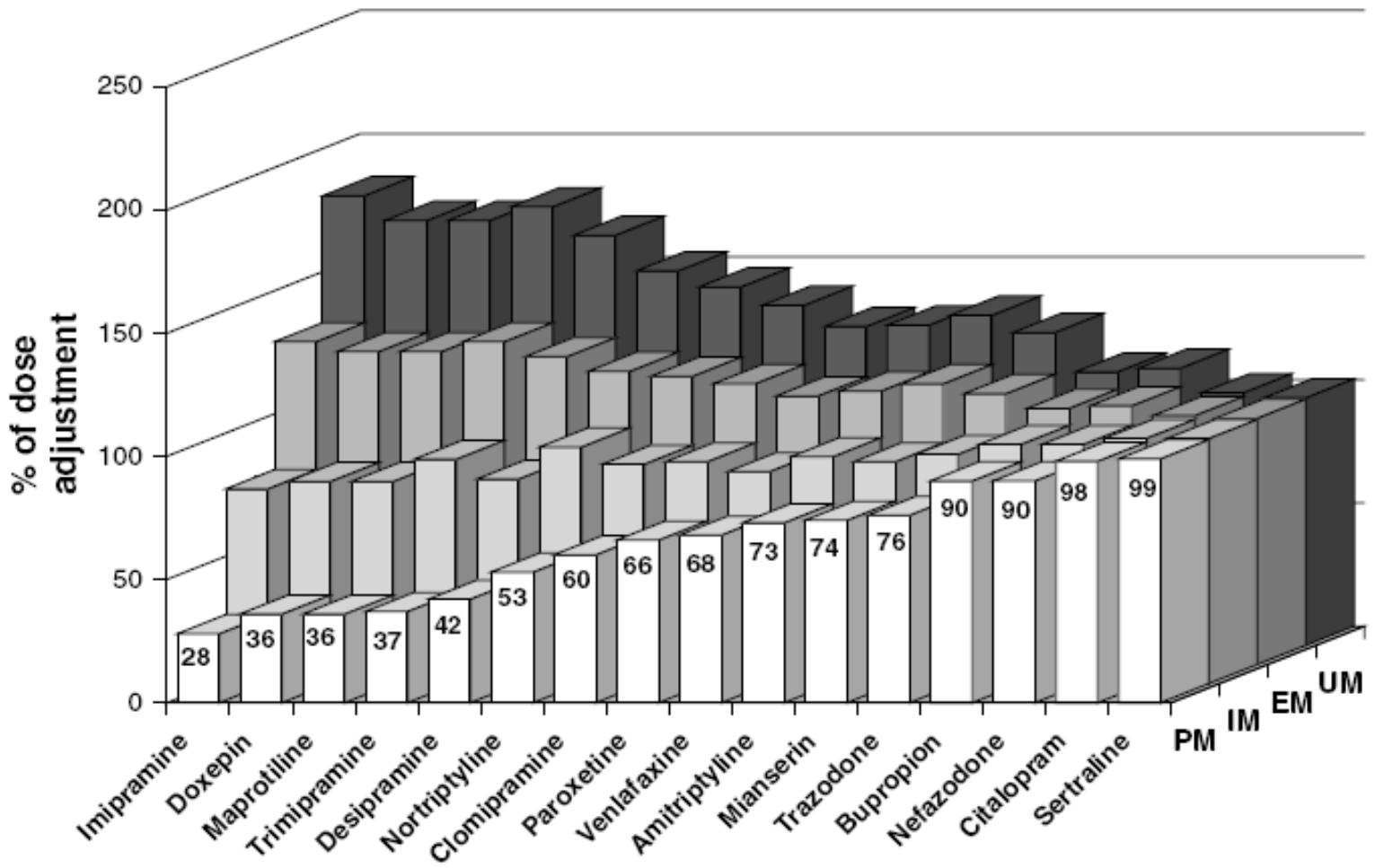
Why Pharmacogenomics?

- "One size fits all pharmacotherapy" is unrealistic
  - Substantial genetic and biologic diversity among people
  - Drug response rates are modest
  - Can we replace trial and error treatment with targeted treatment?
- Adverse effects prevent some drugs from coming to market and limit the utility of others
  - Genetic data could identify patients at high risk for adverse effects


Drug Administered
Absorption
Distribution to Tissues
Drug Concentration in Circulation
Elimination: metabolism or Excretion
Drug Concentration at Site of Action
Pharmacologic Effect
Clinical Response
Toxicity
Efficacy
Pharmacokinetics
Pharmacodynamics

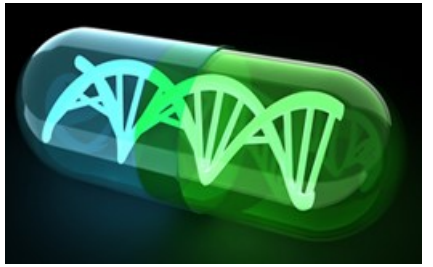
Dose Adjustments for Antidepressants by CYP2D6 Genotype

(Kirchheiner et al, Molec Psychiat. 2004)



Pharmacogenetics: Can We Predict ADHD Drug Pharmacokinetics from DNA Variants?

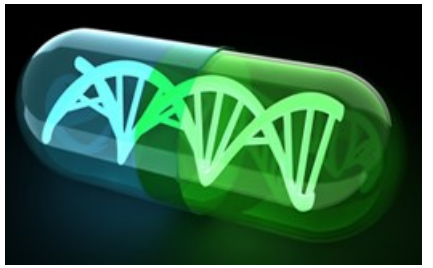
(Froelich, McGough & Stein, CNS Drugs, 2010)



- Rare CES1 variants in poor metabolizers of methylphenidate
- 20% of Caucasians are poor metabolizers for amphetamine due to DNA variants at CYP2D6
- CYP3A4 variants may explain ancestry group differences in amphetamine metabolism.
- CYP2D6 and atomoxetine Ultra-rapid metabolizers:
  - 10% Caucasians; 3% African-Americans

Pharmacogenetics: Can We Predict Drug Response from DNA Variants?

(Myer, Boland & Faraone, Molec Psychiat, 2018)



- Pharmacodynamics: DNA Variants and Clinical Response of ADHD symptoms to Methylphenidate
  - Meta-analysis of variants in 6 genes from 50 studies of ADHD youth

Gene	Odds Ratio	P-value	Heterogeneity	Pub. Bias
LPHN3	1.1	NS	.70	No
DRD4	1.7	.003	.13	No
SLC6A2	2.9	.002	.32	No
SLC6A3	1.4	.009	.00001	Yes
COMT	1.4	.0001	.53	No
ADRA2A	1.7	.0001	.9	No

Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis

(Zhang et al., Schiz Bull, 2016)

- 72 articles reporting on 46 non-duplicated samples (n = 6700, mean follow-up = 25.1 wk) with 38 SNPs from 20 genes/ genomic regions
- 16 SNPs from 10 genes were significantly associated with weight increase
- Hedges' g's = 0.30–0.80, ORs = 1.47–1.9
- Antipsychotic related weight gain is polygenic and associated with specific genetic variants, especially in genes coding for antipsychotic pharmacodynamic targets

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MENTAL HEALTH CLINICIAN

LITERATURE REVIEW Open Access

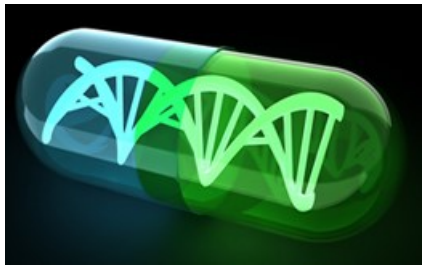
The use of pharmacogenetic testing in patients with schizophrenia or bipolar disorder: A systematic review

Melanie Routhieaux, PharmD[1]
Jessica Keels, PharmD[2]
Erika E. Tillery, PharmD, BCPP, BCGP[3]

Results: A total of 18 articles were included in the final literature review. A wide variety of genes amongst adult patients with varying ethnicities were found to be correlated with the development of schizophrenia or bipolar disorder as well as response to antipsychotics and mood stabilizers.

Discussion: While current studies show a correlation between genetic variations and medication response or disease predisposition for patients with schizophrenia and bipolar disorder, research is unclear on the type of therapeutic recommendations that should occur based on the results of the pharmacogenetic testing. Hopefully interpreting pharmacogenetic results will one day assist with optimizing medication recommendations for individuals with schizophrenia and bipolar disorder.

Pharmacogenetics: Is it Clinically Useful?



- Effects of DNA variants on drug metabolism are strong and thus, theoretically useful
  - But fast and slow metabolizers can be detected via slow titration in clinical practice
- Effects of DNA variants on the pharmacodynamic response are real but weak. Predictive value is low
- Genetic association studies are not sufficient for determining the value of pharmacogenetic testing

Current Controversy: What Type of Data are needed to Show the Utility of Pharmacogenetically Guided Treatment?

- Randomized controlled trials (RCTs) comparing protocolized treatment as usual (PTAU) with pharmacogenetically guided treatment (PGT)
- RCTs comparing TAU with PGT
- Electronic medical record studies comparing TAU with PGT

Pharmacogenetic-Guided Psychiatric Intervention Associated With Increased Adherence and Cost Savings

Jesen Fagerness, JD; Eileen Fonseca, MS; Gregory P. Hess, MD, MBA, MSc; Rachel Scott, PharmD; Kathryn R. Gardner, MS; Michael Koffler, MBA; Maurizio Fava, MD; Roy H. Perlis, MD, MSc; Francis X. Brennan, PhD; and Jay Lombard, DO

Study Design

In this retrospective study, we examined health claims data in order to assess medication adherence rates and healthcare costs

Results

Overall, individuals with assay-guided treatment were significantly more medication adherent ($P = 1.56 \times 10^{-3}$; Cohen's d = 0.511) than patients with standard treatment and demonstrated a relative cost savings of 9.5% in outpatient costs over a 4-month follow-up period, or $562 in total savings.

Received: 7 September 2017 | Revised: 4 January 2018 | Accepted: 10 February 2018

DOI: 10.1002/da.22742

RESEARCH ARTICLE

WILEY AD/AA

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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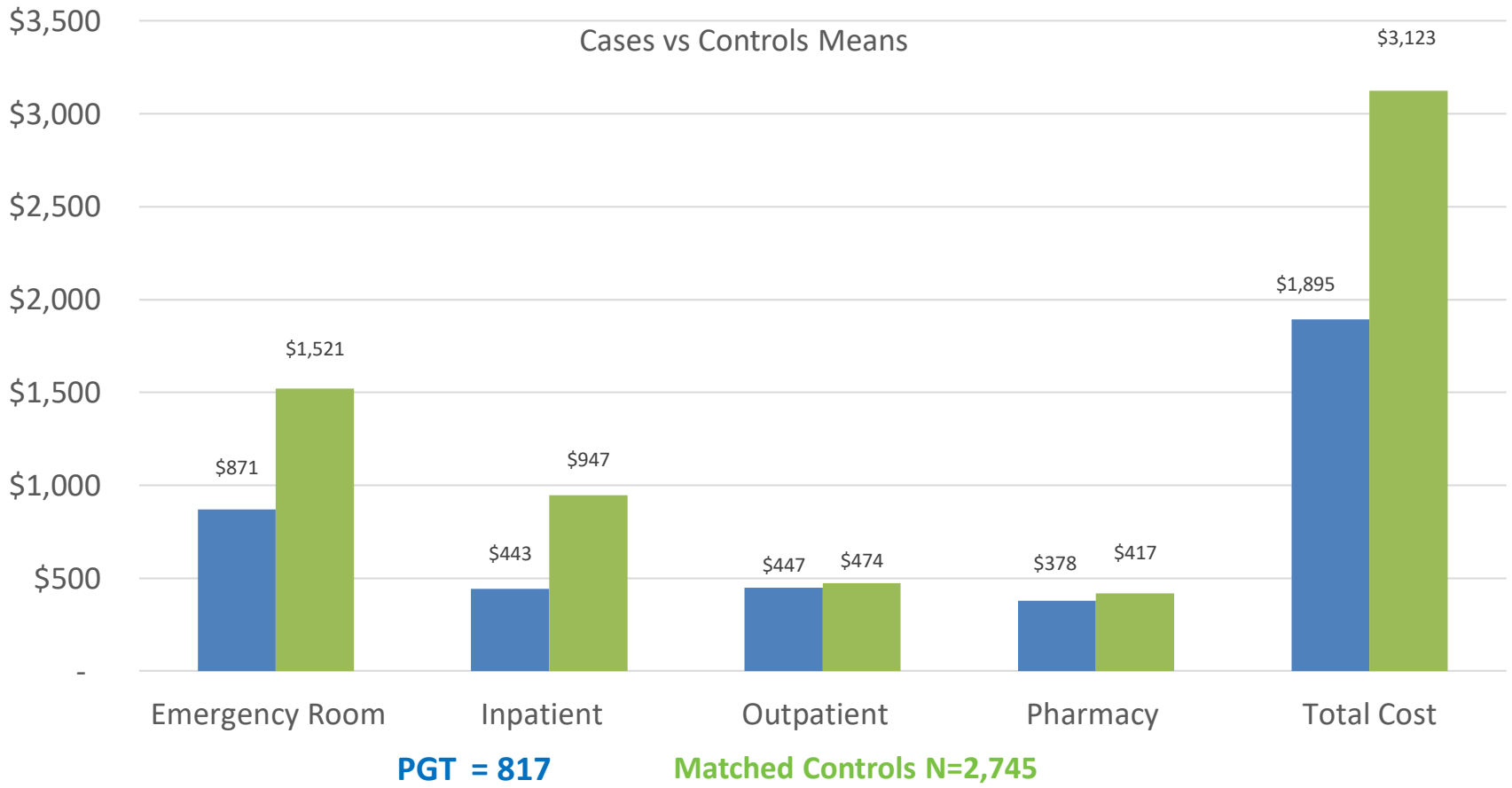
Background: Naturalistic and small randomized trials have suggested that pharmacogenetic testing may improve treatment outcomes in depression, but its cost-effectiveness is not known. There is growing enthusiasm for personalized medicine, relying on genetic variation as a contributor to heterogeneity of treatment effects. We sought to examine the relationship between a commercial pharmacogenetic test for psychotropic medications and 6-month cost of care and utilization in a large commercial health plan.

Methods: We performed a propensity-score matched case-control analysis of longitudinal health claims data from a large US insurer. Individuals with a mood or anxiety disorder diagnosis ($N = 817$)

Pharmacogenetic Testing Leads to significantly Lower Health Care Costs Over 6 months

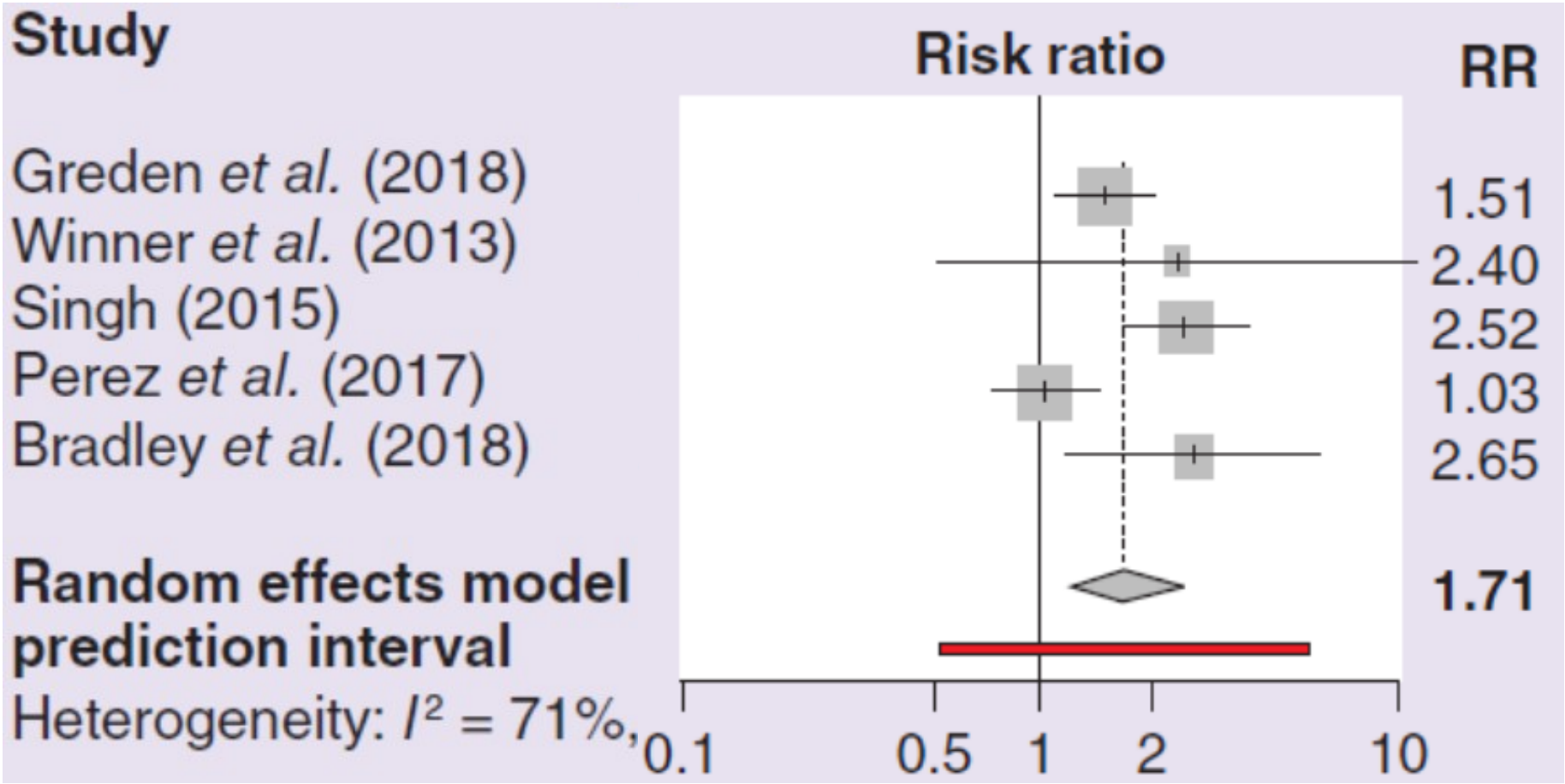
(Perlis et al., Depress. Anxiety, 2018)



Fully adjusted costs $1,948 lower among cases

PGT vs TAU for Depressive Symptom Remission: A Meta-Analysis of Randomized Controlled Trials

(Bousman et al., Pharmacogenomics, 2019)



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Journal of Psychiatric Research

Volume 111, April 2019, Pages 59-67

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

John F. Greden [a], Sagar V. Parikh [a], Anthony J. Rothschild [b], Michael E. Thase [c], Boadie W. Dunlop [d], Charles DeBattista [e], Charles R. Conway [f], Brent P. Forester [g], Francis M. Mondimore [h], Richard C. Shelton [i], Matthew Macaluso [j], James Li [k], Krystal Brown [l], Alexa Gilbert [k], Lindsey Burns [k], Michael R. Jablonski [k], Bryan Dechairo [k, l]

Conclusion: Pharmacogenomic testing did not significantly improve mean symptoms but did significantly improve response and remission rates for difficult-to-treat depression patients over standard of care

Critique of the Pharmacogenetically Guided Treatment Literature

(Zubenko et al., JAMA Psychiat, 2018)

VIEWPOINT

On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment

George S. Zubenko, MD, PhD
Distinguished Life Fellow, American Psychiatric Association, Washington, DC.

Barbara R. Sommer, MD
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California.

Bruce M. Cohen, MD, PhD
Department of Psychiatry, Harvard Medical School, Boston, Massachusetts:

Clinicians hope to see translational uses of powerful new technologies, such as brain imaging and genomic testing, guiding care of patients. In genomics, many newly risen companies promise to address this hope by vigorously marketing pharmacogenetic (Pgen) tests, especially for the treatment of major depressive disorder (MDD). One company's website reports sales of over 650 000 Pgen tests.[1] Does the evidence support such use? The heterogeneous and complex underlying causes and mechanisms of illness and clinical response to treatment in MDD strongly suggest that there will be serious issues limiting or preventing the development of Pgen approaches to treatment choice. Simply put, MDD is determined by a large number of genes, and, except in rare cases, no single gene or limited gene set, even those for drug metabolism and drug targets, determines more than a few percent of the risk of illness or course of treatment.[2-4] Environmental factors (age, sex,

Table. Summary Features of Published Clinical Studies of Pharmacogenetic-Guided Medication Treatment of Major Depressive Disorder[a]

Type of Study	No. of Studies	Total No. of Participants
Open/nonblinded and uncontrolled	5	1700
Retrospective/nonblinded and uncontrolled	1	333
Partially blinded and no protocol-based comparison	4	1186
Blinded and with protocol-based comparison	0	0

[a] Published studies were obtained through Google searches of websites of companies offering pharmacogenetic testing and PubMed searches for genetics, pharmacogenetics, or pharmacogenomics and depression or psychiatry and genetic, pharmacogenetic, or pharmacogenomics testing and depression or psychiatry. Only a few studies showed a statistically significant result, and these results were not corrected for multiple comparisons or nonrandomized assignment.

Features of Published PGT Studies of Depression

(Zubenko et al., JAMA Psychiat, 2018)

Type of Study	No. of Studies	Total No. of Participants
Open/nonblinded and uncontrolled	5	1700
Retrospective/nonblinded and uncontrolled	1	333
Partially blinded and no protocol-based comparison	4	1186
Blinded and with protocol-based comparison	0	0

Are PGT Studies are Biased to Favor PGT?

(Zubenko et al., JAMA Psychiat, 2018)

- In many settings, treatment as usual is below the standard of care.
- Regardless of the validity/utility of pharmacogenetic information, if PGT keeps clinicians within the boundaries of evidenced-based care.
- So, when PGT is better than TAU, we don't know if it is due to the use of pharmacogenomic information or to the use of standard of care protocols

Pharmacogenetics: View from the FDA

(FDA Statement, 11/01/2018)

"FDA is aware of genetic tests that claim results can be used by physicians to identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications. However, **the relationship between DNA variations and the effectiveness of antidepressant medications has never been established**."

PSYCHIATRIC NEWS
AMERICAN PSYCHIATRIC ASSOCIATION

PSYCHOPHARMACOLOGY

Task Force on Gene Testing for Antidepressant Efficacy Concludes Tests Not Yet Ready for Widespread Use

MARK MORAN

Published Online: 19 Jul 2018 | https://doi.org/10.1176/appi.pn.2018.pp6b1

Data supporting gene testing claims flawed:

- Significant associations typically weak
- Effects of PK genes mitigated by titration
- Poor control of protocolized care in clinical trials
- Failure of primary outcomes
- Lack of transparency with regard to the algorithms used to look at multiple genetic variations

Pharmacogenomic Testing in Psychiatry




Gabrielle A. Carlson, MD, Section Editor, Jon McClellan, MD, Stacy Drury, MD, PhD, and Laura Ramsey, PhD

- Genetic testing for drug metabolizing enzymes is not supported as first line approach in terms of cost effectiveness.
- Inclusion of genetic variants with insufficient relevance to drug effectiveness limits commercially available testing panels.
- Tests for drug metabolizing enzymes may have some utility for patients with abnormal side effect profiles and treatment-resistant conditions

Potential Un-intended Consequences of Pharmacogenetically Guided Therapeutics

- The time spent reading and interpreting pharmacogenetic testing reports would be better spent on other diagnostic or therapeutic issues
- Financial cost to the patient
- Following pharmacogenetic guidance may decrease adherence to well-validated evidenced-based treatment guidelines
  - E.g., using a non-stimulant for ADHD because patient is a rapid (or slow metabolizer) of stimulants.

For information about evidenced-based pharmacogenetics, see https://cpicpgx.org/guidelines/

Summary

1. Most psychiatric disorders are polygenic and share genetic risk factors with other psychiatric disorders
2. Both genomic and clinical data support the validity of subthreshold psychiatric diagnoses
3. DNA variants are associated with the pharmacokinetics and pharmacodynamics of drug response
4. Medical record data suggests that pharmacogenetically guided treatment may decrease costs.
5. We need better randomized controlled trials to compare pharmacogenetically guided treatment with protocolized treatment.

Thanks for Listening!

Free CME on Adult ADHD: www.adhdinadults.com

Tweets: @StephenFaraone