Precision Psychiatry:
New Opportunities For Prevention And Treatment

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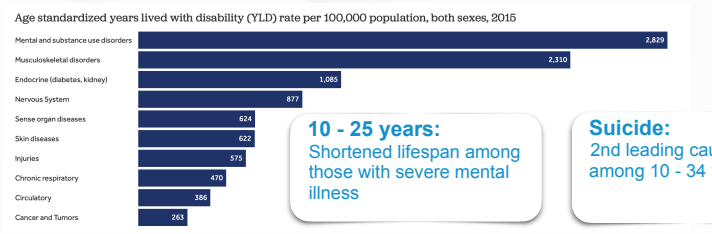
Disclosures

- Scientific Advisory Board of Sensorium Therapeutics (with equity)
- PI of a collaborative study of the genetics of depression and bipolar disorder sponsored by 23andMe for which 23andMe provides analysis time as in-kind support but no payments.
- Grant Support: NIH, Tommy Fuss Fund, Biogen, Inc.

Psychiatric Disorders: Unmet Needs



10 - 25 years: Shortened lifespan among those with severe mental illness

Suicide: 2nd leading cause of death among 10 - 34 year-olds

Nearly $1 Trillion Costs associated with untreated mental health/ substance use disorders

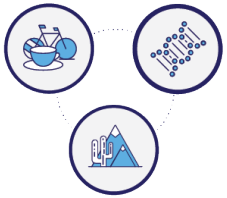
Almost All FDA-approved Medications: Based on mechanisms identified in 1950s and 1960s

Source: www.nimh.nih.gov

The Emergence of "Precision Medicine"

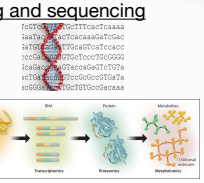
"Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle."

—PMI Working Group Report, 2015

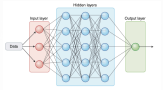


Research Resources For Precision Medicine

- DNA genotyping and sequencing
- Other Omics
- Biobanks
- EHRs
- Digital/mHealth technologies
- Big data methods: machine learning/AI
- Deep phenotyping
- Clinical trials





Major Challenges/Opportunities For Precision Psychiatry

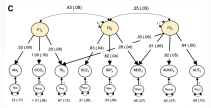
I. **Diagnosis:**
   - Clarifying diagnostic boundaries and etiology-based classification

II. **Risk and resilience:**
   - How do we identify those at risk and promote resilience?

III. **Prevention and early intervention:**
   - What are the actionable targets?

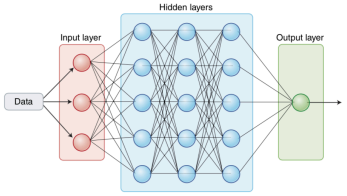
IV. **Treatment Stratification:**
   - Matching patients to treatments to reduce trial-and-error

V. **Precision therapeutics:**
   - Targeting therapies to underlying causes




Precision Risk Stratification

Artificial Intelligence (AI)



Data Sources In The EHR

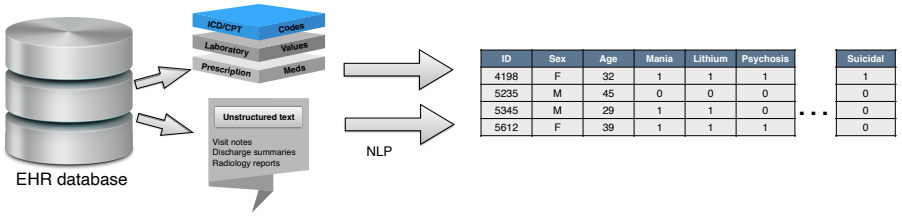
REVIEW ARTICLE

The use of electronic health records for psychiatric phenotyping and genomics

Jordan W. Smoller[1,2,3]

Am J Med Genet. 2018;177B:601–612.

- Vast longitudinal resource of real-world health data
- High-dimensional e.g. Mass General Brigham EHR has 6.5 million patients with 3.5 billion rows of data



ID	Sex	Age	Mania	Lithium	Psychosis		Suicidal
4198	F	32	1	1	1		1
5235	M	45	0	0	0		0
5345	M	29	1	1	0	...	0
5612	F	39	1	1	1		0

Validation of Electronic Health Record Phenotyping of Bipolar Disorder and Control Subjects

Victor M. Castro, M.S., Jessica Minnier, Ph.D., Shawn N. Murphy, M.D., Ph.D., Isaac Kohane, M.D., Ph.D., Susanne E. Churchill, Ph.D., Vivian Gainer, M.S., Tianxi Cai, Sc.D., Alison G. Hoffnagle, M.S., Yael Dai, B.A., Stefanie Block, M.S., Sydney R. Weill, B.A., Mireya Nadal-Vicens, M.D., Ph.D., Alisha R. Pollastri, Ph.D., J. Niels Rosenquist, M.D., Ph.D., Sergey Goryachev, M.S., Dost Ongur, M.D., Ph.D., Pamela Sklar, M.D., Ph.D., Roy H. Perlis, M.D., M.Sc., Jordan W. Smoller, M.D., Sc.D., for the International Cohort Collection for Bipolar Disorder Consortium

Am J Psychiatry 2017; 174:154–162

Validation Study (N = 193)

- Evaluate case and control algorithms compared to gold standard of in-person psychiatrist structured (SCID-IV) interview

Diagnosis	PPV
NLP	0.86
Rule-based	0.80-0.84
Controls	1.0

Genetic validation of bipolar disorder identified by automated phenotyping using electronic health records

Chia-Yen Chen[1,2,3,4,5], Phil H. Lee[1,3,4,5], Victor M. Castro[1,6,7], Jessica Minnier[8], Alexander W. Charney[9,10,11], Eli A. Stahl[9,10], Douglas M. Ruderfer[12], Shawn N. Murphy[2,13,14], Vivian Gainer[2], Tianxi Cai[15], Ian Jones[16], Carlos N. Pato[17], Michele T. Pato[17], Mikael Landén[18,19], Pamela Sklar[9,10,11], Roy H. Perlis[1,3,6] and Jordan W. Smoller[1,3,5]

	EHR Bipolar	Traditionally-Diagnosed
Cases/Control	3330/3952	13902/19279
SNP-heritability	24%	23%

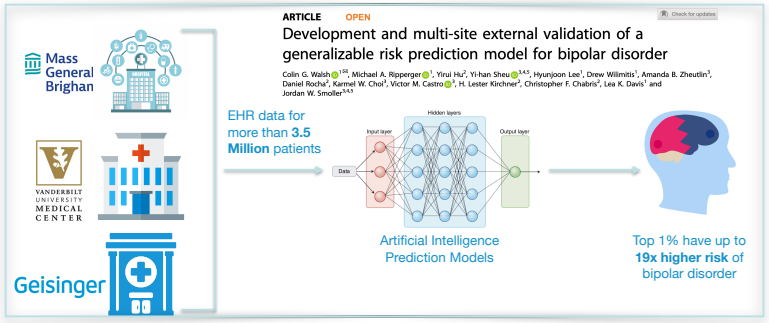
Genetic correlation = .83

Chen et al. *Translational Psychiatry* (2018)8:86

Predicting Bipolar Disorder

PsycheMERGE

- Average delay in diagnosis 6-10 years
- Duration of untreated bipolar disorder associated with more severe and recurrent mood episodes, more frequent suicide attempts



Predicting Bipolar Disorder

PsycheMERGE

- Outcome: Bipolar disorder by algorithm validated against direct clinician interview (PPV > .80) (Castro et al. *Am J Psychiatry,* 2015)
- Features: Structured EHR features prior to first BD ICD code (cases) or last visit (non-cases)
- Each team trained and internally validated one of the types of models: Ridge at MGB; random forests (RF) at VUMC; gradient boosting machines (GBM) at GHS. For external validation, each site tested the remaining two of the three models.

Site	AUROC	Specificity	Sensitivity	PPV	NPV	RR
Vanderbilt (VUMC)	0.84	90	58.2	2.1	>99	5.8
		95	46.9	3.4	>99	9.4
		99	18.9	6.8	>99	18.9
Mass General Brigham (MGB)	0.82	90	56.4	2.1	>99	5.8
		95	39.7	2.9	>99	8.1
		99	12.4	4.5	>99	12.5
Geisinger Health System (GHS)	0.83	90	52.5	1.8	>99	5.5
		95	36.3	2.5	>99	7.6
		99	14.0	4.9	>99	14.8

Performance similar by risk threshold across sites and model types (Ensemble results shown here)

Suicide: The Problem and Unmet Need

1.4 M	Suicide Attempts Annually
35%	Increase in Deaths Since 1999
57%	Increase in Deaths among Young People 2007-2018
2nd	Leading Cause of Death Ages 10 - 34
$503 B	U.S. Annual Costs (including medical, work loss, & quality of life loss)

- Healthcare settings provide crucial venue for prevention
- Most people who attempt or die by suicide are seen by healthcare providers in the preceding weeks

Seen by Provider	
30 Days Prior	90 Days Prior
54%	74%

- **But:** only 28% of people who die by suicide disclose their suicidality to healthcare professionals
- Clinicians do no better than chance at predicting risk

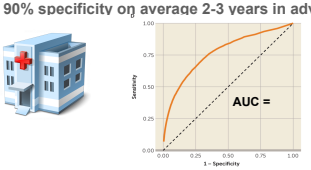
Hedegaard et al. NCHS Data Brief, 2018; Curtin SC. *National Vital Statistics Reports*; 2020; .Ahmedani et al. *J Gen Intern Med*, 2014, *Preventive Med*, 2019; Hallford et al. *Clinical Psychology Review* 101 (2023); Rockett et al. *BMC Public Health*, 2023; Franklin et al. *Psychol Bull.* 2017

Leveraging Big Data And AI/ML

Predicting Suicidal Behavior From Longitudinal Electronic Health Records

Yuval Barak-Corren, M.S., Victor M. Castro, M.S., Solomon Javitt, M.D., Alison G. Hoffnagle, M.S., Yael Dai, B.A., Roy H. Perlis, M.D., M.Sc., Matthew K. Nock, Ph.D., Jordan W. Smoller, M.D., Sc.D., Ben Y. Reis, Ph.D.

Developed and validated suicide risk prediction model (N = 1.7 M). Detects 45% of all suicide attempts/deaths with 90% specificity on average 2-3 years in advance



Original Investigation | Health Informatics

Validation of an Electronic Health Record–Based Suicide Risk Prediction Modeling Approach Across Multiple Health Care Systems

Yuval Barak-Corren, MD; Victor M. Castro, MS; Matthew K. Nock, PhD; Kenneth D. Mandl, MD, MPH; Emily M. Madsen, BS; Ashley Seiger, MSc; William G. Adams, MD; R. Joseph Applegate, BS; Elmer V. Bernstam, MD; Jeffrey G. Klann, PhD; Ellen P. McCarthy, PhD; Shawn N. Murphy, MD, PhD; Marc Natter, MD; Brian Ostasiewski, BS; Nandan Patibandla, MS; Gary E. Rosenthal, MD; George S. Silva, BS; Kun Wei, BS; Griffin M. Weber, MD, PhD; Sarah R. Weiler, PhD; Ben Y. Reis, PhD; Jordan W. Smoller, MD, ScD

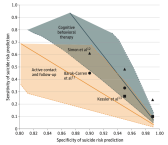
Validated same performance in 5 independent healthcare systems (N = 3.7 M)

JAMA Psychiatry | Original Investigation

Accuracy Requirements for Cost-effective Suicide Risk Prediction Among Primary Care Patients in the US

Eric L. Ross, MD; Kelly L. Zuromski, PhD; Ben Y. Reis, PhD; Matthew K. Nock, PhD; Ronald C. Kessler, PhD; Jordan W. Smoller, MD, ScD

Detailed economic analysis: model performance exceeds cost-effectiveness thresholds



Original Investigation | Psychiatry

JAMA Network Open. 2022;5(1):e2144373. doi:10.1001/jamanetworkopen.2021.44373

Prediction of Suicide Attempts Using Clinician Assessment, Patient Self-report, and Electronic Health Records

Matthew K. Nock, PhD; Alexander J. Millner, PhD; Eric L. Ross, MD; Chris J. Kennedy, PhD; Maha Al-Suwaidi, BS; Yuval Barak-Corren, MD; Victor M. Castro, MS; Franchesca Castro-Ramirez, AM; Tess Lauricella, BA; Nicole Murman, BA; Maria Petukhova, PhD; Suzanne A. Bird, MD; Ben Reis, PhD; Jordan W. Smoller, MD, ScD; Ronald C. Kessler, PhD

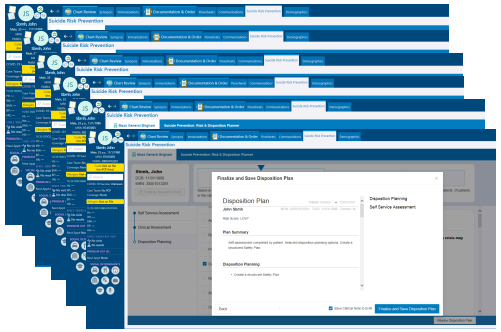
- Prospective study of 1818 patients presenting to ED with psychiatric problems
- Prediction of suicide attempt at 1-month and 6-months:

	Area Under the Curve (S.E.)	
Source	At 1 - Month	At 6 - Month
Clinician Prediction	0.67 (0.04)	0.60 (0.04)
EHR Algorithm	0.71 (0.05)	0.65 (0.04)
Self-Report Survey	0.76 (0.04)	0.77 (0.03)
EHR + Self-Report	0.77 (0.04)	0.79 (0.03)

	Positive Predictive Value for Top Risk Decile	
Source	At 1 - Month	At 6 - Month
EHR + Self-Report	40%	58%

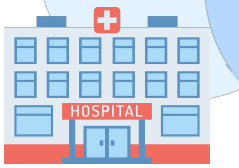
Suicide Risk Prediction/Prevention Clinical Decision Support Tool

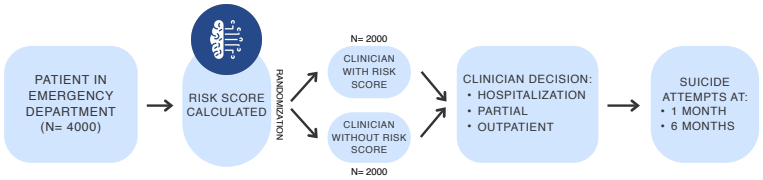
- ✓ SMART-on-FHIR application directly integrated into Epic Hyperspace
- ✓ UI provides user-friendly real-time risk stratification with contextual information to facilitate interpretation
- ✓ Incorporates multiple data sources (e.g. EHR risk score, point-of-care survey)
- ✓ Generates and documents safety plan
- ✓ Guides clinician through care plan



Effectiveness and Implementation of a Clinician Decision Support System to Prevent Suicidal Behaviors

- RCT of machine learning prediction algorithm based on electronic health record and self-report data calculates risk
- Precision treatment rules created to optimize treatment for high-risk patients in the ED





P50 MH129699

CSRP Center for Suicide Research and Prevention

Precision Prevention

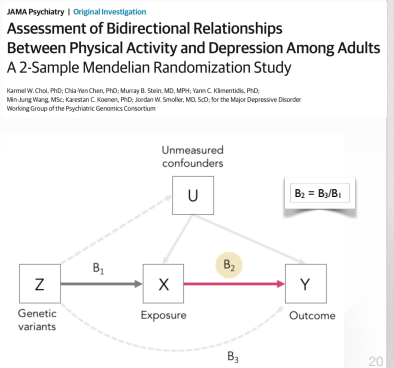
What About Preventing Mood Disorders?

1. Don't have affected relatives
2. Avoid significant childhood adversity
3. Just say "No" to drugs

Is Physical Activity Causally Related To Reduced Risk Of Depression?

Karmel Choi

- Bidirectional Mendelian Randomization (MR) in UK Biobank: use genetic risk variants to "randomize" individuals to higher vs. lower levels of exposure
- Can test causal effect of exposure (X) on outcome (Y)
  - Depression (N = 143,265 from Psychiatric Genomics Consortium)
  - Physical activity: objectively-measured by accelerometer (N = 91,084) in UK Biobank

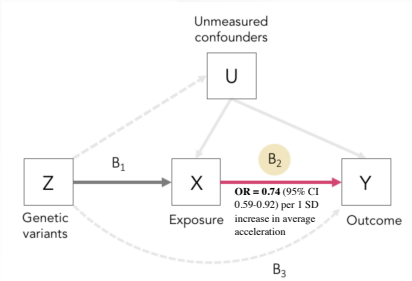


JAMA Psychiatry | Original Investigation

Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults
A 2-Sample Mendelian Randomization Study

Karmel W. Choi, PhD; Chia-Yen Chen, PhD; Murray B. Stein, MD, MPH; Yann C. Klimentidis, PhD; Min-Jung Wang, MSc; Karestan C. Koenen, PhD; Jordan W. Smoller, MD, ScD; for the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium

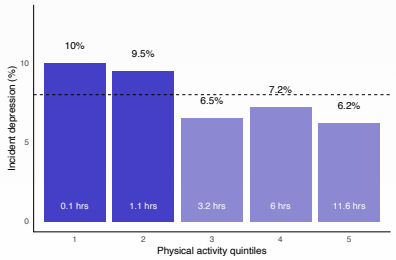
Causal Effect Of Physical Activity On Depression

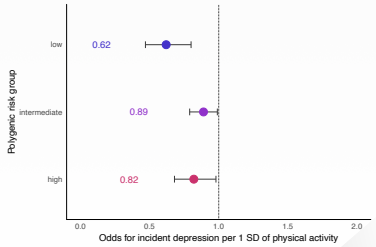


- Rough guide: to get this level of protection, you could replace
  - 15 minutes of sitting with 15 minutes of running, or
  - 1 hour of sitting with 1 hour of moderate activity (e.g. fast walking)

Physical Activity Is Associated With Reduced Incidence Of Depression (Regardless Of Genetic Risk)

- N = 7,971 patients in Partners Biobank
- Stratified by Depression polygenic risk





Choi et al. Depression and Anxiety, 2019

Prospective study of polygenic risk, protective factors, and incident depression following combat deployment in US Army soldiers

Karmel W. Choi[1,2,3,4], Chia-Yen Chen[1,3,4,5], Robert J. Ursano[6], Xiaoying Sun[7], Sonia Jain[7], Ronald C. Kessler[8], Karestan C. Koenen[1,2,3,4], Min-Jung Wang[2], Gary H. Wynn[6], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Laura Campbell-Sills[7], Murray B. Stein[7,9,10] and Jordan W. Smoller[1,2,3,4]

Psychological Medicine

Pre/Post Deployment Study (PPDS)

N=4182 EA ancestry

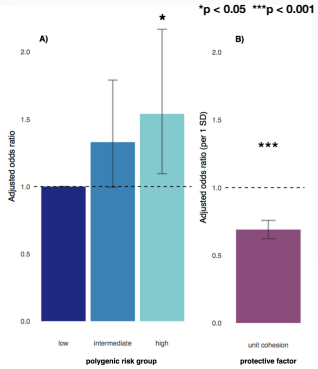
incident depression

unit cohesion

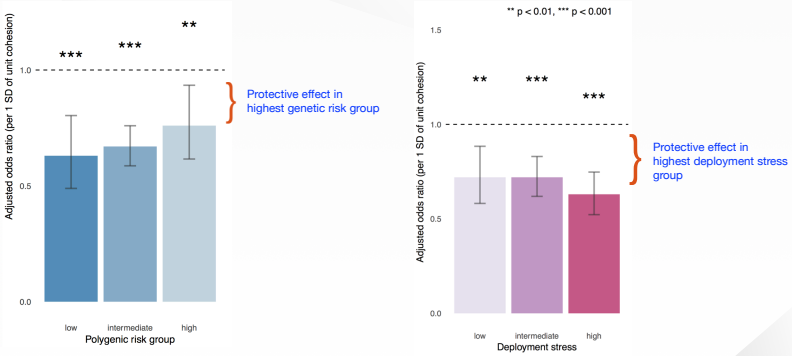
ARMY STARRS
Army Study to Assess Risk and Resilience in Servicemembers

Main Effects Of Genetic Risk And Protective Factors

- Tertiles of polygenic risk score derived from PGC MDD GWAS (N = 173,005)
- Dose-response association with incident depression
- Unit cohesion has protective effect



Unit Cohesion Has Protective Effect Even In Those With High Level Genetic Risk And Stress Exposure



The Protective Effect Of Social Support

nature mental health
Article
https://doi.org/10.1038/s44220-023-00078-0

Social support and depression during a global crisis

Received: 30 May 2022
Accepted: 4 May 2023

Karmel W. Choi, Younga H. Lee, Zhaowen Liu, Daniel Fatori, Joshua R. Bauermeister, Rebecca A. Luh, Cheryl R. Clark, André R. Brunoni, Sarah Bauermeister & Jordan W. Smoller

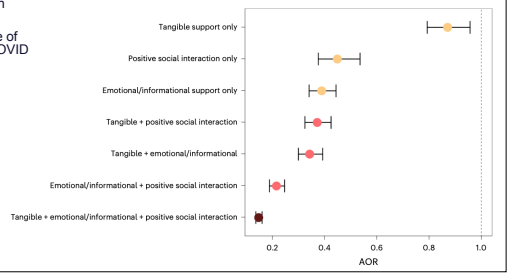
Prospective study of 69,066 participants in the *All of Us* Research Program

Examined associations between social support and the incidence of moderate-severe depressive symptoms in the early months of COVID pandemic.

Exposure type	Exposure	Moderate to severe depression (PHQ-9 total score≥10) AOR	95% CI	*P* value
Overall	Social support	0.45	[0.44–0.46]	$<2.0\times10^{-16}$
Types of social support	Tangible support	0.63	[0.61–0.65]	$<2.0\times10^{-16}$
	Emotional/informational support	0.42	[0.41–0.44]	$<2.0\times10^{-16}$
	Positive social interaction	0.43	[0.41–0.44]	$<2.0\times10^{-16}$

Overall social support was associated with a 55% lower odds of depression.

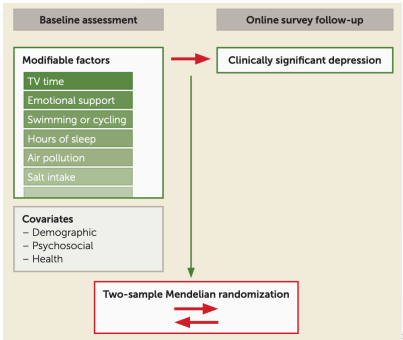
Those with all 3 types of support had 85% lower odds of depression



An Exposure-Wide and Mendelian Randomization Approach to Identifying Modifiable Factors for the Prevention of Depression

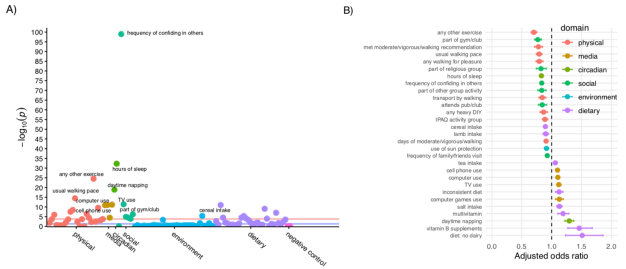
Karmel W. Choi, Ph.D., Murray B. Stein, M.D., M.P.H., Kristen M. Nishimi, Ph.D., Tian Ge, Ph.D., Jonathan R.I. Coleman, Ph.D., Chia-Yen Chen, Sc.D., Andrew Ratanatharathorn, M.A., Amanda B. Zheutlin, Ph.D., Erin C. Dunn, Ph.D., 23andMe Research Team, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Gerome Breen, Ph.D., Karestan C. Koenen, Ph.D., Jordan W. Smoller, M.D., Sc.D.

- UK Biobank sample (N = 123, 794)
- 113K with data on incident depression status 5 years after baseline
- Identified 105 modifiable lifestyle and behavioral factors
- Conducted "factors-wide" scan of association with incident depression
- Validated causal effects using Mendelian randomization

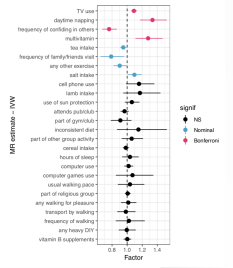


Significant Effects Of Modifiable Factors On Depression Risk

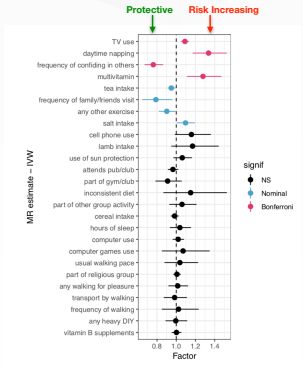
Association Results Between Modifiable Factors and Clinically Significant Depression in the Full Sample, Adjusted for Sociodemographic and Health Factors



Casual Effects of Modifiable Factors on Incident Depression by MR



Factors With A Causal Effect On Developing Depression



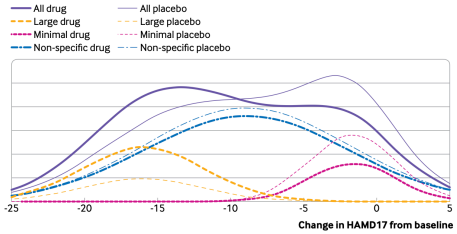
Precision Treatment

Our Current Approach to Treatment

Antidepressant Effects Are Modest…On Average

- In meta-analyses, mean drug advantage vs placebo: < 2 points on HAM-D-17
- But we know that's not the whole story

- Individual participant level analysis of 232 placebo controlled RCTs of AD monotherapy
  - Mean drug vs. placebo difference: 1.75 points
  - But: mixture modeling shows data fit a trimodal distribution of responses
  - Only ~15% of individuals have meaningful drug > placebo effect



Stone et al. 2022 *BMJ*

Big Data and AI to Reduce Trial-And-Error Treatment?

ARTICLE OPEN

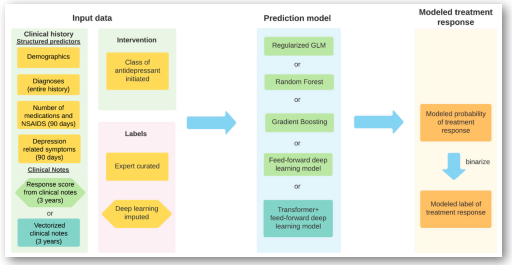
npj Digital Medicine (2023)

AI-assisted prediction of differential response to antidepressant classes using electronic health records

Yi-han Sheu[1,2,3,4,5], Colin Magdamo[5], Matthew Miller[6,7,8], Sudeshna Das[5], Deborah Blacker[3,8] and Jordan W. Smoller[1,2,3,4,8]

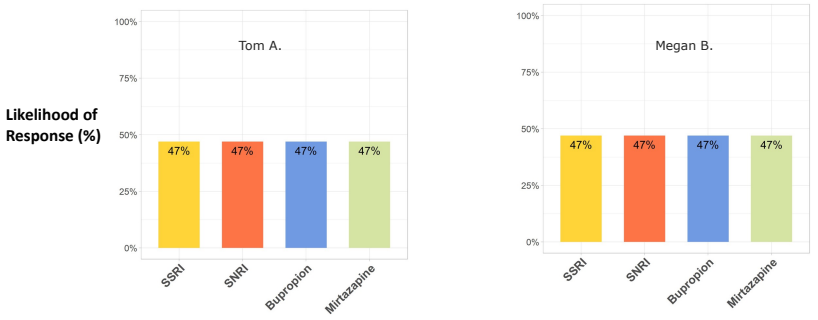
Yi-Han Sheu, MD, MPH, ScD

- EHR data from >17,500 patients with depression who started either:
  - SSRI
  - SNRI
  - Bupropion
  - Mirtazapine
- 38 years of longitudinal data including natural language processing of notes
- Developed AI models to predict treatment response at 4-12 weeks



Big Data and AI to Reduce Trial-And-Error Treatment?

What Clinicians See Today: One Size Fits All



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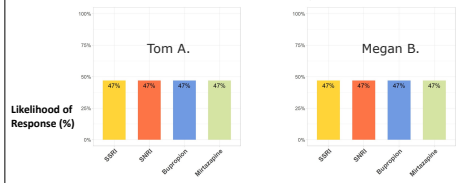
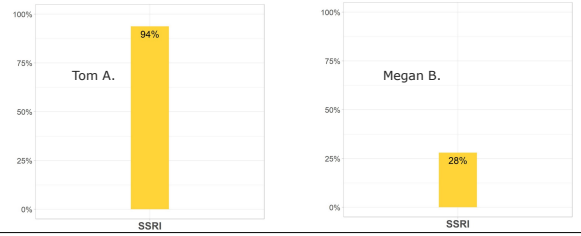


- Correctly predicted response for 74% of patients

Model Predicted Response (%)



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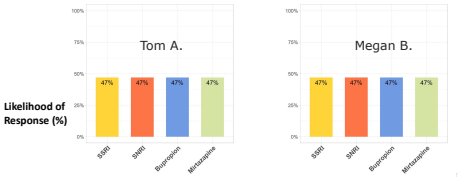
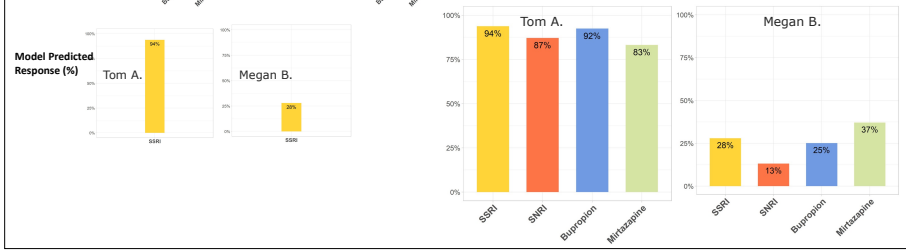


- Correctly predicted response for 74% of patients
- **Key: Can predict response to different antidepressants**

Model Predicted Response (%)



Summary

- New tools and resources are beginning to enable to application of precision medicine to psychiatry by leveraging individual differences
- Urgent need to address major gaps in how we diagnose, treat, and prevent psychiatric illness
- Emphasis on driving “innovation to implementation"
- Opportunities are potentially transformative but building a future of precision medicine in psychiatry will require us to:
  - Leverage large scale, real-world data resources
  - Integrate AI and approaches from clinical psychiatry, genomics, epidemiology, neuroscience, and implementation science