What Should a Psychiatrist Know about Genetics?

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Faculty Disclosure

- **Dr. Nurnberger**: Grant/Research Support—Investigator for Janssen.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

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Learning Objectives

- Describe the evidence supporting the importance of genetic factors in major psychiatric disorders and their treatment
- Assess the value of genetic screening for specific syndromes in patients with autism spectrum disorders and developmental disorders
- Assess the value of pharmacogenomic screening for choice of treatment in major psychiatric disorders

Genetics of Common Disease

- Resolving the genetics of a complex trait, or disease, is more difficult than that of a Mendelian trait
- Typically, large samples of sib pairs are used for linkage studies
- Large case/control samples are used for association studies
- Genetic defects may be a combination of chromosomal anomalies (now including small CNVs), rare variants (< 1% frequency), and common variants

CNV = copy number variant.

Genetics of Common Disease (cont'd)

- Genetic analysis by model-free methods
- Increased attention to epistasis
- Early successes: *BRCA1* and *2,* angiotensinogen for hypertension, human leukocyte antigen, and the insulin receptor for insulin-dependent diabetes mellitus, calpain for non-insulin-dependent diabetes mellitus, genes related to asthma and inflammatory bowel disease, 4 genes related to rare forms of Alzheimer's disease, plus *APoE* related to common forms
- Specific gene variants reported and replicated in schizophrenia, alcohol use disorder, bipolar disorder
- All genes noted account for modest proportion of variance (0.1%–10%)

Genome-Wide Association Studies (GWAS)

- Enables SNP screening of the entire genome at intervals of 10–50 Kb
- Requires sample sizes in the thousands (latest Bipolar Disorder collaborative sample > 20,000 subjects; 36K sample now being analyzed)

SNP = single nucleotide polymorphism.

GWAS Catalog

NHGRI Summary of Significant Genetic Associations from GWAS Studies, January 2017

NHGRI = National Human Genome Research Institute. www.ebi.ac.uk/gwas.

GWAS in Psychiatry

- At the last World Congress of Psychiatric Genetics, new gene variants associated with psychiatric disorders were reported, including > 250 gene variants in Schizophrenia, > 50 in Bipolar Disorder
- All of these variants are associated with modest increases in risk (10%–30%)
- New pathways are implicated by many of these, and these pathways are being investigated

108 Schizophrenia-Associated Genetic Loci

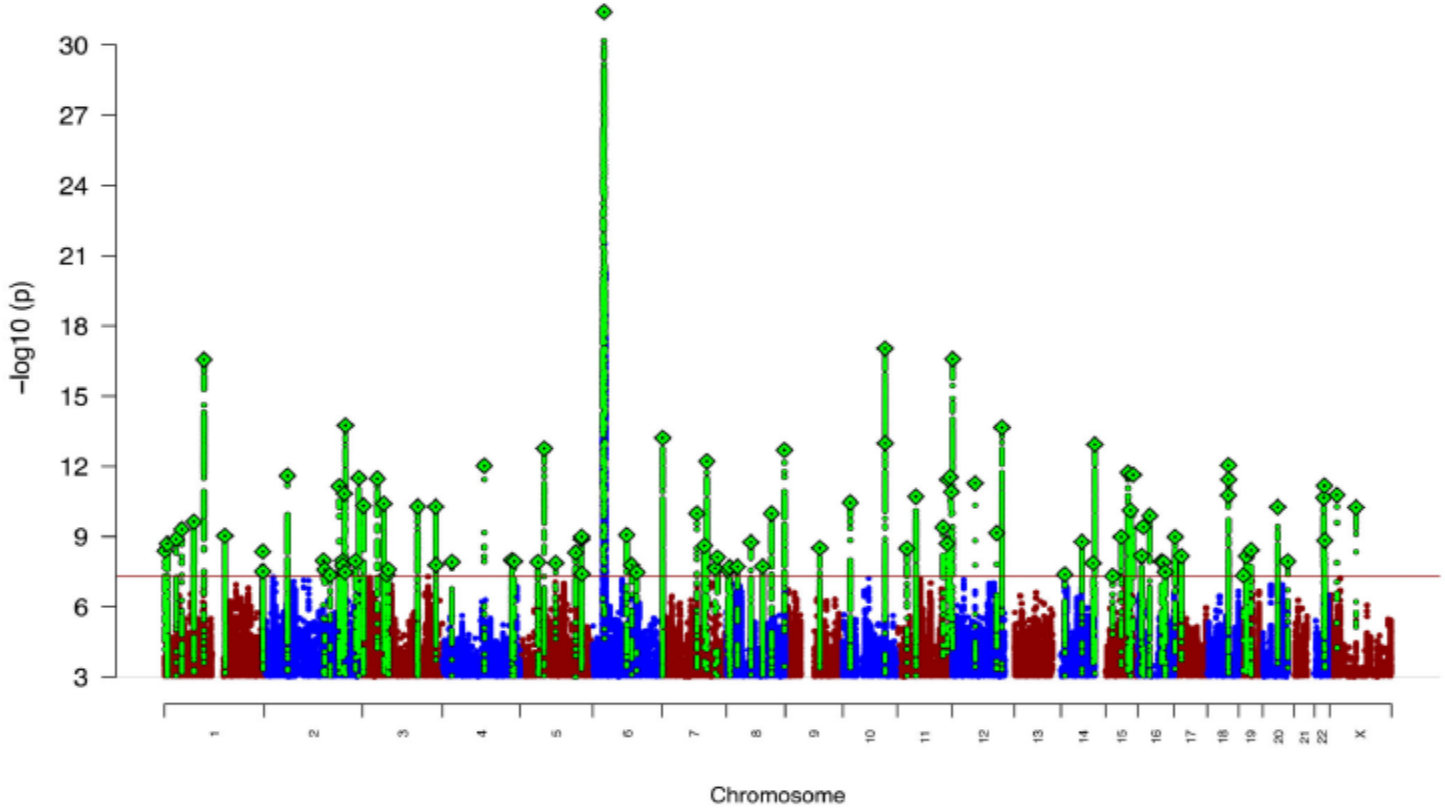
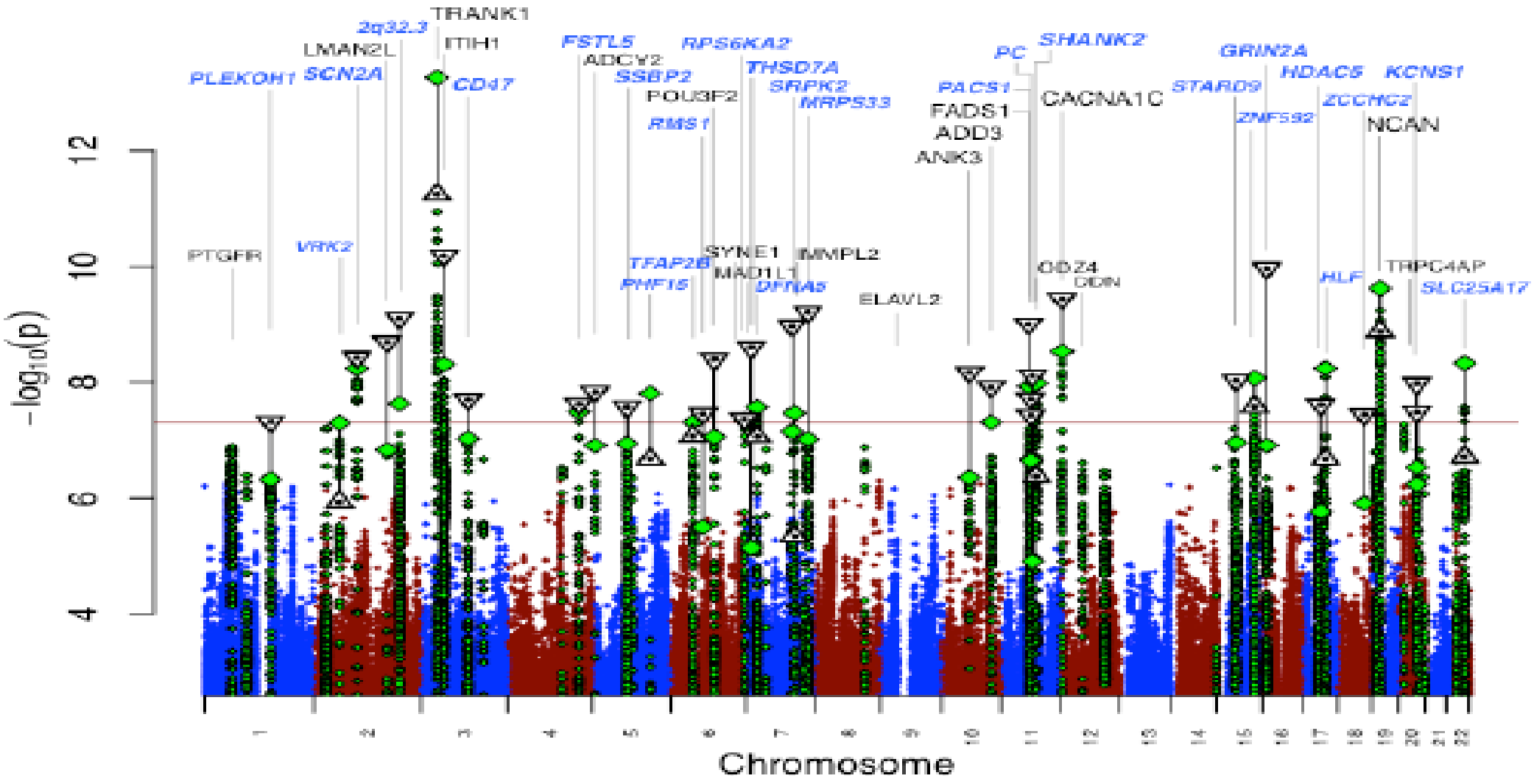


Figure 1. Manhattan plot

Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The x-axis is chromosomal position and the y-axis is the significance of association ($-\log_{10}(P)$).The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in LD with the index SNPs (diamonds) which represent independent genome-wide significant associations.

Ripke S, et al. *Nature*. 2014;511(7510):421-427.

GWAS of Bipolar Disorder, 2019



Stahl EA, et al. *Nat Genet*. 2019;51(5):793-803.

What is a CNV?

- A CNV is a deletion or duplication of a DNA segment
- If it is large (a significant portion of a chromosome), it will be seen microscopically, in a cytogenetic screen (eg, trisomy 21, Fragile X)
- If it is somewhat smaller, it will be detectable by FISH
- If it is smaller yet (but still several kilobases to several megabases), it will be detected by sequencing or microarrays confirmed by CGH or other methods. These are the newly discovered variants now being studied

CGH = comparative genomic hybridization; FISH = fluorescence in situ hybridization.

CNVs in the Human Genome

ABSTRACT

The extent to which large duplications and deletions contribute to human genetic variation and diversity is unknown. Here, we show that large-scale CNPs (about 100 kilobases and greater) contribute substantially to genomic variation between normal humans. Representational oligonucleotide microarray analysis of 20 individuals revealed a total of 221 copy number differences representing 76 unique CNPs. On average, individuals differed by 11 CNPs, and the average length of a CNP interval was 465 kilobases. We observed CNV of 70 different genes within CNP intervals, including genes involved in neurological function, regulation of cell growth, regulation of metabolism, and several genes known to be associated with disease.

CNP = copy number polymorphism.

Sebat J, et al. *Science*. 2004;305(5683):525-528.

Structural Variants in the Human Genome

It is now recognized that the genomes of any 2 individuals in the human population differ more at the structural level than at the nucleotide sequence level. Conservative estimates suggest that CNVs between individuals amount to 4 Mb (1/800 bp) of genetic difference, and less conservative estimates put this figure in the range of 5–24 Mb. By either measure, CNVs account for more nucleotide variation on average than SNPs, which account for approximately 2.5 Mb (1/1,200 bp). Therefore, the total genomic variability between humans is significantly greater than previously thought, amounting to a difference of at least 0.2%, > 0.12% at the structural level and 0.08% at the nucleotide level.

Sebat J. *Nat Genet*. 2007;39(7 Suppl):S3-S5.

Increased Frequency of *De Novo* CNVs in Autism Spectrum Disorders

Sample group	*n*	CNVs de novo	Ratio	*P* value	
				χ^2	Multiplex/simplex
Simplex autism	118	12	0.102	0.0005	0.043
Multiplex autism	77	2	0.026	0.59	
Simplex + multiplex	195	14	0.072	0.0035	
Controls	196	2	0.010		

Sebat J, et al. *Science*. 2007;316(5823):445-449.

Rare CNVs: Risks of Illness for Bipolar Disorder, Schizophrenia, and Autism Spectrum Disorders

CNV Locus	Type	Bipolar Disorder	Schizophrenia	ASD	Risk of Any of These Disorders (%)
1q21.1	Deletion		7.91		7.91
	Duplication		4.50	4.97	9.25
3q29	Deletion		33.56		33.56
7q11.23	Duplication			16.05	16.05
15q11.2	Deletion		2.09		2.09
15q11.2–13.1	Duplication			20.73	20.73
15q13.3	Deletion		8.76	5.42	13.70
16p11.2	Deletion			5.96	5.96
	Duplication	4.19	9.45	7.28	19.56
17p12	Deletion		6.60		6.60
22q11.21	Deletion	26.37	68.25	23.06	82.01
22q11.2	Duplication			2.07	2.07

ASD = autism spectrum disorders.

Gershon ES, et al. *Am J Psychiatry*. 2013;170(9):968-976.

De Novo CNVs: Attributable Risk and Risks of Illness for Schizophrenia, Bipolar Disorder, and Autism Spectrum Disorders

	Odds Ratio	Exposed Attributable Risk (%)	Rate of De Novo CNV if Ill (%)	Illness Risk if De Novo CNV (%)[b]
Bipolar Disorder	4.77	79.0	4.32	4.45
Schizophrenia	6.27	84.1	6.10	5.67
ASD	7.50	86.7	7.18	4.07
Risk of any one of these disorders				13.53

Gershon ES, et al. *Am J Psychiatry*. 2013;170(9):968-976.

Residency Education Committee of the International Society of Psychiatric Genetics (ISPG)

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21st Century Genetics in Psychiatric Residency Training
How do we get there?

It is now well established that different types of genetic variations can increase one's risk for psychiatric disorders. For example, highly penetrant rare variants in hundreds of genes or genomic regions have been strongly associated with ASD, intellectual disability, and developmental delay, while common variants in more than 100 locations in the human genome have been statistically linked to schizophrenia. The translation of these research findings is starting to permeate psychiatric clinical practice in particular areas.

Besterman AD, et al. *JAMA Psychiatry*. 2019 Jan 2; [Epub ahead of print].

Clinical Benefits of Genetic Testing and Counseling in Psychiatry

Clinical Benefit	Example	Implication
Improved etiologic understanding of the disorder	A de novo deletion of 16p11.2 is identified in a patient with ASD	Parents understand that the etiology of their child's condition is due to a new genetic change and not due to a deficiency in their parenting (https://rarediseases.info.nih.gov/diseases/10740/16p112-deletion-syndrome)
Community support for the patient and family	A patient with developmental delay receives a diagnosis of 15q11-q13 duplication syndrome	The patient and family can find resources, advocacy opportunities, and other families affected by this syndrome through the Dup15q alliance (http://www.dup15q.org)
Reproductive counseling and family planning	The parents of a patient with childhood-onset schizophrenia and a de novo 22q11.2 deletion are considering having a second child	The parents are counseled that the chance of having a second child with 22q11.2 deletion syndrome is slightly increased compared with the general population based on studies of siblings of patients with ASD[1] (https://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome)
Ongoing surveillance for known comorbidities	A patient with ASD receives a diagnosis of PTEN deletion	The patient has a known elevated risk of cancer. Ongoing cancer monitoring is provided to the patient
Experimental treatment referrals	A patient with ASD receives a diagnosis of 22q13 deletion syndrome	Possible referral to a clinical trial for IGF-1 therapy (https://www.mountsinai.org/clinical-trials/pilot-treatment-study-of-insulin-like-growth-factor-1-igf-1-in-autism-spectrum-disorder)
Reduce risk of severe medication adverse effects	A patient of Han Chinese ethnicity with bipolar disorder carries the *HLA-B*15:02* variant	The patient would not be administered carbamazepine because of their significantly elevated risk of Stevens-Johnson syndrome[2] (https://www.pharmgkb.org/guideline/PA166105008)

IGF-1 = insulin-like growth factor 1; PTEN = phosphatase and tensin homolog.

Besterman AD, et al. *JAMA Psychiatry*. 2019 Jan 2; [Epub ahead of print].

What Should a Psychiatrist Know about Genetics?

Review and Recommendations from the Residency Education Committee of the ISPG

Current challenges include the following: (1) Genetic testing is recommended in the evaluation of autism and intellectual disability, but its use is limited in current clinical practice. (2) Commercial pharmacogenomic testing is widely available, but its utility has not yet been clearly established. (3) Other methods, such as whole exome and whole genome sequencing, will soon be clinically applicable.

Nurnberger JI Jr, et al. *J Clin Psychiatry*. 2018;80(1).

What should a psychiatrist know about genetics?

- Basic principles of medical genetics
- Family studies and heritability
- Common genetic variants
- Rare genetic variants
- Epigenetics/gene expression
- Pharmacogenetics/pharmacogenomics
- Ethical and social issues
- Principles of risk communication

Nurnberger JI Jr, et al. *J Clin Psychiatry*. 2018;80(1).

Representative Genetic Contribution to Different Psychiatric Disorders

Disorder	Common Variants	Rare Variants	Heritability
Schizophrenia	Clear (100+)[1]	CNVs,[2] SNVs[3]	81%[4]
Bipolar disorder	Clear (30+)[5]	CNVs,[2] SNVs[6]	85%[4]
Major depression	Clear (14)[7]	Unknown	37%[4]
Anxiety disorders	In process	Unknown	Panic: 43%[4] GAD: 28%[4]
OCD	In process	Unknown	40%[8]
Substance use disorders	Clear[9]	Unknown	Cocaine: 72%[4] Alcohol: 56%[4] Cannabis: 48%[4]
Alzheimer's disease	Clear (20+)[10]	Rare Mendelian[10]	75%[4]
Intellectual disability	Clear[11]	CNVs,[2] SNVs[12]	50%[11]
Autism spectrum disorder	Clear[13]	CNVs,[2] SNVs[13]	78%[14]
ADHD	Clear[15]	Unknown	62%[16]
Eating disorders	Clear[17]	Unknown	Anorexia: 60%[4]

ADHD = attention-deficit/hyperactivity disorder; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; SNV = single nucleotide variant.

Nurnberger JI Jr, et al. *J Clin Psychiatry*. 2018;80(1).

Why do today's psychiatric residents need to understand genetics?

A. Clinical situations in which genetic knowledge is already required

1. Estimating empirical risk for psychiatric illness from family structure information and epidemiologic studies
2. Ordering and interpreting genetic tests for autism spectrum disorders and intellectual disability
3. Evaluating the need for pharmacogenomic testing and interpreting the results
4. Addressing the results of direct-to-consumer genetic tests in clinical practice
5. Knowing when to consult genetic counselors and medical geneticists

B. Areas in which new applications of genetics may be expected in the next 1–2 decades

1. Estimating empirical risk in the presence of specific copy number variants and single nucleotide variants
2. Ordering and interpreting genetic tests for rare variants in schizophrenia and bipolar disorder
3. Applying genetic risk scoring in a clinical framework
4. Developing personal genetic profiles for patients and interpretation for treatment decisions and personal prognosis

Nurnberger JI Jr, et al. *J Clin Psychiatry*. 2018;80(1).

What is the present state of genetics education in psychiatric residency programs?

- Formal genetics training from college or medical school may be poorly remembered and no longer current
- Most residents have > 3 hours of genetics training during the residency itself
- Residency training programs frequently do not include faculty with genetics expertise
- Some psychiatrists and trainees may erroneously believe that genetics is peripheral to the understanding and treatment of psychiatric illness
- A related issue is the limited time for didactics in residency programs and the need for prioritization of subspecialty topics

Winner JG, et al. *Acad Psychiatry*. 2010;34(2):115-118. Hoop JG, et al. *Acad Psychiatry*. 2010;34(2):109-114.

National Neuroscience Curriculum Initiative

- Cooperative effort with the American Association of Directors of Residency Training and
- American Psychiatric Association Council on Lifelong Learning and Medical Education
- Funded by the National Institute of Mental Health (R25)

Autism Spectrum Disorders and Other Developmental Disorders

Review of Clinical Applications of Genetic Testing in Autism Spectrum Disorders

Recurrent Structural Abnormalities Associated with Autism Spectrum Disorders

	ASD Penetrance (rate of ASD in carriers)	Neuropsychiatric Pleiotropy (associated neuropsychiatric phenotypes)	Somatic Pleiotropy (associated somatic phenotypes)
Del1q21.1	8%	ID, ADHD, schizophrenia	Microcephaly, heart defect, eye abnormalities, short stature, epilepsy
Dup1q21.1	36%	ID, ADHD, schizophrenia, speech delay	Epilepsy, macrocephaly, heart defect
Del2q23.1	100%	ID, ADHD, language disorder, motor delay	Epilepsy, obesity, brachycephaly, microcephaly, short stature
Del2q37	25%–42%	ID, ADHD	Epilepsy, short stature, obesity, heart defect
Del3q29	27%	ID, speech delay, language disorder, anxiety disorder, schizophrenia, bipolar disorder	Gastrointestinal problems, heart defect, feeding problems, recurrent ear infections, abnormal dentition
Del5q14.3	43%	ID, absent speech	Epilepsy, capillary malformation
Dup7q11.23	41%	ID, ADHD, anxiety disorder, oppositional defiant disorders, speech delay	Epilepsy, macrocephaly, brachycephaly dilatation of ascending aorta, patent ductus arteriosus, chronic obstipation, kidney abnormalities
Del8p23		ID, ADHD	Heart defect, congenital diaphragmatic hernia
Dup15q11-q13	69%	ID, ADHD	Epilepsy, defect, muscle hypotonia, short stature

ID = intellectual disability.

Vorstman JAS, et al. *Nat Rev Genet*. 2017;18(6):362-376.

Recurrent Structural Abnormalities Associated with Autism Spectrum Disorders (cont'd)

	ASD Penetrance (rate of ASD in carriers)	Neuropsychiatric Pleiotropy (associated neuropsychiatric phenotypes)	Somatic Pleiotropy (associated somatic phenotypes)
Del15q11.2	32%	ID, ADHD, schizophrenia, OCD, speech delay	Epilepsy, ataxia, defect
Dup15q11.2	43%	ID, ADHD, speech delay	Epilepsy, ataxia, hypotonia
Dup15q13.2–q13.3	80%	ID, speech delay	Epilepsy, urogenital anomalies, recurrent infections
Del15q13.2–q13.3	60%	ID, ADHD	
Del16p11.2	15%	ID	Epilepsy, hypotonia, sacral dimples, speech articulation problems
Dup16p11.2		Schizophrenia, bipolar disorder	Epilepsy, hypotonia, tremor, ataxia, sacral dimples, speech articulation problems
Dup16p13.11	25%	ADHD, speech delay	Epilepsy
Del17p11.2	Unknown		Epilepsy
Del17q12		Schizophrenia	Macrocephaly, renal anomalies
Del22q11.2	30%	Schizophrenia, ADHD, speech delay, anxiety disorders	(amongst others:) Heart defect, palate abnormalities, hypocalcaemia, feeding difficulties, recurrent infections
Dup22q11.2	18%	ID, ADHD	Heart defect, hearing loss, urogenital anomalies, palate abnormalities
Del22q13.3	> 50%	ID, language disorder	Epilepsy, heart defect, renal anomalies, strabismus

Vorstman JAS, et al. *Nat Rev Genet*. 2017;18(6):362-376.

Genes Associated with Autism Spectrum Disorders by Sequencing Studies

	Chromosome Location	Estimated Percentage of Individuals with ASD in Whom This Variant is Identified	ASD Penetrance (rate of ASD in carriers)	Neuropsychiatric Pleiotropy (associated neuropsychiatric phenotypes)	Somatic Pleiotropy (associated somatic phenotypes)
KATNAL2	18q21.1	0.08%	Unknown	Unknown	Unknown
POGZ	1q21.3	0.08%	Incomplete	ID, speech delay, language delay, schizophrenia	Microcephaly Obesity Impaired vision
TBR1	2q24.2	0.08%	Unknown	ID	Unknown
ADNP	20q13.13	0.10%	Complete	ID, ADHD	Recurrent infections, short stature, heart defect, hypotonia, hypermetropia, epilepsy, hyperlaxity
SYNGAP1	6p21-32	0.10%	Unknown	ID	Epilepsy
GRIN2B	12p13.1	0.13%	Unknown	ID	Epilepsy
ANK2	4q25-q26	0.13%	Unknown	None reported	Heart arrhythmia
ARID1B	6q25.3	0.13%	Incomplete	ID, speech impairment	Short stature, hypertrichosis, cryptorchidism, epilepsy, vision impairment
SCN2A	2q24.3	0.13%	Incomplete	ID, schizophrenia	Epilepsy, episodic ataxia
DYRK1A	21q22.13	0.13%	Incomplete	ID, speech impairment, ADHD, anxiety	Microcephaly, epilepsy, vision impairment, short stature, gastrointestinal symptoms / feeding difficulties
CHD8	14q11.2	0.21%	Incomplete	ID, schizophrenia, speech delay, sleep problems	Macrocephaly, gastrointestinal symptoms

Vorstman JAS, et al. *Nat Rev Genet*. 2017;18(6):362-376.

Organizations Recommending Microarray Testing as Part of Autism Spectrum Disorders Workup

- American Academy of Child and Adolescent Psychiatry

Volkmar F, et al. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237-257.

- American Society of Human Genetics

Miller DT, et al. *Am J Hum Genet*. 2010;86(5):749-764.

- American Academy of Pediatrics

Moeschler JB, et al. *Pediatrics*. 2014;134(3):e903-e918.

- American Academy of Neurology

https://assets.thermofisher.com/TFS-Assets/LSG/brochures/AAN_13_ChromoMicroIntelDisabil.pdf

- International Society of Psychiatric Genetics

https://ispg.net/

- American College of Medical Genetics and Genomics

Schaefer GB, et al. *Genet Med*. 2013;15(5):399-407.

ISPG Statement on Testing for Autism Spectrum Disorders/Intellectual Disability, 2019

Many genetic causes of ID and ASD have been identified. There are now several hundred genes in which copy number and single-gene variants with large effects on brain function cause syndromic or non-syndromic ID and/or ASD. Fragile X molecular testing and CMA, which detects CNV across the entire genome, have long been considered standard of care for the etiological evaluation of global developmental delay, ID, and/or ASD. If such tests fail to establish a diagnosis, a targeted gene panel or WES may be indicated. Although consensus recommendations await publication, WES is available clinically in many countries and is increasingly used as a first-tier test for the evaluation of ID or ASD. Multiple studies have shown that a combination of CMA and WES provides a genetic diagnosis in at least 25% of patients with these conditions. A molecular diagnosis can have important clinical implications and personal utility for patients, and may help inform life planning, access to public benefits, and recurrence risk assessment in relatives.

CMA = chromosomal microarray analysis; WES = whole exome sequencing.

McMahon F, et al. Statement from ISPG Genetic Testing Committee. www.ISPG.net/committees. Accessed July 26, 2019. Schaefer GB, et al. *Genet Med*. 2013;15(5):399-407. Mefford HC, et al. *N Engl J Med*. 2012;366(8):733-743. Moeschler JB, et al. *Pediatrics*. 2014;134(3):e903-e918. Vissers LE, et al. *Nat Rev Genet*. 2016;17(1):9-18.

Variable Implementation of Guidelines

- 80% of parents of individuals with ASD in a Texas study reported receiving no information about genetics
- 34% of children with ASD received genetic testing in a survey of 3371 patients with developmental delay
- Selection of patients for testing only when there are somatic features, low IQ, or dysmorphism is likely to capture only a fraction of cases

Li M, et al. *Patient Educ Couns*. 2016;99(6):1011-1016. Kiely B, et al. *Appl Clin Genet*. 2016;9:93-100.

Why is genetic testing lagging in Autism Spectrum Disorders?

- **Belief that clinical rationale is insufficient**

Solution – Dissemination of information about improved reproductive decision-making

- **Third party payment issues**

Solution – This is improving steadily but more effort on the part of advocacy groups is needed

Why is genetic testing lagging in Autism Spectrum Disorders?

- **Clinician discomfort with genetic testing and its interpretation**

Solution – Involvement of experts. Also increased genetics education for psychiatrists

- This is a goal of the NIMH-funded NNCI program, the NHGRI-funded ISCC program, and the ISPG Task Force

ISCC = Inter-Society Coordinating Committee for Practitioner Education in Genomics; NIMH = National Institute of Mental Health; NNCI = National Neuroscience Curriculum Initiative.

Reasons for Testing

- Diagnostic certainty for the family (and avoidance of unnecessary tests/procedures/treatments)
- Identification of syndromes
- Prognostic significance
- Recurrence risk (what is the chance of an additional case in a sibling or other relative)
- Treatment implications for some known disorders
- Accumulation of knowledge on specific syndromes/loci

Yield of General Medical Screening Tests

- 1508 laboratory tests in 531 patients
- 73 new diagnoses (4.8%) and 60 new therapies (4.0%)
- The range for therapeutic yield varied from 16.5% (lipid profile) to thyroid tests (0.7%)
- CBC was 0.9% and chemistry panel 2.8%

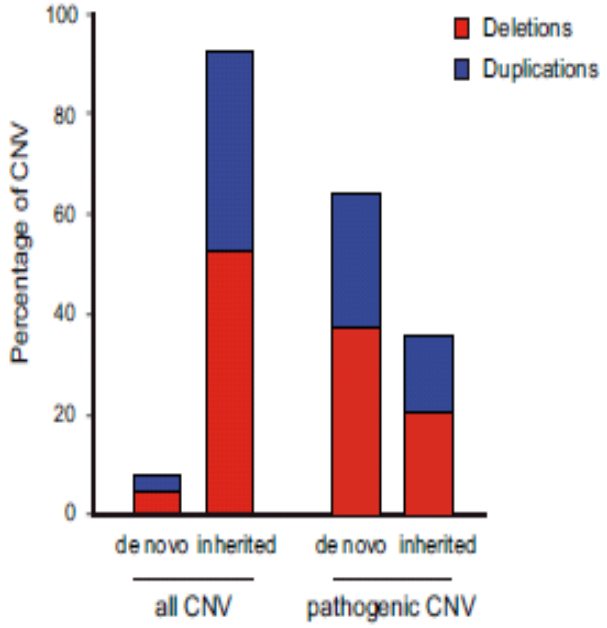
Boland BJ, et al. *Am J Med*. 1996;101(2):142-152.

Chromosomal Microarray Analysis Value to the Family

- Two-thirds of 50 parents receiving genetic testing results felt that they were helpful for the family
- Recurrence risk of ASD with 1 affected sibling is 10% to 15%
- However recurrence risk for an inherited variant (eg, a 22q deletion) is 50%
- This information may also be relevant to other family members (who may be carriers)

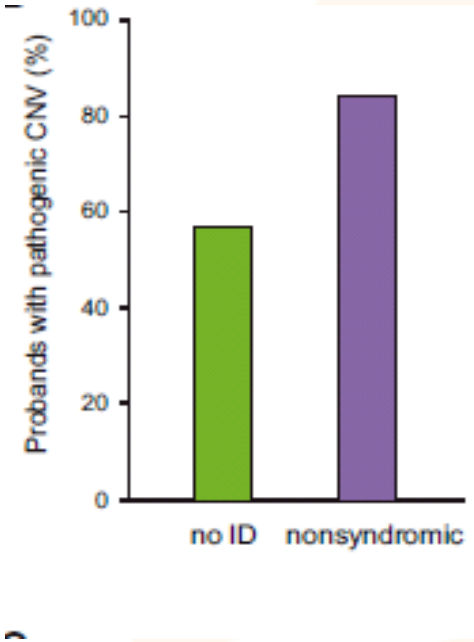
Reiff M, et al. *J Autism Dev Disord*. 2015;45(10):3262-3275. Wood CL, et al. *Autism Res*. 2015;8(1):73-81.

One-third of Pathogenic Variants are Inherited



Pinto D, et al. *Am J Hum Genet*. 2014;94(5):677-694.

Most Individuals with Autism Spectrum Disorders with a CNV are Non-syndromic and Not Intellectually Disabled



Pinto D, et al. *Am J Hum Genet*. 2014;94(5):677-694.

What about treatment? (precision medicine)

- There is some evidence that genetic similarity predicts response of individuals with ASD to methylphenidate or risperidone

- Novel compounds being tested for ASD based on genetic results include mTOR inhibitors, metabotropic glutamate receptor antagonists, glutathione, memantine, and riluzole

mTOR = mammalian target of rapamycin.

McCracken JT, et al. *Pharmacogenomics J*. 2014;14(3):295-302. Correia CT, et al. *Pharmacogenomics J*. 2010;10(5):418-430. Hoekstra PJ, et al. *J Child Adolesc Psychopharmacol*. 2010;20(6):473-477. Nurmi EL, et al. *Transl Psychiatry*. 2013;3:e274.

Specific Treatments for Autism Spectrum Disorder Symptoms Based on Genetics

- Galantamine for patients with 15q13.3 deletion (*CHRNA7* disruption)
- S-adenosyl methionine treatment for patients with Lesch-Nyhan syndrome
- Weight-neutral neuroleptics for patients with 17q12 deletion (risk for both psychosis and diabetes)
- Assistive communication strategies for patients with a *SHANK3* deletion

Cubells JF, et al. *Am J Med Genet A*. 2011;155A(4):805-810. Glick N. *J Inherit Metab Dis*. 2006;29(5):687. Chen BC, et al. *Brain Dev*. 2014;36(7):593-600. Moreno-De-Luca D, et al. *Am J Hum Genet*. 2010;87(5):618-630. Phelan K, et al. *Mol Syndromol*. 2012;2(3-5):186-201.

Need for Genetic Counseling for Parents of Individuals with Autism Spectrum Disorders

- Most parents surveyed in the United States (N=397) and United Kingdom (N=380) want to learn about genetic factors related to their child's condition

- Many in the UK study said that their child's ASD affected their reproductive decision-making; however the majority in both studies substantially overestimated the recurrence risk (10%–15%) by a factor of 2–4 or more

Cuccaro ML, et al. *Am J Med Genet A*. 2014;164A(10):2592-2600. Parr JR, et al. *J Autism Dev Disord*. 2011;41(3):332-340. Wood CL, et al. *Autism Res*. 2015;8(1):73-81.

Pharmacogenomics

Genetic Testing for Susceptibility to Serious Carbamazepine/Oxcarbazepine Side Effects

- **FDA:** TEN and SJS, have been reported during treatment with carbamazepine
- General risk 1–6/10,000; up to 10× higher in some Asian countries
- Studies in patients of Han Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of *HLA-B*15:02* (sensitivity and specificity both > 95%)
- *FDA recommends HLA-B testing in patients with Asian ancestry prior to* starting carbamazepine
- Prior use for > 3 months without symptoms may be considered as an indication of safety
- Newer data suggests that oxcarbazepine should be avoided as well in persons with *HLA-B*15:02,* and implicates *HLA-A*31:01* as a risk factor for SJS/TEN with carbamazepine treatment. “In European, African, and Japanese populations where the carriage rate of *HLA-B*15:02* is less than 1%, *HLA-A*31:01* appears to be the primary driver of carbamazepine-induced SJS/TEN and other hypersensitivity reactions.”

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Dean L. In: Pratt V, et al (Ed). *Medical Genetics Summaries*. Bethesda, MD: National Center for Biotechnology Information (US); 2015 Oct 14. Phillips EJ, et al. *Clin Pharmacol Ther*. 2018;103(4):574-581.

2 Specific Enzymes Have Figured in FDA Warnings for Antidepressants

- Patients who are slow metabolizers based on CYP2C19 should not receive doses of citalopram greater than 20 mg daily

www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related

- There is a similar warning for doses of vortioxetine greater than 10 mg for slow metabolizers based on CYP2D6

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204447s007lbl.pdf

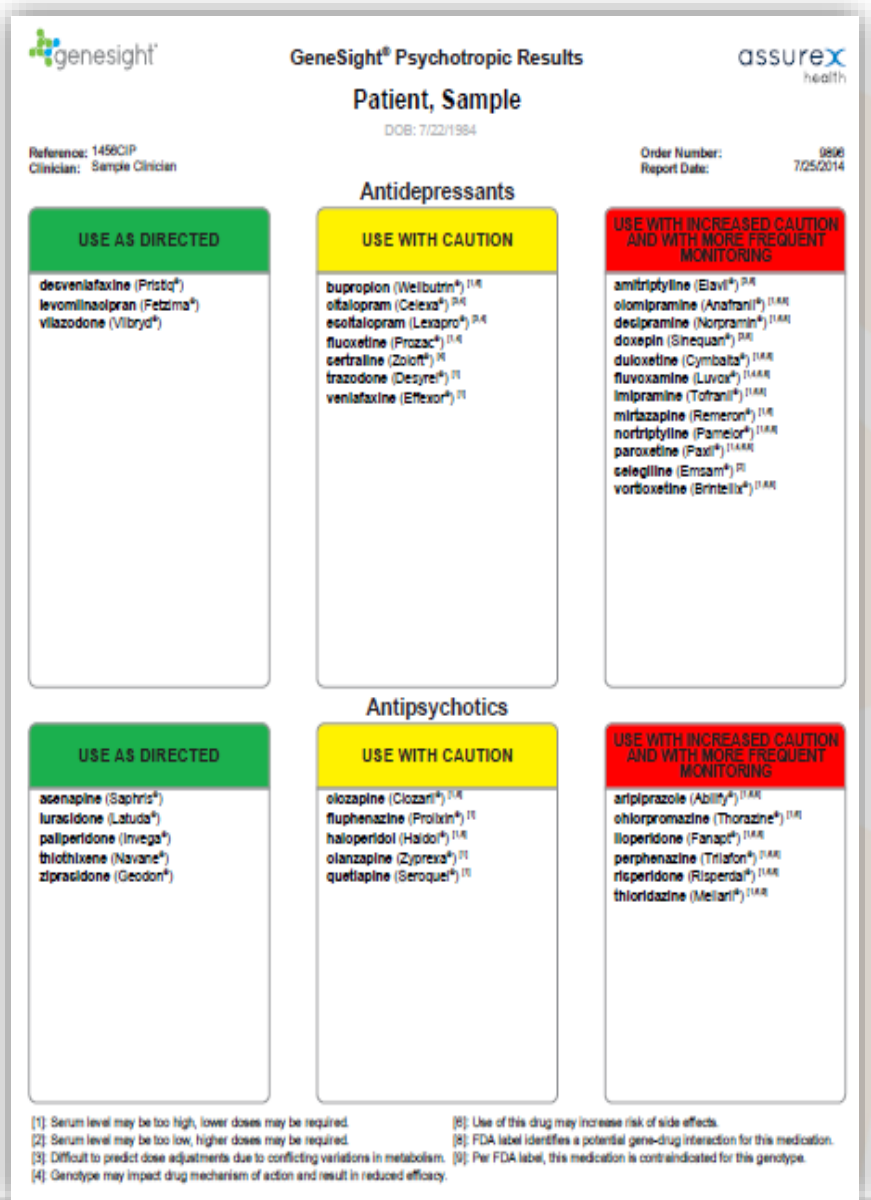
- More specific information is available from the Clinical Pharmacogenetics Implementation Consortium web site

https://cpicpgx.org/

ISPG Statement on Testing for Choice of Treatment, 2019

Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. We recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.

The GeneSight® Psychotropic Report



genesight

GeneSight® Psychotropic Results

assurex health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9896
Report Date: 7/25/2014

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®) **levomilnacipran** (Fetzima®) **vilazodone** (Viibryd®)	**bupropion** (Wellbutrin®) [1,4] **citalopram** (Celexa®) [3,4] **escitalopram** (Lexapro®) [3,4] **fluoxetine** (Prozac®) [1,4] **sertraline** (Zoloft®) [4] **trazodone** (Desyrel®) [7] **venlafaxine** (Effexor®) [7]	**amitriptyline** (Elavil®) [2,8] **clomipramine** (Anafranil®) [1,8,9] **desipramine** (Norpramin®) [1,8,9] **doxepin** (Sinequan®) [2,8] **duloxetine** (Cymbalta®) [1,8,9] **fluvoxamine** (Luvox®) [1,4,8,9] **imipramine** (Tofranil®) [1,8,9] **mirtazapine** (Remeron®) [1,9] **nortriptyline** (Pamelor®) [1,8,9] **paroxetine** (Paxil®) [1,4,8,9] **selegiline** (Emsam®) [9] **vortioxetine** (Brintellix®) [1,8,9]

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
asenapine (Saphris®) **lurasidone** (Latuda®) **paliperidone** (Invega®) **thiothixene** (Navane®) **ziprasidone** (Geodon®)	**olozapine** (Clozaril®) [1,9] **fluphenazine** (Prolixin®) [1] **haloperidol** (Haldol®) [1,9] **olanzapine** (Zyprexa®) [1] **quetiapine** (Seroquel®) [1]	**aripiprazole** (Abilify®) [1,8,9] **chlorpromazine** (Thorazine®) [1,9] **iloperidone** (Fanapt®) [1,8,9] **perphenazine** (Trilafon®) [1,8,9] **risperidone** (Risperdal®) [1,8,9] **thioridazine** (Mellaril®) [1,8,9]

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[8]: FDA label identifies a potential gene-drug interaction for this medication.
[9]: Per FDA label, this medication is contraindicated for this genotype.

Footnotes Explain a Medication's Category

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®)	**bupropion** (Wellbutrin®) [1,6]	**amitriptyline** (Elavil®) [3,8]
levomilnacipran (Fetzima®)	**citalopram** (Celexa®) [3,4]	**clomipramine** (Anafranil®) [1,6,8]
vilazodone (Viibryd®)	**escitalopram** (Lexapro®) [3,4]	**desipramine** (Norpramin®) [1,6,8]
	fluoxetine (Prozac®) [1,4]	**doxepin** (Sinequan®) [3,8]
	sertraline (Zoloft®) [4]	**duloxetine** (Cymbalta®) [1,6,8]
	trazodone (Desyrel®) [1]	**fluvoxamine** (Luvox®) [1,4,6,8]
	venlafaxine (Effexor®) [1]	**imipramine** (Tofranil®) [1,6,8]
		mirtazapine (Remeron®) [1,6]
		nortriptyline (Pamelor®) [1,6,8]
		paroxetine (Paxil®) [1,4,6,8]
		selegiline (Emsam®) [2]
		vortioxetine (Brintellix®) [1,6,8]

[1]: Serum level may be too high, lower doses may be required.
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[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[8]: FDA label identifies a potential gene-drug interaction for this medication.
[9]: Per FDA label, this medication is contraindicated for this genotype.

genesight

GeneSight® Psychotropic Results

assurex health

Patient Genotypes and Phenotypes

Pharmacokinetic Genes

CYP2D6	Poor Metabolizer	*4/*4

CYP2D6 *4: This allele produces no enzyme activity.
CYP2D6 *4: This allele produces no enzyme activity.

Comment: This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP2C19	Ultrarapid Metabolizer	*17/*17

CYP2C19 *17: This allele produces increased enzyme activity.
CYP2C19 *17: This allele produces increased enzyme activity.

Comment: This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

CYP2C9	Intermediate Metabolizer	*1/*2

CYP2C9 *1: This allele produces normal enzyme activity.
CYP2C9 *2: This allele produces reduced enzyme activity.

Comment: This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP3A4	Extensive Metabolizer	*1/*1

CYP3A4 *1: This allele produces normal enzyme activity.
CYP3A4 *1: This allele produces normal enzyme activity.

Comment: This genotype is most consistent with the extensive metabolizer (normal) phenotype.

CYP2B6	Extensive Metabolizer	*1/*1

CYP2B6 *1: This allele produces normal enzyme activity.
CYP2B6 *1: This allele produces normal enzyme activity.

Comment: This genotype is most consistent with the extensive metabolizer (normal) phenotype.

CYP1A2	Extensive Metabolizer	*1/*1

This genotype is most consistent with the extensive metabolizer (normal) phenotype.

Pharmacodynamic Genes

SLC6A4	Reduced Response	S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may experience a delayed response with selective serotonin reuptake inhibitors, or may benefit from non-selective antidepressants.

HTR2A	Reduced Activity	G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

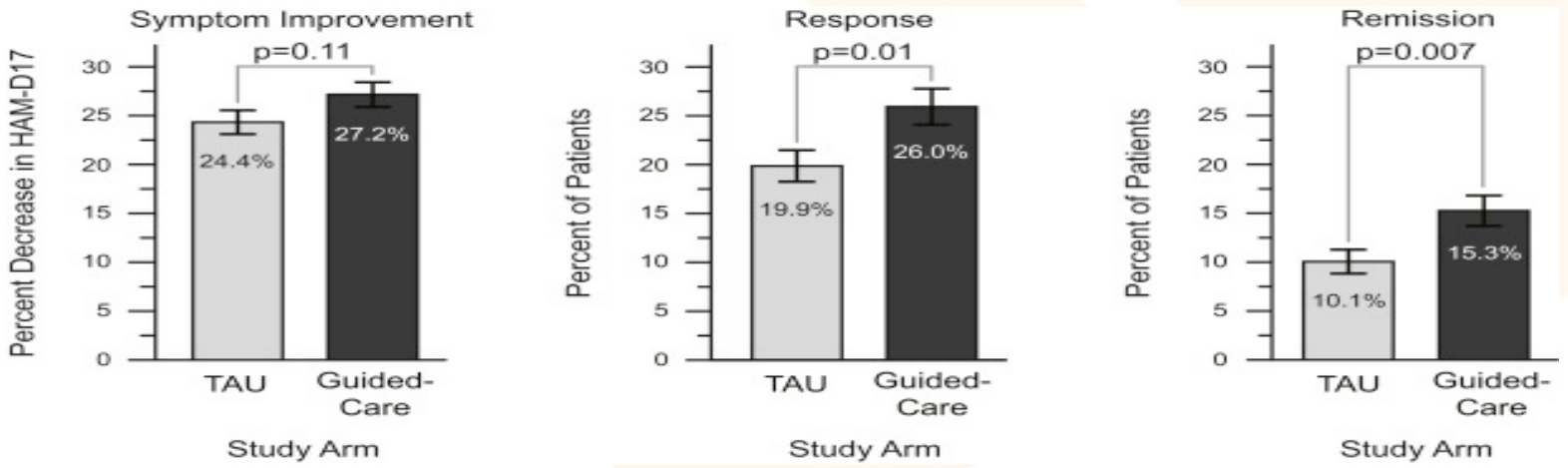
Genomics Used to Improve DEpression Decisions (GUIDED) Trial

- Outpatients (N=1167) diagnosed with MDD and with a patient- or clinician-reported inadequate response to at least 1 antidepressant were enrolled in the GUIDED trial – a rater- and patient-blind RCT
- Patients were randomized to TAU or a pharmacogenomics-guided intervention arm in which clinicians had access to a pharmacogenomic test report to inform medication selections (guided-care)
- Medications were considered congruent ("use as directed" or "use with caution" test categories) or incongruent ("use with increased caution and with more frequent monitoring" test category) with test results
- Unblinding occurred after week 8
- Primary outcome was symptom improvement (change HAM-D-17) at week 8; secondary outcomes were response (≥ 50% decrease in HAM-D-17) and remission (HAM-D-17 ≤ 7) at week 8
- At week 8, symptom improvement for guided-care was not significantly different than TAU (27.2% vs 24.4%, *P*=.107); however, improvements in response (26.0% vs 19.9%, *P*=.013) and remission (15.3% vs 10.1%, *P*=.007) were statistically significant
- Patients taking incongruent medications prior to baseline who switched to congruent medications by week 8 experienced greater symptom improvement (33.5% vs 21.1%, *P*=.002), response (28.5% vs 16.7%, *P*=.036), and remission (21.5% vs 8.5%, *P*=.007) compared to those remaining incongruent

HAM-D-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; RCT = randomized controlled trial; TAU = treatment as usual.

Greden JF, et al. *J Psychiatr Res*. 2019;111:59-67.

GUIDED Trial (cont'd)



N=560 for TAU; N=607 for guided care.
Greden JF, et al. *J Psychiatr Res*. 2019;111:59-67.

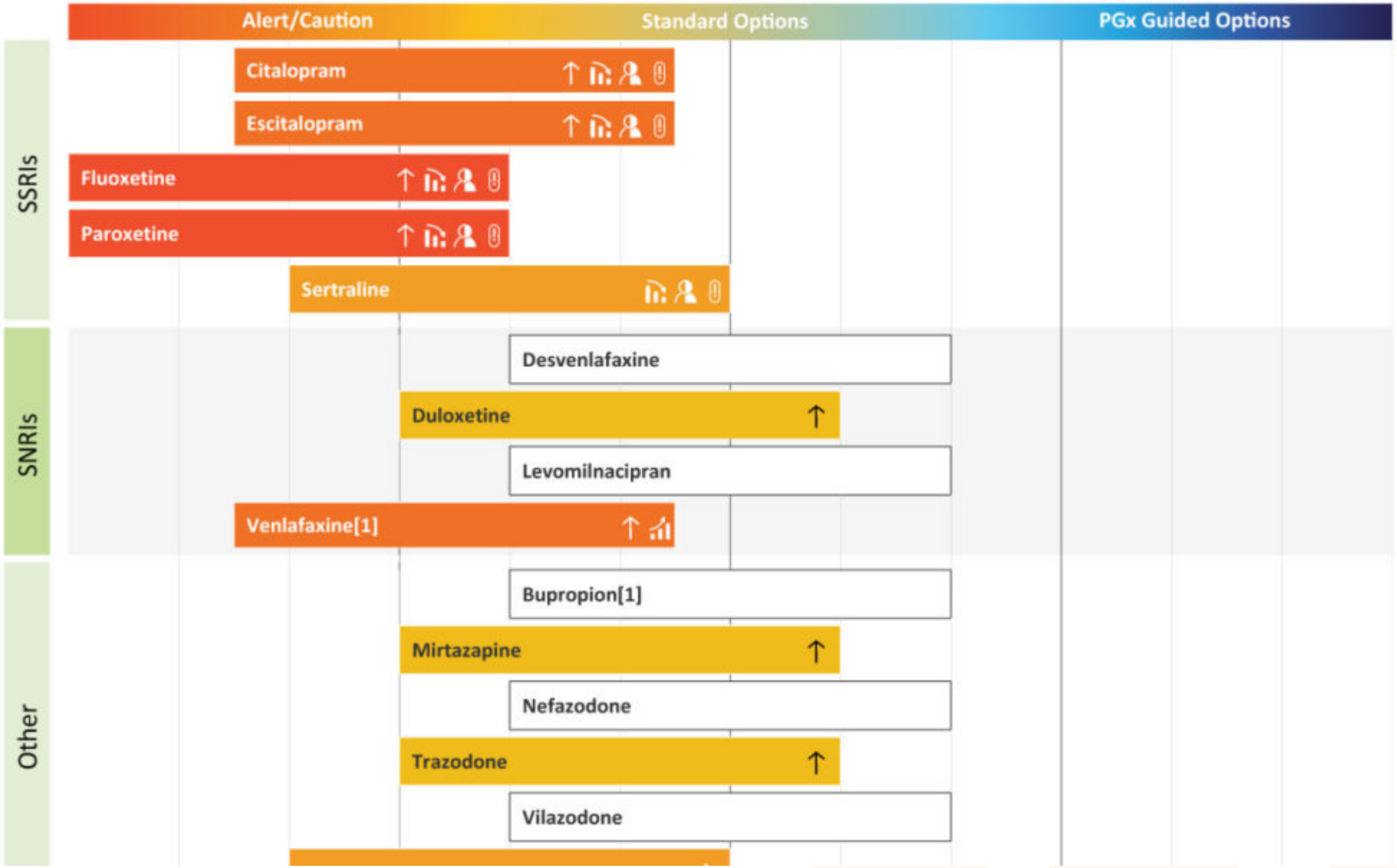
I. PHARMACODYNAMIC GENE VARIATIONS

GENE RESULT	THERAPEUTIC IMPLICATIONS	GUIDE	CLINICAL IMPACT
SLC6A4 S/S [Low Activity]	***Serotonin Transporter (SLC6A4)*** *is a synaptic transporter protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • In Caucasians, **lower likelihood of remission and increased side effect risk with SSRIs** • Potential for increased cortisol release in response to stress		**Assess alternatives to SSRIs** in Caucasians **Therapeutic options: SNRIs** or other **non-SSRI antidepressants** may be considered if clinically indicated
BDNF Val/Met [Altered BDNF secretion]	***Brain-derived Neurotrophic Factor (BDNF)*** *is a protein involved in neuronal development and neural plasticity* • Studies have shown that **Met carriers of *Caucasian ancestry*** may have a **poorer response to SSRIs**, and **improved response to SNRIs or TCAs**, however further studies need to confirm these findings • Studies show that **Met carriers of *Asian ancestry*** may have an **improved response to SSRIs** • **Exercise** has been linked to improvements in cognition and stress response, with **Met carriers showing a more pronounced response**		**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate **Ethnicity dependent antidepressant response**
MTHFR C677T: C/T A1298C: A/C [Low to intermediate activity]	***Methylenetetrahydrofolate Reductase (MTHFR)*** *is an enzyme responsible for the conversion of folic acid to methylfolate which is a cofactor needed for serotonin, norepinephrine, and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • **L-methylfolate supplementation** of SSRIs and SNRIs may result in greater symptom reduction compared to SSRIs/SNRIs alone in major depressive disorder • L-methylfolate may be an effective monotherapy for patients with major depressive disorder		**Therapeutic options: L-methylfolate** may be used if clinically indicated

III. GENE DRUG INTERACTION SUMMARY

CLASS	MEDICATION	PHARMACODYNAMIC ASSOCIATIONS	PHARMACODYNAMIC GENE	DRUG EXPOSURE	PHARMACOKINETIC GENE
	ANTIDEPRESSANTS				
SSRIs	**Citalopram** (Celexa®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2C19, P-gp
SSRIs	**Escitalopram** (Lexapro®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2C19, P-gp
SSRIs	**Fluoxetine** (Prozac®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 2C9
SSRIs	**Fluvoxamine** (Luvox®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 1A2, P-gp
SSRIs	**Paroxetine** (Paxil®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, P-gp
SSRIs	**Sertraline** (Zoloft®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF		2C19, 2B6
	Desvenlafaxine (Pristiq®)				

IV. DEPRESSION SUMMARY



Brennan FX, et al. A Naturalistic Study of the Effectiveness of Pharmacogenetic Testing to Guide Treatment in Psychiatric Patients With Mood and Anxiety Disorders. *Prim Care Companion CNS Disord*. 2015;17(2).

All Gene Report

⊗	A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.	
⚠	Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.	
✓	The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.	
		ACTIONABLE Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.
		INFORMATIVE There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Current Patient Medications

Clopidogrel, Aspirin

⊗ **Clopidogrel** | PLAVIX — **ACTIONABLE**

Significantly Reduced Response to Clopidogrel (CYP2C19: Poor Metabolizer)

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Psychotropic	Anticonvulsants	Carbamazepine (Tegretol, Carbatrol, Epitol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal, Oxtellar XR) Perampanel (Fycompa) Pregabalin (Lyrica) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril)	Brivaracetam (Briviact) Fosphenytoin (Cerebyx) Phenobarbital (Luminal) Phenytoin (Dilantin) Primidone (Mysoline) Zonisamide (Zonegran)	
	Antidementia Agents	Galantamine (Razadyne) Memantine (Namenda)	Donepezil (Aricept)	
	Antidepressants	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Nefazodone (Serzone) Trazodone (Oleptro) Vilazodone (Viibryd) Vortioxetine (Trintellix)	Amoxapine (Amoxapine) Citalopram (Celexa) Escitalopram (Lexapro) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Sertraline (Zoloft)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)

Dosing Guidance

Amitriptyline
Elavil

Non-Response to Amitriptyline (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

Consider an alternative drug, or prescribe amitriptyline at an increased dose and monitor the plasma concentration of amitriptyline and metabolites.

Atomoxetine
Strattera

Non-Response to Atomoxetine (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient may fail to achieve adequate plasma levels of atomoxetine if the drug is prescribed at standard recommended doses. Consider prescribing atomoxetine with careful titration and monitoring for reduced efficacy. There is insufficient data to calculate dose adjustment. Or consider an alternative medication.

Clomipramine
Anafranil

Non-Response to Clomipramine (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

Consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

Test Details

Gene	Genotype	Phenotype	Clinical Consequences
CYP2C19	*8/*8	Poor Metabolizer	Consistent with a significant deficiency in CYP2C19 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP2C9	*11/*11	Poor Metabolizer	Consistent with a significant deficiency in CYP2C9 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP2D6	*1/*1 XN	Ultra-Rapid Metabolizer	Consistent with a significant increase in CYP2D6 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP3A4	*17/*17	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*1/*1	Normal Metabolizer	Consistent with a normal CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
Factor II Factor V Leiden	20210G>A AA 1691G>A GG	No Increased Risk of Thrombosis	The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.
MTHFR	677C>T CC	Normal MTHFR Activity	The patient does not carry the MTHFR C677T mutation (wild-type) and the patient's MTHFR activity is normal. This is not associated with an increased risk of hyperhomocysteinemia.

Pharmacogenomic Tests – Skepticism is Warranted

- Available commercial tests contain a combination of well-supported assessments (eg, CYP2D6) and poorly-supported tests (eg, serotonin transporter assessment – 5-HTLPR)
- Commercial tests generally make recommendations based on proprietary algorithms that combine information from multiple gene variants using rules that are not revealed to practitioners or consumers
- Most testing companies have not conducted controlled trials of their products (an exception is Assurex, and those results were equivocal)
- Peer-reviewed meta-analyses have thus far been critical or modestly positive
- The best supported testing is probably related to CYP2D6 and CYP2C19; even with these enzymes it is not clear that commercial tests provide the best coverage for relevant gene variants

Rosenblat JD, et al. *J Clin Psychiatry*. 2017;78(6):720-729. Rosenblat JD, et al. *J Affect Disord*. 2018;241:484-491. Bousman CA, et al. *Pharmacogenet Genomics*. 2017;27(11):387-393. Solomon HV, et al. *Psychiatry Res*. 2019;271:604-613.

Polygenic Risk Scores

What are polygenic risk scores?

- The methods for calculating PRS have been developed in the last 10 years as a tool to capture the cumulative effects of many genetic loci into a single quantitative metric
- This quantitative score sums the effects of individually associated SNPs from an independent GWAS, enumerates how many risk alleles are carried by that individual at each locus (0, 1, or 2), and weights the risk allele at each locus by (the logarithm of) its effect size. A risk allele is defined as a gene variant that is more commonly found in cases than controls
- PRS can be calculated using different sets of disease-associated variants, and typically different *P*-value thresholds for disease association are used to create a series of PRS for a particular disease or trait
- The common practice is to perform genetic prediction using many independent risk allele SNPs across the genome – including many hundreds of thousands of variants

PRS = polygenic risk scores.

Fullerton JM, Nurnberger JI. *Faculty of 1000*. 2019; In Press.

Predictive Power of Polygenic Risk Scores

- This approach yields greater predictive power across many psychiatric disorders, maximizing the predictive power for discrimination between cases and controls to 82% for schizophrenia, 65% for bipolar disorder, 58% for MDD, and 54% for anxiety

So HC, et al. *Bioinformatics*. 2017;33(6):886-892.

Polygenic Risk Scores: *Limitations and Caveats*

- Informativity of discovery sample
  - Size
  - Exact phenotype
- Independence of discovery sample
- Ethnicity of sample
- PRS includes only common variants

Increasing Predictive Power of Polygenic Risk Scores

- Statistical methods
- Weighting by gene expression or other biological processes
- Increasing sample size for discovery sample

Khera AV, et al. *Nat Genet*. 2018;50(9):1219-1224. Wang D, et al. *Science*. 2018;362(6420).

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

Khera AV, et al. *Nat Genet*. 2018;50(9):1219-1224.

GPS Derivation and Testing for 5 Common, Complex Diseases

Disease	Discovery GWAS (*n*)	Prevalence in validation dataset	Prevalence in testing dataset	Polymorphisms in GPS	Tuning parameter	AUC (95% CI) in validation dataset	AUC (95% CI) in testing dataset
CAD	60,801 cases; 123,504 controls[16]	3,963/120,280 (3.4%)	8,676/288,978 (3.0%)	6,630,150	LDPred ($\rho = 0.001$)	0.81 (0.80–0.81)	0.81 (0.81–0.81)
Atrial fibrillation	17,931 cases; 115,142 controls[30]	2,024/120,280 (1.7%)	4,576/288,978 (1.6%)	6,730,541	LDPred ($\rho = 0.003$)	0.77 (0.76–0.78)	0.77 (0.76–0.77)
Type 2 diabetes	26,676 cases; 132,532 controls[31]	2,785/120,280 (2.4%)	5,853/288,978 (2.0%)	6,917,436	LDPred ($\rho = 0.01$)	0.72 (0.72–0.73)	0.73 (0.72–0.73)
Inflammatory bowel disease	12,882 cases; 21,770 controls[32]	1,360/120,280 (1.1%)	3,102/288,978 (1.1%)	6,907,112	LDPred ($\rho = 0.1$)	0.63 (0.62–0.65)	0.63 (0.62–0.64)
Breast cancer	122,977 cases; 105,974 controls[33]	2,576/63,347 (4.1%)	6,586/157,895 (4.2%)	5,218	Pruning and thresholding ($r^2 < 0.2$; $P < 5 \times 10^{-4}$)	0.68 (0.67–0.69)	0.69 (0.68–0.69)

AUC was determined using a logistic regression model adjusted for age, sex, genotyping array, and the first four principal components of ancestry. The breast cancer analysis was restricted to female participants. For the LDPred algorithm, the tuning parameter ρ reflects the proportion of polymorphisms assumed to be causal for the disease. For the pruning and thresholding strategy, r^2 reflects the degree of independence from other variants in the linkage disequilibrium reference panel, and P reflects the P value noted for a given variant in the discovery GWAS. CI, confidence interval.

GPS = genome-wide polygenic score.

Khera AV, et al. *Nat Genet*. 2018;50(9):1219-1224.

Proportion of the Population at 3-, 4-, and 5-fold Increased Risk for Each of the 5 Common Diseases

High GPS definition	Individuals in testing dataset (*n*)	% of individuals
Odds ratio ≥ 3.0		
CAD	23,119/288,978	8.0
Atrial fibrillation	17,627/288,978	6.1
Type 2 diabetes	10,099 288,978	3.5
Inflammatory bowel disease	9,209 288,978	3.2
Breast cancer	2,369/157,895	1.5
Any of the five diseases	57,115/288,978	19.8
Odds ratio ≥ 4.0		
CAD	6,631/288,978	2.3
Atrial fibrillation	4,335/288,978	1.5
Type 2 diabetes	578/288,978	0.2
Inflammatory bowel disease	2,297/288,978	0.8
Breast cancer	474/157,895	0.3
Any of the five diseases	14,029/288,978	4.9
Odds ratio ≥ 5.0		
CAD	1,443/288,978	0.5
Atrial fibrillation	2,020 288,978	0.7
Type 2 diabetes	144/288,978	0.05
Inflammatory bowel disease	571/288,978	0.2
Breast cancer	158/157,895	0.1
Any of the five diseases	4,305/288,978	1.5

Khera AV, et al. *Nat Genet*. 2018;50(9):1219-1224.

Summary

- An understanding of genetic principles and findings is increasingly valuable in psychiatric practice
- Training programs are generally underserved in this regard
- Genetic testing is part of a clinical workup for ASD/ID
- Pharmacogenomic testing is necessary in some circumstances, but not widely indicated
- Newer methods, such as sequencing and polygenic risk score testing, will likely find clinical application in the near future

Genetic Testing for Clinicians
For ASD/Neurodevelopmental Disorders

- *Should you test*?

Yes, as part of a medical evaluation, genetic testing is indicated

- *What kind of testing should be done*?

Chromosomal microarray and Fragile X testing are standard; whole exome testing may be considered as well

- *When to test*?

Ideally during an initial evaluation in childhood. Testing may still offer additional information for adult patients not previously tested

- *Who does the testing and interpretation*?

A university-based genetics department with genetic counseling expertise is recommended

- *Is this covered by insurance*?

Usually, but not always. It is wise to check in advance

Genetic Testing for Clinicians
For Choice of Antidepressant

- *Should you test*?

Generally not, but consider it for

1. Patients not responding to ≥ 2 antidepressants
2. Patients who are not tolerating treatment with ≥ 2 antidepressants

- *What kind of testing*?

The most valuable information is the patient's status on the metabolic enzymes 2D6 and 2C19. A number of companies offer this as part of a package, or you can order them independently. Take company specific drug recommendations with a grain of salt

- *Is this covered by insurance*?

Often it is. Checking in advance is advisable

Genetic Testing for Clinicians
For Choice of a Mood Stabilizer

- If you are considering starting carbamazepine or oxcarbazepine (if the patient has already been on these ≥ 3 months, it is not necessary)
- It is wise to check HLA status in advance. This is especially true if the patient is of Asian descent, but it is best to check in any case. Reason: To avoid SJS or TEN

➢ *What to check*?

HLA-A and B; the risk genotypes are *HLA-B*15:02* and *HLA-A*31:01*

➢ Who does the testing?

Many medical genetics laboratories will do this. You can also get this information as part of commercial pharmacogenomic screens (some, but not all)

➢ Is this covered by insurance?

Generally

Genetic Testing for Clinicians
For Diagnosis of a Major Psychiatric Disorder

- Testing is generally not recommended at this time

- However, it might be considered in certain situations
  - Multiple siblings in a family are affected
  - A severe condition with onset in childhood
  - The disorder appears to be part of a syndrome (physical stigmata or multisystem involvement)

➢ *What kind of testing*?

- Chromosomal microarray
- Polygenic risk scores are available now, but not likely to be recommended for clinical use in the next several years