Personalized Medicine: Is Genotyping Ready for Prime Time in Psychiatry?

(page 51 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

Stephen M. Stahl, MD, PhD, is an adjunct professor in the department of psychiatry at the University of California, San Diego School of Medicine, and an honorary visiting senior fellow at the University of Cambridge in the UK.

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Speakers Bureau: Dainippon Sumitomo, Forest, Lilly, Merck, Pamlab, Pfizer, Sepracor/Sunovion, Servier, Wyeth
Learning Objectives

• Identify the potential use of pharmacogenetics for optimal patient care

• Explain the molecular principles underlying personalized medicine

• Identify the genetic polymorphisms associated with various mental health disorders and treatment responses

• Interpret pharmacogenomic test results and communicate the findings to patients and families
Pretest Question 1

The patient is a 46-year-old man who has not responded to 3 sequential antidepressant monotherapies. Genetic testing reveals that he is heterozygous for the -141C Insertion/Deletion allele (Ins/Del) for the dopamine 2 receptor gene (DRD2). Based solely on this genetic result, would an atypical antipsychotic be preferred as an augmenting agent for this patient?

1. Yes
2. No
Pretest Question 2

A 34-year-old patient with depression has the S/S genotype for the serotonin transporter gene (SLC6A4). Based solely on this genetic result, what treatment might be preferred for this patient?

1. Selective serotonin reuptake inhibitor
2. Serotonin norepinephrine reuptake inhibitor
3. Noradrenergic tricyclic antidepressant
A 24-year-old woman with depression has just had genetic testing, including testing of the genes for catechol-O-methyltransferase (COMT) and methylenetetrahydrofolate reductase (MTHFR). Her symptoms are theoretically consistent with severe dopamine deficiency with apathy, anhedonia, psychomotor retardation, and cognitive slowing. Based on current literature, what genetic testing results might be most likely?

1. COMT Val/Val and MTHFR (T/T) or (C/T)
2. COMT Val/Val and MTHFR (C/C)
3. COMT Met/Met and MTHFR (T/T) or (C/T)
4. COMT Met/Met and MTHFR (C/C)
Genetics & Epigenetics

**GENETICS**
The sequence of DNA that is inherited

**EPIGENETICS**
The process of determining if a given gene is expressed

### Genes Relevant to Psychiatric Illness Risk and/or Treatment Response

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>SLC6A4</td>
<td>Serotonin transporter (SERT), also called serotonin reuptake pump, responsible for termination of serotonin action</td>
</tr>
<tr>
<td>Dopamine</td>
<td>DRD2</td>
<td>Dopamine 2 receptor, target of antipsychotic drugs, theoretically overactive in psychosis and underactive in Parkinson's disease</td>
</tr>
<tr>
<td>Glutamate</td>
<td>CACNA1C</td>
<td>Voltage-gated channel for calcium</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP450</td>
<td>Hepatic enzyme system that metabolizes many psychotropic drugs</td>
</tr>
<tr>
<td>Dopamine</td>
<td>COMT</td>
<td>Enzyme responsible for degradation of dopamine and norepinephrine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>MTHFR</td>
<td>Predominant enzyme that converts inactive folic acid to active folate</td>
</tr>
</tbody>
</table>
SLC6A4
(Serotonin Transporter)
SLC6A4
(Serotonin Transporter)
SLC6A4 Polymorphisms and Serotonergic Activity

IF

SLC6A4 activity is:  SERT expression is:  5HT reuptake is:  Synaptic 5HT is:

High \([L(A)/L(A)]\)

Low \([\text{presence of } S \text{ or } L(G)]\)
SLC6A4, Stress, and Depression

• Caspi et al.: 5-HTTLPR S allele associated with greater sensitivity to stress

• 55 follow-up studies assessing if 5-HTTLPR moderates relationship between stress and depression

• 2 meta-analyses of a subset of those studies found no association

• More recent meta-analysis included all relevant studies (54) exploring the interaction

SLC6A4, Stress, and Depression: Karg et al. Meta-Analysis

- Included 54 studies
- 5-HTTLPR S allele associated with increased risk of developing depression under stress (P=.00002)
- By type of stressor, there was an association between S allele and increased stress sensitivity in:
  - Childhood maltreatment group (P=.00007)
  - Specific medical condition group (P=.0004)
  - Stressful life events group (P=.03)
- Using only the studies from previous meta-analysis, there was no evidence of association

Karg K. Arch Gen Psychiatry 2011;68(5):444-54.
SLC6A4 and Antidepressant Efficacy

2007 Meta-analysis:
- Worse remission rate with SS
- Worse response rate with SS and SL
- Slower response with SS

2010 Meta-analysis:
- No significant effect on antidepressant response
- For remission, significant effect only for SS vs. SL/LL

# SLC6A4 and Antidepressant Side Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>I/l and I/s n/N</th>
<th>s/s n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahasi 2002</td>
<td>5/24</td>
<td>11/30</td>
<td>5.41 0.45 [0.13, 1.56]</td>
<td>5.41</td>
<td>0.45 [0.13, 1.56]</td>
</tr>
<tr>
<td>Perlis 2003</td>
<td>7/27</td>
<td>8/9</td>
<td>6.21 0.04 [0.00, 0.42]</td>
<td>6.21</td>
<td>0.04 [0.00, 0.42]</td>
</tr>
<tr>
<td>Murphy 2004</td>
<td>34/189</td>
<td>14/55</td>
<td>12.42 0.64 [0.32, 1.31]</td>
<td>12.42</td>
<td>0.64 [0.32, 1.31]</td>
</tr>
<tr>
<td>Kato 2006</td>
<td>18/40</td>
<td>21/60</td>
<td>6.45 1.52 [0.67, 3.44]</td>
<td>6.45</td>
<td>1.52 [0.67, 3.44]</td>
</tr>
<tr>
<td>Popp 2006</td>
<td>19/92</td>
<td>6/17</td>
<td>5.61 0.48 [0.16, 1.46]</td>
<td>5.61</td>
<td>0.48 [0.16, 1.46]</td>
</tr>
<tr>
<td>Hu 2007</td>
<td>124/1352</td>
<td>45/303</td>
<td>46.64 0.58 [0.40, 0.84]</td>
<td>46.64</td>
<td>0.58 [0.40, 0.84]</td>
</tr>
<tr>
<td>Smits 2007</td>
<td>137/158</td>
<td>43/51</td>
<td>6.04 1.21 [0.50, 2.94]</td>
<td>6.04</td>
<td>1.21 [0.50, 2.94]</td>
</tr>
<tr>
<td>Tanaka 2008</td>
<td>6/31</td>
<td>15/41</td>
<td>7.28 0.42 [0.14, 1.24]</td>
<td>7.28</td>
<td>0.42 [0.14, 1.24]</td>
</tr>
<tr>
<td>Wilkie 2008</td>
<td>11/126</td>
<td>4/37</td>
<td>3.94 0.79 [0.24, 2.64]</td>
<td>3.94</td>
<td>0.79 [0.24, 2.64]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>361/2039</td>
<td>167/603</td>
<td>100.00 0.64 [0.49, 0.82]</td>
<td>100.00</td>
<td>0.64 [0.49, 0.82]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 13.34, df=8 (P=0.10) I² = 40.0%
Test for overall effect: Z = 3.49 (P=0.0005)

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SLC6A4
(Serotonin Transporter)

What is the practical implication?
Treatment-resistant depression patients with the S or L(G) alleles may be less likely to respond to and more likely to have side effects on an SSRI/SNRI, so maybe the next medication should be from another class.
DRD2
(D2 Receptor)
DRD2
(D2 Receptor)
DRD2 Polymorphisms

- 141C Ins/Del (rs1799732) polymorphism represents a deletion (versus insertion) of cytosine at position –141, located in the 5’ promoter region of the DRD2 gene.

- Biologic explanation for association of -141C Ins/Del polymorphism with schizophrenia/antipsychotic response is currently unknown.
  - In vitro data associate Del with lower expression of D2 receptor.
  - In vivo data associate Del with higher density of D2 receptors in striatum.

DRD2 and Antipsychotic Response

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight (%)</th>
<th>Odds Ratio Mantel-Haenszel Fixed-Effects Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lencz et al. (43)</td>
<td>13.5</td>
<td>0.42 (0.12–1.42)</td>
</tr>
<tr>
<td>Malhotra et al. (12)</td>
<td>16.5</td>
<td>0.18 (0.04–0.85)</td>
</tr>
<tr>
<td>Shen et al. (18)</td>
<td>21.9</td>
<td>0.73 (0.32–1.67)</td>
</tr>
<tr>
<td>Wu et al. (46)</td>
<td>27.2</td>
<td>0.38 (0.16–0.94)</td>
</tr>
<tr>
<td>Xing et al. (14)</td>
<td>14.2</td>
<td>1.43 (0.60–3.42)</td>
</tr>
<tr>
<td>Yamanouchi et al. (37)</td>
<td>6.6</td>
<td>1.39 (0.41–4.79)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>0.65 (0.43–0.97)</td>
</tr>
</tbody>
</table>

Heterogeneity: χ²=9.23, df=5 (p=0.10); I²=46%
Test for overall effect: z=2.13 (p=0.03)
DRD2 and Antipsychotic-Induced Weight Gain: Preliminary Data

Weight change (y-axis) is expressed as the log of the ratio of weight at a given time point relative to baseline weight.

N=58 first-episode schizophrenia patients. Average olanzapine dose was higher in Del carriers; time-by-genotype interaction remained marginally significant in secondary analyses. Lencz T et al. Pharmacogenetics Genomics 2010;20:569-72.
What is the practical implication?

TRD patients with the Del allele may have a less satisfactory drug response and more weight gain, so maybe choose something other than augmentation with an atypical antipsychotic.
CACNA1C
(Voltage-Gated Calcium Channel)
CACNA1C
(Voltage-Gated Calcium Channel)
CACNA1C Gene Polymorphisms

- CACNA1C expression: AA>AG>GG
- Polymorphisms may lead to calcium channel disturbances, excess neuronal excitability, and excess glutamate
- This may lead to increased depolarization of selective limbic regions associated with mood and perception
- The CACNA1C rs1006737 A allele has been associated with risk for:
  - Bipolar disorder
  - Mood disorder recurrence
  - Possibly MDD and schizophrenia

CACNA1C and Risk for Bipolar Disorder

Combined analysis of Wellcome Trust Case Control Consortium (WTCCC), STEP-UCL, and ED-DUB-STEP2.
CACNA1C and Subcortical Brain Morphology

N=41 euthymic patients and 50 healthy controls
CACNA1C and Brain Activation (1)

AA: Greater Hippocampal Activity During Encoding of Aversive Images

n=57 GG, 43 GA, 16 AA

\(P=0.001\) uncorrected, \(P_{\text{FDR}}=0.05\), \(z=3.20\) for right hippocampus; \(P=0.003\) uncorrected, \(P_{\text{FDR}}=0.05\), \(z=2.77\) for left hippocampus

AA: Greater Prefrontal Activity (Less Efficient) During N-Back Test

n=146 GG, 141 GA, 29 AA

\(P=2.8e-05\) uncorrected, \(P_{\text{FDR}}=0.01\), \(z=4.03\) for the first cluster; \(P=5.67e-05\) uncorrected, \(P_{\text{FDR}}=0.01\), \(z=3.86\) for the second cluster

CACNA1C and Brain Activation During Recall

CACNA1C
(Voltage-Gated Calcium Channel)

What is the practical implication?
TRD patients with the A allele may be bipolar spectrum rather than unipolar and may benefit from mood stabilizers, theoretically especially lamotrigine and others that reduce glutamate.
CYP450
Hepatic Enzyme System
CYP450
Hepatic Enzyme System

1A2  2D6  2C9  2C19  3A4

1 = Family
A = Subtype
1 = Gene product
# CYP450 Polymorphisms

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic Basis</th>
<th>Clinical Consequences</th>
<th>Alleles Causing the Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>More than 2 active gene copies on same allele or increased expression of a single gene</td>
<td>Lack of response to parent drug Increased adverse drug reaction due to increased metabolite or active drug production</td>
<td>CYP2C19<em>17 CYP2D6</em>1/*2 x N (gene duplication/multi-duplication)</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>2 functional alleles</td>
<td>Ordinary response</td>
<td>CYP2C9<em>1 CYP2C19</em>1 CYP2D6*1</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>1 defective allele or 2 partially defective alleles</td>
<td>Higher parent drug levels Decreased metabolite formation</td>
<td>CYP2C9<em>2 CYP2D6</em>10 CYP2D6*41</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>2 defective alleles</td>
<td>Higher parent drug levels Increased risk for adverse drug reactions</td>
<td>CYP2C9<em>3 CYP2C19</em>2 CYP2C19<em>3 CYP2D6</em>4 CYP2D6*5</td>
</tr>
</tbody>
</table>
CYP450
Hepatic Enzyme System

What is the practical implication?
Combining phenotyping via therapeutic drug levels with genotyping CYP450 enzymes, TRD patients who are fast metabolizers with low drug levels and poor therapeutic effects are probably not noncompliant and may require very high oral dosing or alternate routes of administration. TRD patients who are slow metabolizers with high drug levels and side effects may require low levels to tolerate and respond to medications that are substrates of the affected enzyme.
Catechol-O-methyltransferase (COMT)
Catechol-O-methyltransferase (COMT)

Dopamine transporter (DAT)

MAO-A or B destroys DA

MAO-A or B destroys DA

COMT destroys DA

DA
COMT Genotypes

- The COMT gene contains a highly functional and common variation (position 472, guanine to adenine substitution)
- Causes valine to methionine change in peptide sequence of COMT enzyme at codon 108/158 (val$^{108/158}$ met)
- Results in COMT enzyme activity that is significantly reduced:

<table>
<thead>
<tr>
<th>Allele</th>
<th>met/met</th>
<th>&lt;</th>
<th>met/val</th>
<th>&lt;</th>
<th>val/val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>low</td>
<td></td>
<td>intermediate</td>
<td></td>
<td>high</td>
</tr>
</tbody>
</table>

### COMT and Prefrontal DA

- The prefrontal cortex has few dopamine transporters.
- Thus, dopamine inactivation in PFC is more dependent on COMT metabolism.

<table>
<thead>
<tr>
<th>If COMT activity is:</th>
<th>Synaptic DA concentrations are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (_{\text{val/val}})</td>
<td>Low</td>
</tr>
<tr>
<td>Low (_{\text{met/met}})</td>
<td>Higher</td>
</tr>
</tbody>
</table>

COMT and Cognition

Val carriers

- Reduced COMT activity
- Higher levels of dopamine
- More efficient information processing

n-back

Met/Met carriers

COMT and Schizophrenia

WCST Perseverative errors
(t-scores)

Schizophrenics (N=181)
Unaffected siblings of schizophrenics (N=218)
Controls (N=58)

COMT Genotype

Val/val Val/met Met/met

aWCST Perseverative error scores were transformed to t-scores and normalized for age and education based on population means

Higher t-scores indicate better performance

Egan MF et al. Proc Natl Acad Sci USA. 2001

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COMT and SSRI Response

* Adjusted for age, gender, and family history of psychiatric disorders
**p<0.05 for change from week 1 to week 6

# Adjusted for age, gender, and family history of psychiatric disorders
*p<0.05 compared to met/met (for val/val compared to either val/met or met/met)
**p<0.01 (for val/val compared to either val/met or met/met)
Catechol-O-methyltransferase (COMT)

What is the practical implication?
TRD patients with the val allele theoretically may have lower dopamine and thus cognitive and working memory problems. They may be less likely to respond to an SSRI, so perhaps choose an antidepressant with a different mechanism, theoretically one that boosts dopamine.
Methylenetetrahydrofolate Reductase (MTHFR)
Formation of L-methylfolate

Folic acid (synthetic)

- DHFR (dihydrofolate reductase)
  - Dihydrofolate (dietary)
  - THF
  - Tetrahydrofolate

- MTHFR (methylene tetrahydrofolate reductase)
  - L-methylfolate
  *Genetically regulated*
MTHFR Polymorphisms

**IF**

MTHFR activity is:
- High\(_{(C/C)}\)
- Low\(_{(C/T \text{ or } T/T)}\)

**THEN**

- L-methylfolate is:
- Homocysteine is:
- Methylation is:
The MTHFR TT genotype is associated with a significantly higher risk of schizophrenia,\textsuperscript{1-3} including greater negative symptoms\textsuperscript{4} and cognitive impairment\textsuperscript{5,6}

MTHFR Polymorphism & Executive Function

The MTHFR 677C>T polymorphism contributes to impaired executive function (cognitive deficits) in schizophrenia patients independent of its effects on negative symptoms.

Fig. 2. Percent of subjects in each genotype group able to complete at least one category on the Wisconsin Card Sort Test ($\chi^2 = 10.125, df = 2, p = .006$).


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The MTHFR 677T allele is associated with a 3.6-fold greater risk for developing atypical antipsychotic-associated metabolic syndrome, and the TT genotype may place individuals at greater risk for insulin resistance with greater central adiposity (p=0.0001).¹


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Genetic Risk Factor for Schizophrenia: MTHFR Polymorphism and Homocysteine

- Homozygous (TT) genotype of the MTHFR 677C>T polymorphism plus a 5µmol/l higher homocysteine level was associated with a 70% higher risk of schizophrenia.

- Homocysteine levels are reported to be 54% higher in patients with schizophrenia than in controls (16.3 µM vs. 10.6 µM) (p<0.0001).
Reduced MTHFR Activity and Schizophrenia: Dopamine

- Methylation is required for:
  - De novo synthesis of biopterin, the cofactor for the rate-limiting enzyme of dopamine formation, so hypomethylation may lead to low dopamine synthesis
BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase
BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase
BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase

BH
4
biopterin
MTHFR
folate
L-MF
CH₃
H
H
H
H
H
BH
BH
4

tyrosine

BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase

folate → MTHFR → L-MF → biopterin → BH → DA → NE
BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase

- BH4 cofactor
- Tyrosine hydroxylase
- MTHFR
- Folate
- Biopterin
- BH4
- DA
- NE
BH4 Cofactor for Synthesis of DA From Tyrosine Hydroxylase
Reduced MTHFR Activity and Schizophrenia: Dopamine

- Methylation is required for:
  - Silencing of COMT synthesis, so hypomethylation may lead to high COMT levels and high DA destruction (and thus low DA levels)
Gene Expression

Activated gene

RNA

gene product

Activated gene
Gene Silencing: Methylation

L-methylfolate

SAMe → Me → DNMT

\[ \text{SAMe} = S\text{-adenosyl-methionine} \]
\[ \text{DNMT} = \text{DNA methyltransferase} \]
Gene Silencing: Methylation

L-methylfolate

\[ \text{SAMe} \rightarrow \text{Me} \rightarrow \text{DNMT} \]
Gene Silencing: Methylation

Silenced gene
Methylenetetrahydrofolate Reductase (MTHFR)

What is the practical implication?
TRD patients with the T allele theoretically have lower methylation capacity, higher homocysteine, and lower dopamine. It is not clear whether these patients are more likely to respond to L-methylfolate or SAMe.
MTHFR-COMT Methylation Interaction
Genetic Interactions of MTHFR With COMT: Epistasis

MTHFR-677C

5,10-Methylene THF

Methionine

SAMe

CH₃ CH₃ CH₃

COMT promoter

DA

DA

DA

DA

DA

DA

DA

DA

5-Methyl THF

DA

DA

DA

DA

DA

DA

DA

DA

MTHFR-677T

5,10-Methylene THF

DA

DA

DA

DA

DA

DA

DA

DA

DA

DA

DA

DA

DA

DA


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The Triple Whammy: MTHFR and Biopterin

- **Gene Allele**
  - COMT Val
  - MTHFR T

- **Downstream Effect**
  - 2-4 times higher COMT activity than Met form
  - More COMT
  - Reduced biopterin

- **Effect on PFC DA**
  - Less DA
  - Less DA
  - Less DA

Interactive Effects of MTHFR and COMT on Executive Functioning in Schizophrenia: Epistasis

Case Example:

“Psychiatric” Parkinsonism as the Phenotype of MTHFR-COMT Methylation Interaction?

Is this the result of both an epistatic and epigenetic tongue-twisting molecular interaction?

What are the practical implications of managing such patients?
Patient Intake and History

- The patient is a 54-year-old man admitted to a German hospital for a major depressive episode (MDE).
- His first MDE was at age 30; since then, he has had periodic MDEs lasting 2–3 months almost every fall/winter.
- His first inpatient admission due to MDE was at age 37.
- He was admitted again as an inpatient at ages 43 and 45.
- However, he received no psychopharmacological treatment other than sporadic St. John's Wort for any of these episodes; he seemed to respond to this.
Patient History

- Age 47: Hospitalized with MDE (depressed mood, psychomotor retardation, cognitive impairment, reduced drive, sleep problems, delusions of guilt, suicidal thoughts)

- Treated with psychotropic medications for the first time:
  - Mirtazapine 45 mg/day
  - Risperidone 3 mg/day
  - Valproic acid 2000 mg/day
  - Lorazepam 2.5 mg/day

- Slight improvement but continued drive reduction, concentration deficits, psychomotor retardation, and suicidal thoughts
Patient History

- Developed EPS with risperidone and was switched to quetiapine 400 mg/day, still with only partial improvement
- Mirtazapine was switched to sertraline 200 mg/day; he experienced some additional improvement
- The patient then received a series of 18 ECT sessions, while continuing only sertraline
- He reached full remission and was discharged, with maintenance ECT and continuation of sertraline recommended
Patient History and Current Symptoms

• The 54-year-old patient presents now with depressed mood, severe lack of drive, concentration deficits, memory problems, slow thinking, extreme fatigue, rigid facial expressions and gestures, and suicidal thoughts.

• Could be characterized, in part, as "psychiatric parkinsonism" with lack of drive, concentration and memory problems, psychomotor retardation, slower thinking (bradyphrenia), motor rigidity, and problems with facial expressions and emotional gestures.

• He is not taking any medication.

• No significant medical or family history.

• Smokes regularly; does not drink or use illicit drugs.

• He is not married and does not have any children.
Poll Question 1

Based on the patient's history and current symptom profile, testing of which of the following genes might be useful?

1. SLC6A4 (serotonin transporter)
2. SLC6A4 and catechol-O-methyltransferase (COMT)
3. SLC6A4, COMT, and methylenetetrahydrofolate reductase (MTHFR)
4. SLC6A4, COMT, MTHFR, and voltage-dependent calcium channel L-type, alpha 1c subunit (CACNA1C)
5. SLC6A4, COMT, MTHFR, CACNA1C, and dopamine receptor D2 (DRD2)
## Patient Genotyping Results

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene</th>
<th>Protein</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT</td>
<td>SLC6A4</td>
<td>SERT</td>
<td>L(A)/L(A)</td>
</tr>
<tr>
<td>DA</td>
<td>DRD2</td>
<td>D2 receptor</td>
<td>(Ins/Ins)</td>
</tr>
<tr>
<td>DA</td>
<td>COMT</td>
<td>Enzyme</td>
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</tr>
</tbody>
</table>
Poll Question 2

Based on the patient's symptoms, history, and genetic testing results, which of the following would you prescribe?

1. Serotonergic antidepressant
2. Dopaminergic antidepressant
3. Any antidepressant plus an atypical antipsychotic
4. Any antidepressant plus a stimulant
5. A pro-dopaminergic antidepressant plus L-methylfolate
6. ECT
# Patient Genotyping Results: Interpretation

<table>
<thead>
<tr>
<th>Pathway</th>
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<th>Protein</th>
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<tbody>
<tr>
<td>5HT</td>
<td>SLC6A4</td>
<td>SERT</td>
<td>L(A)/L(A)</td>
</tr>
<tr>
<td>DA</td>
<td>DRD2</td>
<td>D2 receptor</td>
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Theoretically has greater likelihood of responding to SSRI vs. those with S or L(G) allele, but…

Having Val/Val for COMT theoretically suggests less likelihood of positive outcome with SSRI

Theoretically, the effect of the COMT Val allele on DA, possibly combined with the effect of the MTHFR T allele, could explain his severe cognitive impairments ("prefrontal dopamine" hypothesis) Could also explain his "psychiatric parkinsonism" as well as his EPS on a low (3 mg) dose of risperidone
Case Outcomes

• Before the genetic testing results are known, sertraline 100 mg/day is started due to his previous response to it
  – Of the SSRIs, sertraline has the most dopaminergic activity due to some ability to block the dopamine transporter (DAT)
  – DAT is minimally present in the prefrontal cortex; thus, sertraline may benefit the patient's psychiatric parkinsonism but may not address his cognitive symptoms

• Lithium is added due to the frequency of MDE recurrence, but it is not tolerated (severe tremor) and is stopped after 10 days

• He experiences sufficient improvement after 4 weeks on sertraline and is discharged after 6 weeks

• If he continues to experience dopamine-related symptoms, he may benefit from augmentation with bupropion, a stimulant, or L-methylfolate
Genes Relevant to Psychiatric Illness Risk and/or Treatment Response

Summary
Genes Relevant to Psychiatric Illness Risk and/or Treatment Response: Summary

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<tr>
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<tr>
<td>Dopamine</td>
<td>COMT</td>
<td>Patients with the homozygous Val/Val genotype may be less likely to respond to SSRI treatments and may be more likely to have cognitive symptoms</td>
</tr>
<tr>
<td>Metabolism</td>
<td>MTHFR</td>
<td>Presence of the 677 T allele (C/T or T/T) is associated with decreased MTHFR activity, leading to increased homocysteine and decreased methylation capacity; it is also associated with increased risk of schizophrenia and particularly cognitive/negative symptoms</td>
</tr>
<tr>
<td>Metabolism</td>
<td>MTHFR-COMT methylation interaction</td>
<td>In low methylation states, such as that caused by the MTHFR T allele, dopamine is degraded at a higher rate. This effect is exacerbated in patients who carry both the MTHFR 677 T allele and the high-activity COMT 158 Val/Val genotype</td>
</tr>
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## Genes Relevant to Psychiatric Illness Risk and/or Treatment Response: Summary

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<tr>
<td>Serotonin</td>
<td>SLC6A4</td>
<td>Carriers of the Short (S) or L(G) alleles may be more likely to experience adverse effects from SSRIs; they may also be less likely to remit with SSRIs or may respond more slowly</td>
</tr>
<tr>
<td>Dopamine</td>
<td>DRD2</td>
<td>Del allele carriers (Del/Ins or Del/Del) may demonstrate less satisfactory antipsychotic drug response compared to Ins/Ins individuals; they may also have higher risk of antipsychotic-induced weight gain</td>
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<tr>
<td>Glutamate</td>
<td>CACNA1C</td>
<td>The A allele has been associated with elevated rates of mood disorder recurrence and relapse</td>
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<tr>
<td>Metabolism</td>
<td>CYP450</td>
<td>Allelic variations in CYP450 2C19 and 2D6 can affect efficiency of metabolism</td>
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Case Example:

Personalized Medicine in Practice
Patient Intake

- A 55-year-old man is admitted to a German hospital because of severely impaired concentration, depressed mood with suicidal thoughts, insomnia, brooding, and feelings of guilt
- He has had these symptoms for approximately 5 months
- He is separated and has 4 sons
- He denies any drug or alcohol abuse
- There is no family history of mental illness
- This is the patient's first depressive episode; he has had no drug treatment prior to this hospitalization
- He is treated as an inpatient with mirtazapine 45 mg/day but exhibits no response
Poll Question 3

Based on the patient's history and current symptom profile, testing of which of the following genes might be useful?

1. SLC6A4 (serotonin transporter)
2. SLC6A4 and catechol-O-methyltransferase (COMT)
3. SLC6A4, COMT, and methylenetetrahydrofolate reductase (MTHFR)
4. SLC6A4, COMT, MTHFR, and voltage-dependent calcium channel L-type, alpha 1c subunit (CACNA1C)
5. SLC6A4, COMT, MTHFR, CACNA1C, and dopamine receptor D2 (DRD2)
## Patient Genotyping Results

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Poll Question 4

Based on the patient's symptoms, history, and genetic testing results, which of the following would you prescribe?

1. Serotonergic antidepressant
2. Noradrenergic and/or dopaminergic antidepressant
3. Any antidepressant plus an atypical antipsychotic
4. Any antidepressant plus a stimulant
Patient Genotyping Results: Interpretation

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Theoretically would reduce his likelihood of remitting with an SSRI

Theoretically, the effect of the COMT Val allele on DA, possibly combined with the effect of the MTHFR T allele, could explain his severe cognitive impairments ("prefrontal dopamine" hypothesis)
Case Outcomes

• Switched to nortriptyline 200 mg/day (his serum levels are low, and this dose is required for his levels to reach therapeutic range)
  – Having S/S alleles for SLC6A4, he may be less likely to remit with SSRI treatment than those with the L(A) alleles
  – Having Val/Val alleles for COMT also theoretically suggests that he would be less likely to have positive outcomes with an SSRI

• Quetiapine is added due to his delusions of guilt
  – Having Ins/Ins alleles for DRD2 theoretically suggests that he may respond better to atypical antipsychotic augmentation in comparison to individuals with the Del allele

• Lorazepam 2 mg/day is prescribed as needed
• He experiences a good response to nortriptyline and quetiapine and is released on this combination
• If his symptoms relapse, augmentation with L-methylfolate could be considered
Summary

• Genetic testing as a clinical tool is still in its infancy, but it has the potential to inform treatment decisions

• Genotyping may be especially useful for patients who do not respond to or tolerate a drug as expected

• Caution is essential when bringing genetic testing into the selection of treatment in clinical practice