Incorporating Pharmacogenomics into Your Clinical Mental Health Practice

April 12, 2023
Housekeeping

• Participants’ microphones and cameras are turned off
• Place questions for presenters in the chat at the right. There will be a Q&A session at the end of our program during which our presenters will address as many of your questions as we can
• You may download a copy of today’s slides in the “Files” box to the right
• After the program, please remember to complete your program evaluation in TMS within 15 days
Disclosures

• VHA received a donation from Sanford Health to fund PGx implementation and to provide panel-based PGx testing (Sanford Imagenetics laboratory)

• Myriad Genetics donated PGx test kits for the PRIME Care study

• This presentation includes information about PGx testing products used in VHA care. Neither VHA nor any of the speakers have a financial interest in any of the testing products discussed

• The views expressed in this webinar are those of the presenters and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government
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<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
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<tr>
<td>12:00pm - 12:15pm</td>
<td>Introductory Remarks and Overview</td>
<td>David Oslin</td>
</tr>
<tr>
<td>12:15pm – 1:00pm</td>
<td>Pharmacogenomics (PGx) Overview</td>
<td>Jill Bates</td>
</tr>
<tr>
<td>1:00pm – 1:45pm</td>
<td>PGx within Mental Health Treatment</td>
<td>Shawn Dalton</td>
</tr>
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<td>1:45pm – 1:55pm</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>1:55pm – 2:40pm</td>
<td>Current PGx Research</td>
<td>David Oslin</td>
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<td>2:40pm – 2:55pm</td>
<td>Clinical Case Examples</td>
<td>Anna Daily</td>
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<td>Mariana Mendez-Tadel</td>
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<td>2:55pm – 3:40pm</td>
<td>Integrating PGx into Your Practice</td>
<td>Deepak Voora</td>
</tr>
<tr>
<td>3:40pm – 4:00pm</td>
<td>Q&amp;A Panel (Moderator: David Oslin)</td>
<td>All Faculty</td>
</tr>
<tr>
<td>4:00pm</td>
<td>Adjourn</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacogenomics (PGx) Overview

Jill Bates, PharmD, MS, BCOP, DipACLM, FASHP
Acting Deputy Executive Director, National Pharmacogenomics Program
Durham VA Health Care System
Quadruple Aim

• Better health
• Better patient experience
• Lower costs
• Improved clinician satisfaction
Pharmacogenomics

• Genetic variability in response to medication therapy
• History dates back to 510 B.C. when Pythagoras observed certain individuals had a fatal reaction to fava beans while others did not
• The term *pharmacogenetics* was introduced in 1957
• The term *pharmacogenomics* evolved to clarify inclusivity of the entire spectrum of genes that determine medication response

Germline vs Somatic Pharmacogenomics

Somatic mutations
- Occur in nongermline tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only (for example, breast)
Nonheritable

Mutation in egg or sperm
Heritable
All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Human Genome Project

• Carried out from 1990-2003
• Produced the first draft of the human genome in 2003 accounting for 90% of the human genome
• Completed a full sequence of the human genome in 2022
• Sequenced select other organisms as well (i.e., *E. coli*, baker’s yeast, fruit fly, nematode, and mouse)
• Based on Sanger sequencing technology

Human Genome Project Fact Sheet (Accessed 3/10/23).
Types of Pharmacogenomic Variants

• Aneuploidy
• Structural variants
  • For example, Copy number variant (CNV)
• Single nucleotide polymorphism (SNP)
  • Substitution
    • Synonymous/silent
    • Nonsynonymous/missense
    • Truncation/nonsense
    • Extension/stop loss
• Short insertions/deletions (InDels)
  • Can cause frameshifts, stop loss, or stop gain

Next-Generation Sequencing Technology

Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata (Accessed 3/10/23).
Reality of Current Testing Methodologies

• Targeted methods
  • Genotyping
  • Fluorescence in situ hybridization (FISH)
  • Sanger sequencing
  • Next-generation sequencing
  • Quantitative real-time polymerase chain reaction (RT-PCR)
  • Immunohistochemistry (IHC)

• Non-targeted methods
  • Karyotyping
  • Arrays
## Frequency of Actionable PGx Variants Among Veteran Pharmacy Users

Table 1. Projected Frequency of Actionable Pharmacogenetic Variants Among Veterans Health Administration Pharmacy Users

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Effect</th>
<th>Population With Actionable Genotypes, No. (%)</th>
<th>Drugs Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>*2,*3,*5,*6,*8,*11</td>
<td>Decreased function</td>
<td>2 633 813 (33.9)</td>
<td>Warfarin, phenytoin</td>
</tr>
<tr>
<td>VKORC1</td>
<td>1639G&gt;A</td>
<td>Increased warfarin sensitivity</td>
<td>4 529 536 (58.3)</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*2,*3,*4,*8</td>
<td>Decreased function</td>
<td>2 035 572 (26.2)</td>
<td>Clopidogrel, ticlopidine, esculizopram, amitriptyline</td>
</tr>
<tr>
<td></td>
<td>*17</td>
<td>Increased function</td>
<td>3 348 594 (43.1)</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>CYP206</td>
<td>*2,*3,*4,*5,*6,*8,*10,*17,*29,*41</td>
<td>Decreased or no function</td>
<td>318 544 (4.1)</td>
<td>Codeine, tramadol, fluoxamine, paroxetine, nortriptiline, ondansetron</td>
</tr>
<tr>
<td></td>
<td>Gene duplication</td>
<td>Increased function</td>
<td>264 158 (3.4)</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*1</td>
<td>Dosage increase recommended</td>
<td>1 926 801 (24.8)</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>SLC01B1</td>
<td>*5</td>
<td>Increased myopathy risk</td>
<td>1 988 956 (25.6)</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>*80</td>
<td>Decreased function</td>
<td>870 168 (11.2)</td>
<td>Atazanavir, ritonavir</td>
</tr>
<tr>
<td>TPMT</td>
<td>*2,*3</td>
<td>No function</td>
<td>450 623 (5.8)</td>
<td>Azathioprine, mercaptopurine, thioguanine</td>
</tr>
<tr>
<td>DPYD</td>
<td>*2A,D949V</td>
<td>No function or reduced function</td>
<td>69 924 (0.9)</td>
<td>Capecitabine, fluorouracil</td>
</tr>
<tr>
<td>G6PD</td>
<td>202A/376G</td>
<td>Deficient</td>
<td>380 699 (4.9)</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>IFNL3</td>
<td>rs12879860</td>
<td>Unfavorable response</td>
<td>6 433 029 (82.8)</td>
<td>Pegylated interferon</td>
</tr>
<tr>
<td>HLA-A</td>
<td>*31:01</td>
<td>Hypersensitivity reaction</td>
<td>372 929 (4.8)</td>
<td>Carbamazepine, oxcarbazepine</td>
</tr>
<tr>
<td>HLA-B</td>
<td>*57:01</td>
<td>Hypersensitivity reaction</td>
<td>435 684 (5.6)</td>
<td>Abacavir, phenytoin</td>
</tr>
<tr>
<td></td>
<td>*58:01</td>
<td>Severe cutaneous adverse reactions</td>
<td>295 230 (3.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*15:02</td>
<td>Stevens-Johnson syndrome or toxic epidermal necrolysis</td>
<td>551 515 (0.1)</td>
<td>Allopurinol, carbamazepine, oxcarbazepine</td>
</tr>
</tbody>
</table>

• Over a 4-year period, **1 out of 2 Veterans** will newly be prescribed a medication informed by PGx; and,

• Genetic test results reveal clinically significant findings that impact new prescriptions in approximately **1 in 10 Veterans**
Influencers of Genomic Variability

• Germline PGx genes that encode for
  • Drug metabolizing enzymes
  • Drug transporters
  • Drug targets
  • Immune response
Pharmacogenomics Can Influence:

- Dose
- Choice of Medication
PGx Nomenclature

• Ordinarily, DNA variants are named using Human Genome Variation Society (HGVS) nomenclature
• PGx often uses “star nomenclature”
  • Haplotype = variants or combinations of variants in a gene that are linked together on a single chromosome
  • Haplotype = allele = allelic variation often used interchangeably
  • Results of PGx tests commonly reported as diplotypes (or haplotype pairs)
  • *1 is wild type

Star Allele Nomenclature

CYP 3A5
Gene

*3 /*3
Genotype, diplotype, variant

Poor Metabolizer
Predicted Phenotype
# Standardized “ADME” Phenotypes

## Drug Metabolizing Enzymes

<table>
<thead>
<tr>
<th>Phenotype: drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)</th>
<th>Ultrarapid metabolizer</th>
<th>Rapid metabolizer</th>
<th>Normal metabolizer</th>
<th>Intermediate metabolizer</th>
<th>Poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased enzyme activity compared to rapid metabolizers</td>
<td>Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers</td>
<td>Fully functional enzyme activity</td>
<td>Decreased enzyme activity (activity between normal and poor metabolizer)</td>
<td>Little to no enzyme activity</td>
</tr>
<tr>
<td></td>
<td>Two increased function alleles, or more than 2 normal function alleles</td>
<td>Combinations of normal function and increased function alleles</td>
<td>Combinations of normal function and decreased function alleles</td>
<td>Combinations of normal function, decreased function, and/or no function alleles</td>
<td>Combination of no function alleles and/or decreased function alleles</td>
</tr>
</tbody>
</table>

## Drug Transporters

<table>
<thead>
<tr>
<th>Phenotype: transporters (SLCO1B1)</th>
<th>Increased function</th>
<th>Normal function</th>
<th>Decreased function</th>
<th>Poor function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased function</td>
<td>Increased transporter function compared to normal function.</td>
<td>Fully functional transporter function</td>
<td>Decreased transporter function (function between normal and poor function)</td>
<td>Little to no transporter function</td>
</tr>
<tr>
<td>Normal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| One or more increased function alleles | Combinations of normal function and/or decreased function alleles | Combinations of normal function, decreased function, and/or no function alleles | Combination of no function alleles and/or decreased function alleles |

SLCO1B1*1/*14 | SLCO1B1*1/*1 | SLCO1B1*1/*5 | SLCO1B1*5/*5 |

### High Risk Genotype Status

<table>
<thead>
<tr>
<th>Phenotype: high-risk genotype status (HLA-B)</th>
<th>Positive</th>
<th>Negative</th>
<th>Detection of high-risk allele</th>
<th>Homozygous or heterozygous for high-risk allele</th>
<th>High-risk allele not detected</th>
<th>No copies of high-risk allele</th>
<th>HLA-B*15:02</th>
</tr>
</thead>
</table>

Incidental Findings

• Some pharmacogenes may identify increased risk for certain health conditions
  • Examples: G6PD deficiency and Gilbert’s syndrome

• Identify risk and support patients through next steps if any
  • Examples referrals to a specialist (hematology, hepatology) and/or genetic counseling
• As of December 31, 2020 there are 299 drugs with PGx information included in the labeling

• Most labels do not provide specific recommendations regarding dose or drug selection

• FDA released a table of drug-gene interactions that contains information for which FDA believes there is sufficient scientific evidence categorized into 3 sections

• Low concordance between CPIC guidelines and FDA recommendations (i.e., 3%)

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- International consortium that serves to facilitate use of pharmacogenomics tests for patient care
- Assists in translating genetic laboratory test results into actionable prescribing decisions for affected drugs
- Creates, curates and publicly distributes peer-reviewed, evidence-based, updatable and detailed gene/drug clinical practice guidelines
### CPIC Gene-Drugs Database

#### Search Results

<table>
<thead>
<tr>
<th>#</th>
<th>Gene</th>
<th>Drug</th>
<th>Guideline</th>
<th>CPIC Level</th>
<th>PharmGKB Level of Evidence</th>
<th>PGX on FDA Label</th>
<th>CPIC Publications (PMID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>CYP3A5</td>
<td>tacrolimus</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td></td>
<td>25801146</td>
</tr>
<tr>
<td>217</td>
<td>CYP3A4</td>
<td>tacrolimus</td>
<td></td>
<td>C</td>
<td>2A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Showing 1 to 2 of 2 entries (filtered from 359 total entries)
Pharm-GKB

• National Institutes of Health (NIH)-funded resource that provides information about how human genetic variation affects response to medications
<table>
<thead>
<tr>
<th>Annotated Drugs</th>
<th>Curated Pathways</th>
<th>Clinical Guideline Annotations</th>
<th>Drug Label Annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>662</td>
<td>147</td>
<td>132</td>
<td>605</td>
</tr>
</tbody>
</table>
Dutch Pharmacogenomic Working Group Guidelines

- Reviewed >100 drug gene pairs as of 7/1/2020
- Identified 60 drug gene pairs as actionable meaning adjustment of medication is necessary
- Give the results of the PREPARE trial may see a revived use

PGx Test Results – Part of the Bigger Picture

• **Always** consider pharmacogenomics test results in the context of your patient

• PGx is **one piece of the puzzle**
Phenoconversion

• Phenomenon whereby an individual acquires phenotypic poor metabolizer protein function
  • Most extensively studied for CYP2D6
  • Drug-induced phenomenon
    • Identify susceptible drugs
    • Identify co-medications that can cause
    • Employ dosing strategies to reconcile during and following phenoconversion

Potential PGx Benefits

- One-time testing that can be reused by all providers for **life of patient**
- Less trial and error with medications
- Fewer adverse drug reactions (and associated encounters)
- Lower use of opioid medications
- Greater Veteran satisfaction/trust in provider
- Improved adherence with medications
Risks of PGx Testing

• Pharmacogenomic testing is considered low-risk like any other laboratory testing
• Safeguards are in place to protect Veteran privacy with samples/data sent outside VA to contract laboratories
• Federal and VA policies protect against discrimination
PGx Ethical, Legal, and Social Implications

- Incidental findings
- Confidentiality and privacy
- Use and storage of genetic information
- Liability
- Off-label use
- Use of racial and ethnic categories
- Availability and access to PGx services
- Direct to consumer PGx testing
- Informed consent

PGx Oral Informed Consent

• Key elements to consider for clinical PGx testing
  • Overview of testing available
  • Describe medicines the test results influence
  • Describe the purpose of PGx testing
  • How the sample is obtained, stored, used
  • Incidental findings that may occur
  • How test results will be shared
  • How to get any questions answered
  • Risks, benefits, limitations
  • Confidentiality (i.e., Genetic Information Non-discrimination Act (GINA), military genetic information protection)

PGx Perceptions

• Vest et al. found that providers had limited experience and knowledge of PGx testing and its evidence base
• Providers were hopeful that PGx could increase their precision in depression prescribing and improve patient engagement
• Providers were concerned about potential misinterpretation of PGx results and how to incorporate testing into their workflow
• Primary care providers were less familiar and comfortable with application of PGx testing to antidepressant prescribing than psychiatric providers

Economic Evaluation of Germline PGx

• Approximately 1 in 6 prescriptions involve high risk PGx
• Only about 25% of currently available tests and 20% of tests with likely clinical utility have associated cost-utility data

PGx cost-effectiveness by indication
  • Cancer
    • Annual patient savings with pharmacogenomics irinotecan dose reduction: $272.34
    • Savings of $415 per patient receiving voriconazole for fungal infection
  • Psychiatry
  • Cardiology
  • Geriatric medicine
  • Pain

A Case for Clinical Decision Support

• Clinical decision support (CDS) has been identified as a critical tool for the implementation of precision medicine into routine patient care
• Electronic health record vendor support for pharmacogenomics is still emerging
• Consider whether consultants or external vendor support is needed

Clinical Utility of CDS

• In a post-hoc analysis of data from an open-label, randomized, observational trial
  • No increase in medication-related problems when CDS and PGx strategies were employed
  • Identification of more serious medication related problems and subsequent recommendation acceptance was higher in CDS and PGx arm
• PGx-directed CDS changed prescribing patterns in a prospective study of a preemptive PGx genotyping cohort (n=2,279)

Unique to Genomics-based CDS

Goal: Maximize the clinical value of the genomic result

Five key elements:
1. Facilitate convenient access to genomic info for the lifetime of the patient
2. Provide clinical interpretation of test results and recommendations
3. Enter genomic results and interpretations in discrete EMR fields to facilitate CDS and future retrieval
4. Provide drug-specific pharmacotherapy recommendations based on test results and the clinical interpretation
5. Deploy CDS to guide application of PGx at the points of prescribing and dispensing

CDS Needs a “Trigger”

• Type of clinical decision support
  • Active
  • Passive

• Structured data is needed to implement active and many forms of passive CDS

• Structured data needs (include laboratory services)
  • Determine interpretation data to display as discrete element
  • Store PGx information as structured data/discrete element

CDS Gaps and Barriers
Barriers to PGx Implementation

- Varying levels of provider expertise
- Attaining provider buy-in and acceptance
- Reimbursement for genetic testing
- Genotyping and result interpretation
- Laboratory and workflow challenges
- Electronically structured data and providing CDS
- Cost (false reassurance with dropping cost of NGS)

Educating the Workforce

• Qualitative evaluation of 25 physicians revealed that the prospect of receiving unsolicited genomic results raises important concerns
  • Actionability – especially with regard to lack of knowledge
  • Need for clinical decision support
  • Potential patient harm
  • Workflow issues i.e. unreimbursed time
  • Roles of providers responding to unsolicited genomic results

• A survey of pharmacists (n=737) demonstrated disparity in knowledge of general genetics according to years since graduating pharmacy school
  • Mean total positive attitude increased with self-reported level of knowledge of pharmacogenomic testing

PGx Pharmacy Landscape Survey

Survey deployed February 2021

- 674 responses
- Respondents:
  - 71% of respondents have not completed any training in PGx course work
  - 82% have a scope of practice

<table>
<thead>
<tr>
<th>Practice Area</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>49 (7.3)</td>
</tr>
<tr>
<td>Primary care</td>
<td>232 (34.4)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Mental health</td>
<td>128 (19.0)</td>
</tr>
<tr>
<td>Oncology</td>
<td>54 (8.0)</td>
</tr>
<tr>
<td>Administration</td>
<td>41 (6.1)</td>
</tr>
<tr>
<td>Other</td>
<td>142 (21.1)</td>
</tr>
<tr>
<td>No response</td>
<td>8 (1.2)</td>
</tr>
</tbody>
</table>
Please identify any of the following pharmacogenomics tests that you have utilized as part of your practice.

- Cytogenetics
- RNA testing
- Protein testing
- Inheritable diseases
- Somatic PGx
- Germline PGx
- None

N = 674
Have you ordered any of the following?

<table>
<thead>
<tr>
<th>Orders</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Companion diagnostic matched to a drug prescribed</td>
<td>21</td>
<td>517</td>
<td>123</td>
</tr>
<tr>
<td>Complementary diagnostic matched to a drug prescribed</td>
<td>37</td>
<td>524</td>
<td>98</td>
</tr>
<tr>
<td>Changed medications or adjusted dosing based on germline PGx</td>
<td>75</td>
<td>470</td>
<td>112</td>
</tr>
</tbody>
</table>

N = 674
Which of the following pharmacogenomics resources have you used in practice or are familiar with and could use in practice where applicable?

N = 674
How comfortable are you in performing the following patient care services?

<table>
<thead>
<tr>
<th>Service</th>
<th>Average Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applying genomic data to optimize medication use for patient care</td>
<td>32</td>
</tr>
<tr>
<td>Educating patients about family history, genomic risk, and PGx test results as they relate to health behaviors</td>
<td>30</td>
</tr>
<tr>
<td>Recommend strategies regarding the potential use of handling incidental findings with PGx test results</td>
<td>26</td>
</tr>
<tr>
<td>Recommend genomic screening for early detection and diagnosis</td>
<td>24</td>
</tr>
<tr>
<td>Apply PGx drug dosing guidelines in practice and guide healthcare providers on their appropriate use and interpretation</td>
<td>33</td>
</tr>
<tr>
<td>Educate patients and healthcare providers about privacy and other potential concerns with PGx data</td>
<td>29</td>
</tr>
</tbody>
</table>
1. Comfort applying genomic data to optimize medication use for patient care
Stratified Results by PHASER and Non-PHASER Respondents

5. Comfort applying PGx dosing guidelines in practice and guiding providers on use and interpretation
Summary

• PGx is a proactive patient safety and medication optimization strategy

• Scientific advancements have led to an evolution in thought from “when will we use PGx” to “how will we use PGx” in practice

• Leaders should support systems that promote shared decision making and consider ethical concerns associated with PGx

• Implementing PGx is highly interprofessional and relies on strategic infrastructural support for success
PGx within Mental Health Treatment

Shawn Dalton, PharmD, BCPS, BCACP, BCPP, VHA-CM
National Program Manager – Telepharmacogenomics
National Telepharmacogenomics Program
VA Durham Health Care System
Do These All Work Equally Well in Everyone?

https://doctorlib.info/pharmacology/stahls-essential-psychopharmacology-4/7.html
Do Antidepressants Work?

• **Sugarman 2014 Meta-Analysis**
  - Paroxetine marginally more effective than placebo for depression or anxiety based on FDA data
  - Placebo had 80% magnitude of change of paroxetine
  - Majority of response seen early in treatment
  - Question if response seen is detectable in clinic for majority of patients

• **Almohammad 2022 health related quality of life in depression analysis**
  - Did not evaluate depression scales, focus on QOL measurements
  - Health related quality of life does not improve while taking antidepressants for depression

Sugarman et al PLoS ONE 9(8): e106337
Almohammad et al. PLoS ONE 17(4):e0265928
Primarily focused on SERT, 5HT-1A receptor, and serotonin levels

- No association of decreased CSF levels of serotonin and depression
- Antidepressants strongly associated with decreased levels of serotonin
- No difference or lower number of 5HT-1A autoreceptors in people with depression
- Evidence more strongly supports that increased levels of serotonin cause depression

Author’s conclusion

- Antidepressants probably don’t work as serotonin is not a core component of depression

What’s missing here?

Molecular Psychiatry: https://doi.org/10.1038/s41380-022-01661-0
Complexity of Neurotransmission

- Assumes adequate intake and bioavailability:
  - Thiamine
  - Riboflavin
  - Niacin
  - Pyridoxine
  - Pantothenic acid
  - Biotin
  - Folate
  - Cyanocobalamin
  - Vitamin C
  - Vitamin D
  - Vitamin E
  - Calcium
  - Iodine
  - Iron
  - Magnesium
  - Selenium
  - Essential fatty acids
  - Zinc
  - Choline
  - Methionine
  - Tyrosine
  - Tryptophan
  - Macros/water
  - Many others (i.e. copper, phosphorus, potassium, sodium, etc)

Link: Oregon State University
Personalized/Precision Medicine:
Present, Future, or Never Will Be?

Precision medicine research enables development and delivery of the right patient intervention.
Towards Precision Psych Care

- Microbiome
- Therapeutic Monitoring
- Pharmacogenomics/Medical Genetics/Epigenetics
- Nutrition/Lifestyle/Activity
- Other ‘-omes’ (proteomics, metabolomics, connectomics, genomics, others)

- Biomarkers/Individual Testing/Imaging
- Environment/Exposures/Inputs
- Interventional Procedures/Devices/Data/Al
- Individual Factors (mindset, beliefs, psychology, etc)

Adapted from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0849-x
PGx: A Small Piece of the Whole Patient
Example in Psychiatry

Today’s focus is only one small piece of the puzzle, pharmacogenomics

https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0849-x
Key Components of PGx

Pharmacokinetic Pharmacogenomics
(focus today)
- Effect of the body on the drug
- CYP450 enzyme and protein transporter pathways mainly

Pharmacodynamic Pharmacogenomics
(intensive research area)
- Effect of the drug on the body
- Serotonin reuptake transporter, dopamine receptors, etc
- Limited number of genes included in many commercial PGx panels

Epigenetics
(early stages of knowledge)
- Modifications of gene expression that do not include genetic code alterations
- Occurs ‘above’ the level of genetics, limited clinical application currently

Phenoconversion & Drug Interactions
(must consider regardless of PGx)
- Mismatch between genotype-predicted metabolism and the impact
- NOT accounted for in PGx testing, must be estimated by the clinician
Focus on Pharmacokinetics
Drug Metabolism by Function

CYP2D6: Can It Predict Personality Traits? Genetics Explained - SelfDecode Supplements
Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) Guidelines

• Do not inform if testing is warranted, focus on clinical application assuming testing was already completed

• CPIC guidelines
  • SSRIs (paroxetine, fluvoxamine, citalopram, escitalopram, sertraline), TCAs (amitriptyline and nortriptyline focused but likely applies to most TCAs), atomoxetine
    • Focused in PHASER panel
  • Carbamazepine, oxcarbazepine, phenytoin

• DPWG covers a wide range of drugs
  • Broader range of antidepressants, antipsychotics
PharmGKB Levels of Evidence

Clinical Annotation Levels of Evidence

1A: Clinical guideline or FDA approved labeling
1B: High level of association but not guideline or labeling

3: Low level association with at least one study suggesting association

2A: Moderate level of evidence for well established gene variants in multiple cohorts
2B: Moderate level of evidence of association but may have small study discrepancies

4: Evidence does not support an association

https://www.pharmgkb.org/page/clinAnnLevels
CYP450 Metabolic Pathways

CYP450 Distributions

- **CYP3A4**
  - Few common variants (>1% of population) that impact metabolism
  - Many rare variants not well characterized
  - Hundreds of polymorphisms of uncertain clinical impact

CYP3A4 Relevant Psychiatric Medications

- **Primary metabolic pathway(s)**
  - Fluoxetine, levomilnacipran, milnacipran, mirtazapine, trazodone, venlafaxine, vilazodone, aripiprazole, brexipiprazole, haloperidol, lurasidone, quetiapine, carbamazepine, alprazolam, buspirone, clonazepam, diazepam, midazolam, triazolam, zolpidem

- **Secondary metabolic pathway(s)**
  - Citalopram, escitalopram, sertraline, vortioxetine, amitriptyline, cariprazine, clozapine, risperidone, ziprasidone, oxcarbazepine, chlorpromazine
PGx Interventions for Meds Prescribed through CYP3A4

• PharmGKB lists 69 clinical annotations with prescribing consideration

• Psychiatric
  • Level 1A
    • Quetiapine(M)
  • Level 2A
    • Fentanyl(D)
  • Level 3
    • Fentanyl(M,E), alprazolam(E,M,T), sufentanil(E,D,T,M), midazolam(O), methadone(T), carbamazepine(M), buprenorphine(D,E), quetiapine(M), oxycodone(M), risperidone(M)

https://www.pharmgkb.org/gene/PA130/clinicalAnnotation
### Wording in table taken from the Dutch guidelines February 2022 update.

<table>
<thead>
<tr>
<th>Allele/Genotype/Phenotype</th>
<th>Drug</th>
<th>Description</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 IM</td>
<td>Quetiapine</td>
<td>This gene variation reduces the conversion of quetiapine to inactive metabolites and a metabolite with antidepressant effect. However, the effect on the plasma concentration of quetiapine is limited (20% increase) and it is not known whether this has any clinical consequences. The relationship between the plasma concentration and clinical effect is weak for quetiapine.</td>
<td>No action is needed for this gene-drug interaction.</td>
</tr>
<tr>
<td>CYP3A4 PM</td>
<td>Quetiapine</td>
<td>The plasma concentration of quetiapine is 3.2-fold higher in these patients. In addition, the formation of the active metabolite N-desalkylquetiapine, which is probably responsible for the antidepressant effect, should be reduced. The gene variation results in reduced activity of the enzyme CYP3A4, which converts quetiapine to N-desalkylquetiapine and an inactive metabolite.</td>
<td>Indication DEPRESSION: choose an alternative. Aripiprazole appears to be less dependent on CYP3A4 for metabolism. Olanzapine is not metabolised by CYP3A4. OTHER INDICATIONS: use 30% of the standard dose.</td>
</tr>
</tbody>
</table>
Frequency of Psychiatric Pharmacogenomic Variants

CYP2B6 Phenotype Frequency

https://www.pharmgkb.org/page/pgxGeneRef
CYP2B6 Relevant Psychiatric Medications

• Primary metabolic pathway(s)
  • Bupropion

• Secondary metabolic pathway(s)
  • Sertraline, vortioxetine, amitriptyline, valproic acid, diazepam, temazepam, ketamine, methamphetamine, tramadol, selegiline, MDMA
PGx Interventions for Meds Prescribed through CYP2B6

• PharmGKB lists 64 clinical annotations with prescribing consideration

• Psychiatric
  • Level 1A
    • None
  • Level 2A
    • Bupropion(M), methadone(M)
  • Level 3
    • Tramadol(M), ketamine(M), mirtazapine(E,O), nicotine, bupropion(E), MDMA(M), methadone(D,E,M,T)

https://www.pharmgkb.org/gene/PA123/clinicalAnnotation
Bupropion, Methadone, and CYP2B6

- Bupropion
  - Level 2A
  - Known kinetic variation based on phenotype, clinical significance unknown

- Methadone
  - Level 2A
  - Known kinetic variation based on phenotype, clinical significance unknown

https://www.pharmgkb.org/gene/PA123/clinicalAnnotation
Frequency of Psychiatric Pharmacogenomic Variants

CYP2C19 Phenotype Frequency

https://www.pharmgkb.org/page/pgxGeneRef
CYP2C19 Relevant Psychiatric Medications

• Primary metabolic pathway(s)
  • Citalopram, escitalopram, sertraline, amitriptyline, nortriptyline, diazepam

• Secondary metabolic pathway(s)
  • Fluoxetine, venlafaxine, vilazodone, clozapine, valproic acid, clomipramine, imipramine, melatonin, atomoxetine
PGx Interventions for Meds Prescribed through CYP2C19

• PharmGKB lists 77 clinical annotations with prescribing consideration

• Psychiatric
  • Level 1A
    • Citalopram(T), doxepin(M), escitalopram(M), clomipramine(M), amitriptyline(M), imipramine(M), trimipramine(M), sertraline(M)
  • Level 2A
    • None
  • Level 3
    • MDMA(M,T), clobazam(D,M), diazepam(M), bupropion(O), venlafaxine(M,T), phenytoin(E)
  • Level 4
    • Citalopram(E), venlafaxine(T), methadone(M), valproic acid(T)

D: Dosage
E: Efficacy
M: Metabolism/kinetics
T: Toxicity
O: Other
### Table 3 Dosing recommendations for CYP2C19 and SSRIs

#### Table 3a Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Ultrarapid</td>
<td>Increased metabolism when compared to extensive metabolizers. Lower plasma</td>
<td>Consider an alternative drug not predominantly metabolized by CYP2C19.</td>
<td>Moderate</td>
</tr>
<tr>
<td>metabolizer</td>
<td>concentrations will increase probability of pharmacotherapy failure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Extensive</td>
<td>Normal metabolism</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Intermediate</td>
<td>Reduced metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Poor</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher</td>
<td>Consider a 50% reduction of recommended starting dose and titrate</td>
<td>Moderate</td>
</tr>
<tr>
<td>metabolizer</td>
<td>plasma concentrations may increase the probability of side effects.</td>
<td>to response or select alternative drug not predominantly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>metabolized by CYP2C19.</td>
<td></td>
</tr>
</tbody>
</table>

## Table 3b Dosing recommendations for sertraline based on CYP2C19 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Ultrarapid metabolizer</td>
<td>Increased metabolism when compared to extensive metabolorizers.</td>
<td>Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2C19 Extensive metabolizer</td>
<td>Normal metabolism</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Intermediate metabolizer</td>
<td>Reduced metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Poor metabolizer</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Consider a 50% reduction(^{a}) of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.</td>
<td>Optional</td>
</tr>
</tbody>
</table>

Frequency of Psychiatric Pharmacogenomic Variants

### Table 1: Assignment of likely CYP2C9 phenotypes based on genotypes

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal metabolizer</td>
<td>2</td>
<td>An individual carrying two normal function alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>1.5</td>
<td>An individual carrying one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR two decreased function alleles</td>
<td>*1/*2, *1/*3, *2/*2</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>0.5</td>
<td>An individual carrying one no function allele plus one decreased function allele; OR two no function alleles</td>
<td>*2/*3, *3/*2</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>n/a</td>
<td>An individual carrying allele combinations with uncertain and/or unknown function alleles</td>
<td>*1/*7, *1/*10, *7/*10, *1/*57</td>
</tr>
</tbody>
</table>

*Assignment of allele function and associated citations can be found at [https://www.pharmgkb.org/page/pgxGeneRef](https://www.pharmgkb.org/page/pgxGeneRef) and CYP2C9 Allele Functionality Table in refs. 1,2). For a complete list of CYP2C9 diplotypes and resulting phenotypes, see the CYP2C9 Genotype to Phenotype Table in refs. 1,2. *3See the CYP2C9 Frequency Table in refs. 1,2 for population-specific allele and phenotype frequencies.

![CYP2C9 Frequency Activity Score](image)

https://www.pharmgkb.org/page/pgxGeneRef
CYP2C9 Relevant Psychiatric Medications

• Primary metabolic pathway(s)
  • None, worth noting this is the primary NSAID pathway

• Secondary metabolic pathway(s)
  • Fluoxetine, amitriptyline, valproic acid, diazepam, phenobarbital, phenytoin, THC

• Level 3 Associations
  • Doxepin(E), olanzapine(T), phenytoin(D,M,T), valproic acid(D,M)
  • Phenytoin has level 1A associations in epilepsy, unclear if they translate to psychiatry

D: Dosage
E: Efficacy
M: Metabolism/kinetics
T: Toxicity
O: Other
Frequency of Psychiatric Pharmacogenomic Variants

CYP2D6 Frequency Activity Score

Table 1. Assignment of likely phenotypes based on diplotype.

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (≤ 0.05% of patients)</td>
<td>&gt; 2.0</td>
<td>An individual carrying duplications of functional alleles</td>
<td>(*/2/*1/4/*4, */1/*2/*4, */2/*2/*4)</td>
</tr>
<tr>
<td>Normal metabolizer (~72.98% of patients)</td>
<td>1.0-2.0</td>
<td>An individual carrying two normal function alleles or two decreased function alleles or one normal and one function allele or one normal function and decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0-2.0.</td>
<td>3/*1/4, */1/*2/*4, */2/*2/*4, */3/*3/*4, */4/*4/*4</td>
</tr>
<tr>
<td>Intermediate metabolizer (~1.13% of patients)</td>
<td>0.5</td>
<td>An individual carrying one decreased function and one non-function allele</td>
<td>4/*4, 3/*5/*5, 3/*6, */6/*6</td>
</tr>
<tr>
<td>Poor metabolizer (~1.60% of patients)</td>
<td>0</td>
<td>An individual carrying only non-function alleles</td>
<td>4/*4, 3/*5/*5, 3/*6, */6/*6</td>
</tr>
</tbody>
</table>

https://www.pharmgkb.org/page/pgxGeneRef
CYP2D6 Relevant Psychiatric Medications

• Primary metabolic pathway(s)
  • Fluvoxamine, fluoxetine, amitriptyline, nortriptyline, desipramine, paroxetine, venlafaxine, aripiprazole, brexpiprazole, cariprazine, haloperidol, risperidone, amphetamine, atomoxetine, propranolol

• Secondary metabolic pathway(s)
  • Duloxetine, Citalopram, escitalopram, mirtazapine, sertraline, trazodone, vilazodone, olanzapine, vortioxetine, clozapine, quetiapine, buspirone, chlorpromazine, propranolol
PGx Interventions for Meds Prescribed through CYP2D6

- PharmGKB lists 125 clinical annotations with prescribing consideration

Psychiatric
  - **Level 1A**
    - Amitriptyline(T,M), aripiprazole(M), atomoxetine(M,T), clomipramine(T,M), codeine(E,T,M), desipramine(M,T), doxepin(M), fluvoxamine(M), haloperidol(M), hydrocodone(E,M), imipramine(M,T,O), metoprolol(D,M), nortriptyline(M,T), paroxetine(M), risperidone(M), tramadol(E,M,T), trimipramine(M), venlafaxine(M,T)
  - **Level 2A**
    - Mirtazapine(M), oxycodone(M), tramadol(D)
  - **Level 3**
    - Amitriptyline(M), atomoxetine(M), citalopram(E,O), codeine(T), dextromethorphan(O), donepezil(O), escitalopram(E), fentanyl(M,O), fluoxetine(M), galantamine(O), hydrocodone(T), iloperidone(T), methadone(E,M,O) methylphenidate(T), metoprolol(E,M), olanzapine(T), oxycodone(T), risperidone(M), sertraline(D), thioridazine(O), venlafaxine(M), vortioxetine(M)
  - **Level 4**
    - Citalopram(T), methadone(M-allele specific), oxycodone(E,T), propranolol(O)

https://www.pharmgkb.org/gene/PA128/clinicalAnnotation
### Table 2a: Dosing recommendation for paroxetine based on CYP2D6 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 Ultrarapid metabolizer</td>
<td>Increased metabolism to less active compounds when compared to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.</td>
<td>Select alternative drug not predominantly metabolized by CYP2D6.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2D6 Extensive metabolizer</td>
<td>Normal metabolism</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2D6 Intermediate metabolizer</td>
<td>Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 Poor metabolizer</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Select alternative drug not predominantly metabolized by CYP2D6 or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.</td>
<td>Optional</td>
</tr>
</tbody>
</table>
### CPIC CYP2D6 Antidepressants

#### Table 2b Dosing recommendation for fluvoxamine based on CYP2D6 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 Ultrarapid metabolizer</td>
<td>No data available for CYP2D6 ultrarapid metabolizers.</td>
<td>No recommendation due to lack of evidence&lt;sup&gt;c&lt;/sup&gt;.</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2D6 Extensive metabolizer</td>
<td>Normal metabolism</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2D6 Intermediate metabolizer</td>
<td>Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 Poor metabolizer</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Consider a 25–50% reduction&lt;sup&gt;d&lt;/sup&gt; of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Optional</td>
</tr>
</tbody>
</table>
## Venlafaxine

<table>
<thead>
<tr>
<th>ALLELE/GENOTYPE/PHENOTYPE</th>
<th>DRUG</th>
<th>DESCRIPTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 UM</td>
<td>venlafaxine</td>
<td>It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite O-desmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine.</td>
<td>1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine 2. if necessary, increase the dose to 100% of the standard dose 3. if dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline</td>
</tr>
<tr>
<td>CYP2D6 IM</td>
<td>venlafaxine</td>
<td>There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.</td>
<td>It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline. - if it is not possible to avoid venlafaxine and side effects occur 1. reduce the dose 2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.</td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>venlafaxine</td>
<td>There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.</td>
<td>It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline. - if it is not possible to avoid venlafaxine and side effects occur 1. reduce the dose 2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum. Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this gene variation.</td>
</tr>
<tr>
<td>Phenotype</td>
<td>CYP2D6 ultrarapid metabolizer</td>
<td>CYP2D6 normal metabolizer</td>
<td>CYP2D6 intermediate metabolizer</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>CYP2C19 ultrarapid or rapid metabolizer</td>
<td>Avoid amitriptyline use&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Consider alternative drug not metabolized by CYP2C19&lt;sup&gt;4,8&lt;/sup&gt;</td>
<td>Consider alternative drug not metabolized by CYP2C19&lt;sup&gt;4,8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers),&lt;sup&gt;4,8&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Strong</td>
<td>Initiate therapy with recommended starting dose&lt;sup&gt;1&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Strong</td>
<td>Consider a 25% reduction of recommended starting dose&lt;sup&gt;1,9&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Moderate</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid amitriptyline use&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Initiate therapy with recommended starting dose&lt;sup&gt;1&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Strong</td>
<td>Consider a 25% reduction of recommended starting dose&lt;sup&gt;1,9&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
</tr>
<tr>
<td></td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Strong</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Avoid amitriptyline use&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose&lt;sup&gt;1,9&lt;/sup&gt; Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Moderate</td>
<td>Avoid amitriptyline use&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Moderate</td>
<td>Classification of recommendation&lt;sup&gt;5&lt;/sup&gt;: Optional</td>
</tr>
</tbody>
</table>

### CPIC Guideline

**Dosing for adults and children**

**Therapeutic drug monitoring suggested**

### Atomoxetine

#### Table 2: Dosing recommendations for atomoxetine based on CYP2D6 genotype for children

| Phenotype | A5 | Implication | Therapeutic recommendation | Classification of recommendation* |
|-----------|----|-------------|-----------------------------|--------------------------------)-- |
| CYP2D6 ultrarapid metabolizer | >2 | Based on very limited data available for CYP2D6 ultrarapid metabolizers taking atomoxetine, it is unlikely ultrarapid metabolizers would achieve effective serum concentrations for the intended effect at standard dosing. | Initiate with a dose of 0.5 mg/kg/day and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2-4 hours after dose administration. If > 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. | Moderate |
| CYP2D6 normal metabolizer | 1.5-2 | Normal metabolizers of atomoxetine have a lower likelihood of response as compared to poor metabolizers. This is associated with increased discontinuation due to lack of efficacy as compared to poor metabolizers. | Initiate with a dose of 0.5 mg/kg and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If > 200 ng/mL, consider a proportional dose increase to approach 400 ng/mL. | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (phenotype screening) | 1.0> (>10% present) | Possibly higher atomoxetine concentrations as compared to normal metabolizers but questionable clinical significance. Normal metabolizers with A5 of 1.0 or more are at an increased risk of increased discontinuation as compared to poor metabolizers. | Initiate with a dose of 0.5 mg/kg and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If > 200 ng/mL, consider a proportional dose increase to approach 400 ng/mL. | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (phenotype screening) | 1.0> (>20% present) | Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared to normal metabolizers. Individuals with A5 of 1.0 with CYP2D6*20 may be at an increased risk of increased discontinuation as compared to poor metabolizers. | Initiate with a dose of 0.5 mg/kg and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If > 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose. | Moderate |
| CYP2D6 intermediate metabolizer | 0.5 | Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared to normal metabolizers. Intermediate metabolizers may be at an increased risk of discontinuation as compared to poor metabolizers. | Initiate with a dose of 0.5 mg/kg/day and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If > 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose. | Moderate |
| CYP2D6 poor metabolizer | 0 | Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared to non-poor metabolizers. This may increase the occurrence of side effects, but also a greater improvement of ADHD symptoms as compared with poor metabolizers in those who tolerate treatment. Poor metabolizer status is associated with lower final dose requirements as compared to poor metabolizers. | Initiate with a dose of 0.5 mg/kg/day and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If > 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose. | Strong |

#### Table 3: Dosing recommendations for atomoxetine based on CYP2D6 genotype for adults

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>A5</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 ultrarapid metabolizer</td>
<td>&gt;2</td>
<td>Based on very limited data available for CYP2D6 ultrarapid metabolizers taking atomoxetine, it is unlikely ultrarapid metabolizers would achieve effective serum concentrations for the intended effect at standard dosing.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2-4 hours after dose administration. If &gt; 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 normal metabolizer</td>
<td>1.5-2</td>
<td>Normal metabolizers of atomoxetine have a lower likelihood of response as compared to poor metabolizers. This is associated with increased discontinuation due to lack of efficacy as compared to poor metabolizers.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If &gt; 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 normal metabolizer or intermediate metabolizer (phenotype screening)</td>
<td>1.0&gt; (&gt;10% present)</td>
<td>Possibly higher atomoxetine concentrations as compared to normal metabolizers but questionable clinical significance. Normal metabolizers with A5 of 1.0 or more are at an increased risk of increased discontinuation as compared to poor metabolizers.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and increase to 1.3 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If &gt; 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 normal metabolizer or intermediate metabolizer (phenotype screening)</td>
<td>1.0&gt; (&gt;20% present)</td>
<td>Decreased metabolism of atomoxetine higher atomoxetine concentrations as compared to normal metabolizers. Individuals with A5 of 1.0 with CYP2D6*20 may be at an increased risk of increased discontinuation as compared to poor metabolizers.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If &gt; 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 intermediate metabolizer</td>
<td>0.5</td>
<td>Decreased metabolism of atomoxetine higher atomoxetine concentrations as compared to normal metabolizers. Intermediate metabolizers may be at an increased risk of discontinuation as compared to poor metabolizers.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If &gt; 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2D6 poor metabolizer</td>
<td>0</td>
<td>Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared to non-poor metabolizers. This may increase the occurrence of side effects, but also a greater improvement of ADHD symptoms as compared with poor metabolizers in those who tolerate treatment. Poor metabolizer status is associated with lower final dose requirements as compared to poor metabolizers.</td>
<td>Initiate with a dose of 0.5 mg/kg/day and in the absence of adverse events after 2 weeks, consider obtaining a plasma peak concentration (2-4 hours after dose administration). If &gt; 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.</td>
<td>STRONG</td>
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<table>
<thead>
<tr>
<th>ALLELE/GENOTYPE/PHENOTYPE</th>
<th>DRUG</th>
<th>DESCRIPTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 UM</td>
<td>aripiprazole</td>
<td>-</td>
<td>NO action is needed for this gene-drug interaction. The genetic variation decreases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is no evidence that this increases the risk of reduced effectiveness.</td>
</tr>
<tr>
<td>CYP2D6 IM</td>
<td>aripiprazole</td>
<td>-</td>
<td>NO action is needed for this gene-drug interaction. The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.</td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>aripiprazole</td>
<td>-</td>
<td>The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite. Administer no more than 10 mg/day or 300 mg/month (66-75% of the standard maximum dose of aripiprazole).</td>
</tr>
<tr>
<td></td>
<td>brexiprazole</td>
<td>-</td>
<td>NO action is required for this gene-drug interaction. The gene variation results in a reduction of the exposure to brexiprazole, but there are no indications supporting a decrease in efficacy.</td>
</tr>
<tr>
<td>CYP2D6 IM</td>
<td>brexiprazole</td>
<td>-</td>
<td>NO action is required for this gene-drug interaction. There are indications supporting an increase in the exposure to brexiprazole, but no indications supporting an increase in side effects in patients with this gene variation.</td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>brexiprazole</td>
<td>-</td>
<td>The risk of side effects is theoretically increased, because the gene variation reduces the metabolism of brexiprazole. Use half of the standard dose.</td>
</tr>
</tbody>
</table>

https://www.pharmgkb.org/guidelineAnnotation/PA166104937
https://www.pharmgkb.org/guidelineAnnotation/PA166184527
### DPWG Guideline

**Haloperidol & Risperidone**

<table>
<thead>
<tr>
<th>ALLELE/GENOTYPE/PHENOTYPE</th>
<th>DRUG</th>
<th>DESCRIPTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 IM</td>
<td>haloperidol</td>
<td>The genetic variation results in a higher plasma concentration, but the effect is small and no clinically significant effects were found.</td>
<td>NO action is required for this gene-drug interaction.</td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>haloperidol</td>
<td>There are indications for an increased risk of side effects. The genetic variation leads to decreased conversion of haloperidol, resulting in plasma concentrations that are approximately 1.7-fold higher.</td>
<td>Use 60% of the standard.</td>
</tr>
<tr>
<td>CYP2D6 UM</td>
<td>haloperidol</td>
<td>There are indications of a risk of reduced effectiveness. The genetic variation leads to an increased conversion of haloperidol, resulting in a plasma concentration that is approximately 40% lower.</td>
<td>Use 1.5 times the standard dose or choose an alternative. Antipsychotics that are not metabolised by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, perphenazine, quetiapine, olanzapine or clozapine.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALLELE/GENOTYPE/PHENOTYPE</th>
<th>DRUG</th>
<th>DESCRIPTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 IM</td>
<td>risperidone</td>
<td>The percentage of patients with therapy failure increases from 16% to 37%. The gene variation leads to a high ratio of the active metabolite (9-hydroxyrisperidone (paliperidone)) compared to risperidone, which crosses the blood-brain barrier more effectively.</td>
<td>Choose an alternative or titrate the dose according to the maximum dose for the active metabolite (paliperidone) (oral 12 mg/day for adults and children from 15 years of age weighing at least 51 kg and 5 mg/day for children from 15 years of age weighing less than 51 kg; intramuscular 75 mg per 2 weeks).</td>
</tr>
<tr>
<td>CYP2D6 UM</td>
<td>risperidone</td>
<td>There is little evidence to support an increase in side effects caused by the gene variation. The gene variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.</td>
<td>NO action is needed for this gene-drug interaction.</td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>risperidone</td>
<td>The percentage of patients with therapy failure increased from 16% to 26%. The gene variation increases the plasma concentration of risperidone plus the active metabolite and increases the proportion of risperidone in this ratio, which is more effective at crossing the blood-brain barrier.</td>
<td>Use 67% of the standard dose. If problematic side effects originating in the central nervous system occur despite this reduced dose, then reduce the dose further to 50% of the standard dose.</td>
</tr>
</tbody>
</table>

[https://www.pharmgkb.org/guidelineAnnotation/PA166104988](https://www.pharmgkb.org/guidelineAnnotation/PA166104988)
[https://www.pharmgkb.org/guidelineAnnotation/PA166104943](https://www.pharmgkb.org/guidelineAnnotation/PA166104943)
How About CYP1A2? It’s Complicated

- Nomenclature and naming highly inconsistent making literature review complicated
- Food, drugs, environment all impact activity levels which are not reflected in the genotype

https://www.mayocliniclabs.com/api/sitecore/TestCatalog/DownloadTestCatalog?testId=610041
CYP1A2 Relevant Psychiatric Medications

• **Primary metabolic pathway(s)**
  • Duloxetine, fluvoxamine, mirtazapine, clozapine, olanzapine, propranolol

• **Secondary metabolic pathway(s)**
  • Nortriptyline, desipramine, haloperidol, ziprasidone, clonazepam

• **Level 3 Associations**
  • Caffeine(M,T), carbamazepine(M), antipsychotic QTc association(T), clozapine(T,M,O), escitalopram(T), olanzapine(E), paroxetine(E,D,T)

D: Dosage  
E: Efficacy  
M: Metabolism/kinetics  
T: Toxicity  
O: Other
Frequency of Psychiatric Pharmacogenomic Variants

https://www.pharmgkb.org/page/pgxGeneRef
Frequency of Psychiatric Pharmacogenomic Variants

HLA-A*31:01 Frequency Table

https://www.pharmgkb.org/page/pgxGeneRef
HLA Relevant Psychiatric Medications

- HLA-B*1502 and HLA-A*3101
  - Predictor for serious skin reactions, i.e. SJS
  - Relationship best understood with carbamazepine

Table 1: Association of HLA variations with SJS/TEN

<table>
<thead>
<tr>
<th>HLA Allele</th>
<th>Carbamazepine</th>
<th>Oxcarbazepine</th>
<th>Lamotrigine</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*1502</td>
<td>OR=80.70(^1)</td>
<td>OR=26.4(^4)</td>
<td>OR=2.40(^6)</td>
<td>OR=5.65(^9)</td>
</tr>
<tr>
<td>HLA-A*3101</td>
<td>OR=5.65(^1)</td>
<td>Not significant(^5)</td>
<td>Not significant(^8)</td>
<td>Not significant(^8)</td>
</tr>
</tbody>
</table>

https://genesight.com/white-papers/get-to-know-a-gene-hla-b1502-and-hla-a3101/
Pharmacogenetic testing should be viewed as a decision-support tool

Recommendations:
- HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine
- Evidence to support widespread pharmacogenetic tests is inconclusive
- Providers are encouraged to integrate PGx results (when already available) into their medication selection and dosing decisions
  - How will you approach the patient with PGx test results from another provider wanting PGx applied to their psych care?
- CYP2C19 and CYP2D6
  - Most beneficial for individuals with inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial
Discordance Between Organizations

• CPIC uses published peer-reviewed literature
  • Source of recommendations is known
• FDA has access to all clinical trial data
  • Source/data for recommendations is unknown
• FDA table includes psych meds where CPIC guidelines do not yet exist
  • Amphetamine, aripiprazole, brexpiprazole, clozapine, venlafaxine, vortioxetine, perphenazine, amoxapine, diazepam, propranolol, protriptyline, risperidone
• DPWG guidelines also provide different recommendations and cover a different array of medications
• How often do guidelines in psychiatry or pain agree on clinical recommendations?
• Relative consensus that CYP2D6, CYP2C19, HLA-B*1502, HLA-A*3101 are meaningful/useful for psychiatry

Psychiatric Pharmacodynamic Genes: The Short List

- Available on numerous commercial panels
- ADRA2A, BDNF, COMT, CRHR1, FKBP5, GRIK1, GRIK4, GRIN2B, HTR1A, HTR2A, MTHFR, DBH, DRD2, SLC6A2, SLC6A4, ABCB1, OPRM1, UGT2B15 and many others
  - All level 3 in relation to psychiatry

3: Low level association with at least one study suggesting association

Level 3
Psychiatrically Focused Phenoconversion
(Per Flockhart table available at https://drug-interactions.medicine.iu.edu/MainTable.aspx, other references often rate degree of inhibition and induction differently)

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>2B6</th>
<th>1A2</th>
<th>2C19</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>clopidogrel</td>
<td>amiodarone</td>
<td>armodafinil</td>
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<tr>
<td></td>
<td>thiotepa</td>
<td>cimetidine</td>
<td>chloramphenicol</td>
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<td>ticlopidine</td>
<td>citalopram</td>
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<tr>
<td></td>
<td>voriconazole</td>
<td>esomeprazole</td>
<td>citralopram</td>
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<tr>
<td>abiraterone</td>
<td></td>
<td>flurbiprofen</td>
<td>felbamate</td>
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<tr>
<td>amiodarone</td>
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<td>fluconazole</td>
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<td>bupropion</td>
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<td>fluvoxamine</td>
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<tr>
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<td>isoniazid</td>
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<td>chlorpromazine</td>
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<td>ketoconazole</td>
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<tr>
<td>cocaine</td>
<td></td>
<td>naproxen</td>
<td>naproxen</td>
</tr>
</tbody>
</table>

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual’s response to that particular medication, e.g. making it ineffective.

- A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A Moderate inhibitor is one that causes a 2-fold to < 5-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A Weak inhibitor is one that causes a 1-2.5-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.
- A In-Vitro Only In-Vitro Only Inhibitor strength.
- TSD Inhibitor strength level is under review.

2D6
- diphenhydramine
- doxepin
- duloxetine
- halofantrine
- hydroxyzine
- loracarlatin
- metoprolol
- metoprolol tartrate
- methadone
- metoclopramide
- midodrine
- moclobemide
- panobinostat
- paroxetine
- perphenazine
- promethazine
- quinidine
- rolaperidone
- sertraline
- terbinafine (oral)
- triethylamine
- tramadol
- tramadone
- verapamil
- nifedipine
- nefazodone
- esomeprazole
- fluconazole
- netupitant
- omeprazole
- pantoprazole
- idelalisib
- indinavir
- ifraconazole
- ivermectin
- ketconazole
- lesinurad
- letrozole
- riboflavin
- mifepristone
- tadalafil
- telithromycin
- tucatinib
- verapamil
- voriconazole
- efavirenz
- fluvoxamine
- fostinetin
- lufonavir
- simprevir
- voriconazole
Psychiatrically Focused Phenoconversion

(Per Flockhart table available at https://drug-interactions.medicine.iu.edu/MainTable.aspx, other references often rate degree of inhibition and induction differently)

### Inducers

<table>
<thead>
<tr>
<th>1A2</th>
<th>2B6</th>
<th>2C8</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>2E1</th>
<th>3A457</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-naphthoflavone</td>
<td>artemisinin</td>
<td>rifampin</td>
<td>carbamazepine</td>
<td>carbamazepine</td>
<td>enzalutamide</td>
<td>enzalutamide</td>
<td>barbiturates</td>
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<td>dabrafenib</td>
<td>efavirenz</td>
<td>efavirenz</td>
<td>etermovir</td>
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<td>nevirapine</td>
<td>nevirapine</td>
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<td>rifampin</td>
<td>rifampin</td>
<td>rifampin</td>
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<td>charcoal-grilled meat</td>
<td>phenobarbital</td>
<td>st. john's wort</td>
<td>st. john's wort</td>
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<td>st. john's wort</td>
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<td>alendronate</td>
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<td>rifampin</td>
<td>roflumilast</td>
<td>st. john's wort</td>
<td>st. john's wort</td>
<td>etermovir</td>
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<td>st. john's wort</td>
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<td>etermovir</td>
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<td>letrozol</td>
<td>letrozol</td>
<td>troglitazone</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>vemurafenib</td>
</tr>
</tbody>
</table>
PGx, especially kinetic relationships, have adequate data for use in Psychiatry

- CYP2D6 and CYP2C19 currently offer the most clinically relevant information
- Best used as a ‘probability shifter’ versus a definitive answer
- Over time, pharmacodynamic PGx is anticipated to have higher impact

No PGx test accounts for drug interactions

- Phenoconversion from drugs, food, & substances NOT accounted for on a PGx test
- Pharmacoepigenetics is in early stages, may matter more than pharmacogenomics?
- Clinician must use PGx data in conjunction with knowledge of drug/food metabolism and drug/food/environment interactions for accurate interpretation

Complex disease states will likely be the last to validate or invalidate the benefit of PGx

- Polygenic scoring tools that include genetics and PGx may drastically shift care
- Genetics of the conditions themselves are not well understood
Conclusion

• PGx has potential to narrow the scope of medication selection and serve as an added tool for treatment selection

• Treatment response to medications is relatively low across psychiatric diagnosis and side effect rates are high, PGx may assist in shifting risk/benefit profiles of medication

• Growing evidence (i.e., ISPG) supports the use of CYP2D6 and CYP2C19 testing, particularly in patients with difficulty tolerating medications or in those with poor treatment response

• PGx is not a replacement for clinical judgment, evidence-based practice, or clinical decision making
References

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- Krebs et al. Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of good. Human Genomics volume 13, Article number: 39 (2019)
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References

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- Lexicomp and pharmgkb (for each specific drug:gene pathway)
- Pharmacogenomics guidelines (DPWG) | Ubiquitous Pharmacogenomics (U-PGx) (upgx.eu)
- VA/DoD treatment guidelines: VA/DoD Major Depressive Disorder Clinical Practice Guideline
Contact/Inquiries/Networking

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National Pharmacogenomics Program

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Break
Current PGx Research

David Oslin, MD
Associate Chief of Staff for Behavioral Health
Director, VISN 4 Mental Illness Research, Education, and Clinical Center
Corporal Michael J. Crescenz VA Medical Center (Philadelphia)
Precision Mental Health Care

- Measurement-Based Care (PROM)
- Patient Experience
- Adherence
- Comorbidities
- Cost
- Family History
- Adverse Effects
- Current Treatments
- Biomarkers including genomics / PGx
- Imaging
- Passive Health Monitoring
- Neuropsych testing
- Neuropsych testing
- Imaging
- Biomarkers including genomics / PGx
- Current Treatments
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- Current Treatments
- Biomarkers including genomics / PGx
- Imaging
- Neuropsych testing
- Measurement-Based Care (PROM)
- Patient Experience
- Adherence
- Comorbidities
- Cost
- Family History
- Adverse Effects
- Current Treatments
- Biomarkers including genomics / PGx
- Imaging
- Neuropsych testing
What Is the Evidence?
• “There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants”

• This was prior to the 2 most recent trials and recognized the relatively small samples in most of the trials
Current State of Evidence for Depression Treatment

• Several small trials and non-randomized
• 5 randomized trials of reasonable size
  • Bradley et al 2017 – 685 subjects, NeuroIDgenetix
  • Perez et al 2017 – 280 subjects, Neuropharmagen
  • Perlis et al 2020 – 304 subjects, Genecept
  • Greden et al 2019 – 1167 subjects, GeneSight
  • Oslin et al 2022 – 1944 subjects, GeneSight
GUIDED: Large-Scale Pragmatic Trial of PGx in Patients with MDD

• Multi-center trial (60 participating sites)
• Funded by Assurex (now Myriad Genetics): GeneSight PGx battery
• 1167 consenting adults with MDD who had failed at least one 8-week trial of an AD in the current episode
• Random assignment, double blind assessment (patients and raters)
• Outcomes evaluated over 12 weeks
• Primary and secondary hypotheses specified, exploratory tests in “congruent” and “incongruent” subgroups
Medication congruency with the pharmacogenomic test increased 11.8% in the PGx-guided-care arm while it stayed constant for the TAU arm (note scale is not 0 – 100%).

GUIDED: Depression Outcomes

Treatment guided by pharmacogenomic testing resulted in a 50% improvement in remission rates and a 30% increase in response rates at week 8 compared to TAU. Symptom improvement in the guided-care arm trended toward significance at week 8 compared to TAU.

PRIME Care Study

• VA-funded multi-site RCT aimed to enroll 2000 Veterans with depression at 22 sites

• Patient/provider dyads randomly assigned to:
  
  • Pharmacogenomic (PGx) Guided Group: received results of the PGx battery right after randomization
  
  • Usual Care Group: received results after 6 months of treatment as usual

• Outcomes measured over 6 months from randomization by blinded centralized outcome group (via telephone)
Inclusion / Exclusion Criteria

- Determined by provider (via referral form):
  - Symptomatic MDD (Single or Recurrent)
  - Starting or switching an antidepressant as monotherapy
  - Exclusions:
    - Active substance use disorder, bipolar illness, psychosis, borderline or antisocial personality disorder
    - Currently prescribed antipsychotic medication, methadone, buprenorphine, or naltrexone
    - Requiring hospitalization or urgent care services at the outset of treatment

- Determined by self report / chart review
  - PHQ-9 > 9
  - Age 18 - 80
### Baseline Demographics and Social Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmacogenomic-guided group (n=966)</th>
<th>Usual care group (n=978)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD) year</td>
<td>48 (15)</td>
<td>47 (15)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>229 (24)</td>
<td>262 (27)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>737 (76)</td>
<td>716 (73)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American/Black, No. (%)</td>
<td>185 (19)</td>
<td>167 (17)</td>
</tr>
<tr>
<td>Asian Pacific Islander, No. (%)</td>
<td>31 (3)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Native American/Alaskan, No. (%)</td>
<td>10 (1)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>644 (67)</td>
<td>688 (70)</td>
</tr>
<tr>
<td>Other/Mixeda, No. (%)</td>
<td>90 (9)</td>
<td>84 (9)</td>
</tr>
<tr>
<td>Refused, No. (%)</td>
<td>6 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Hispanic, No. (%)</td>
<td>113 (12)</td>
<td>104 (11)</td>
</tr>
<tr>
<td><strong>Financial status, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have just enough to get along</td>
<td>482 (50)</td>
<td>492 (50)</td>
</tr>
<tr>
<td>Are comfortable</td>
<td>338 (35)</td>
<td>352 (36)</td>
</tr>
<tr>
<td>Can't make ends meet</td>
<td>127 (13)</td>
<td>116 (12)</td>
</tr>
</tbody>
</table>
## Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Pharmacogenomic-guided group (n=966)</th>
<th>Usual care group (n=978)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 score, mean (SD) (inclusion criteria &gt;9)</td>
<td>17.5 (4.3)</td>
<td>17.5 (4.3)</td>
</tr>
<tr>
<td>Treatment refractory, No. (%)</td>
<td>288 (30)</td>
<td>301 (31)</td>
</tr>
<tr>
<td>GAD-7 score, mean (SD)</td>
<td>14.1 (4.8)</td>
<td>13.9 (5.0)</td>
</tr>
<tr>
<td>PTSD presence, No. (%)</td>
<td>566 (59)</td>
<td>562 (58)</td>
</tr>
<tr>
<td>PCL-5 score in those with PTSD, mean (SD)</td>
<td>51.5 (12.0)</td>
<td>51.8 (12.0)</td>
</tr>
<tr>
<td>Suicidal ideation (C-SSRS) (moderate or higher risk), no/N. (%)</td>
<td>187/597 (31)</td>
<td>190/596 (32)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinks per week, median (IQR)</td>
<td>0 (3)</td>
<td>0 (4)</td>
</tr>
<tr>
<td>Recent regular (last 3 months) marijuana use, No. (%)</td>
<td>227 (23)</td>
<td>238 (24)</td>
</tr>
<tr>
<td>Other recent regular (last 3 months) drug use, No. (%)</td>
<td>15 (2)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Current tobacco use, No. (%)</td>
<td>256 (27)</td>
<td>250 (26)</td>
</tr>
<tr>
<td>VR-12 mental composite score, mean (SD)</td>
<td>23.8 (10.6)</td>
<td>24.9 (10.2)</td>
</tr>
<tr>
<td>VR-12 physical composite score, mean (SD)</td>
<td>37.9 (13.4)</td>
<td>36.4 (13.1)</td>
</tr>
</tbody>
</table>
Percent Remission (≤5 on the PHQ-9)

Pooled effect of group over time OR=1.28 (1.05-1.57) p=0.02
Response and Remission

Response (>50% decrease in the PHQ-9)

Pooled effect of group over time
OR=1.25 (1.07-1.46) p=0.005

Symptom Improvement (ΔPHQ-9)

Pooled effect of group over time
OR=0.56 (0.17 to 0.95) p=0.005
A Closer Look at PTSD and TRD

Response at 12 weeks

OR 1.62 (1.04, 2.52)

OR 1.80 (1.08, 2.99)

OR 1.42 (0.93, 2.16)

OR 1.12 (0.62, 2.01)

No PTSD/TRD

TRD Only

PTSD Only

PTSD & TRD

Usual Care

PGx Guided
PGx and Adverse Drug Reactions (ADRs)
PREPARE Study

- 6944 patients
- 93.5% carried 1 actionable genotype
- 25% had an actionable genotype and were exposed to that medication

doi: 10.1016/S0140-6736(22)01841-4
Next Steps for Implementing PGx More Broadly

• Provider and patient education
  • Tests don’t currently provide treatment subtypes or response types
  • Tests don’t identify the “best medication”
  • The number needed to test for this specific question is 5.

• Testing
  • Which test
  • Which patients

• Clinical decision support
  • Informatics investments are needed to display clinical decision support at the time of prescribing
  • Investments (i.e., pharmacy) are needed to create and continuously update decision support recommendations
Which Patients?

- **Choices**
  - By provider / interest – typically driven by complexity for providers.
  - Treatment refractory patients – those being referred for ketamine/esketamine, TMS, ECT, ect
  - Those with >1 psychotropic but still symptomatic – broader than treatment refractory.
  - By diagnosis
    - Depression, PTSD, Bipolar
Clinical Case Examples

Anna Daily, DNP, PMHNP
*Lead Nurse Practitioner, MHCL*
*Women’s Mental Health Champion*
*MHCL VVC Champion*
*Cincinnati VA Medical Center*

Mariana Mendez-Tadel, MD
*Attending Psychiatrist*
*Corporal Michael J. Crescenz VA Medical Center (Philadelphia)*
Integrating PGx into Your Practice

Deepak Voora, MD

Acting Executive Director, VA National Pharmacogenomics Program
National Oncology Program Office
Veterans Health Administration
Agenda

• How to select a PGx test
• How to order a PGx test
• Interpreting a PGx test result
• PGx care coordination
• Future directions
How to Select a PGx Test
How to Select a PGx Test

• Main ‘pharmacogenes’ related to psychotropics
  • \textit{CYP2D6}
  • \textit{CYP2C19}
  • \textit{CYP2B6}
  • \textit{CYP3A4}
  • \textit{CYP1A2}
  • \textit{HLA-A} and \textit{HLA-B}

• Many others with emerging levels of evidence

• \textbf{How many and which genes do you want to test for?}
Individual Genes Approach

Pros
• Best for 1-3 genes
• Most likely to be available on existing lab contracts
  • No need for additional contract
  • Pricing fixed/negotiated
• Minimal ‘incidental findings’
• Simple consent

Cons
• Tests are not standardized or ‘vetted’ by VA
  • Alleles, interpretations
• Often will not come with therapeutic recommendations
• Data are not integrated into medical record
  • E.g., CYP2C19 use for clopidogrel
Panel-Based PGx Tests

**Pros**

- Multiple genes → single drug
  - $CYP2D6$ & $CYP2C19$
- Multiple drugs ← single gene
  - $CYP2C19$ & clopidogrel
- $\downarrow$ Cost $\uparrow$ efficiency
  - Fewer orders/tests over time
  - Cost of a panel ~ cost of a gene
- 1 in 2 Veterans will be prescribed another PGx drug over 4 years
- Frequently accompanied by therapeutic recommendations

**Cons**

- Responsibility for additional genetic data
  - Storage over time
  - Updates
  - Coordination with health care providers
- No standardization for evidence used for recommendations
  - CPIC, DPWG, Pubmed, proprietary
- Consent may have to include information about heritable conditions
- Report may not mention non-psychotropics impacted
- At non-PHASER sites incidental findings are responsibility of provider
Non-Proprietary Panel-Based PGx Tests

**Pros**
- Usually provide transparency with recommendations
  - Exemplars:
    - Sanford Imagenetics, OneOme, Invitae, Tempus
  - Some on federal supply schedule
    - Exemplars: Millennium

**Cons**
- Some will not provide therapeutic recommendations only genetic test results
  - Exemplars: ARUP, Quest
Proprietary PGx-panels

**Pros**
- Proprietary algorithm that interprets test results
  - *Claim* to be superior to CPIC, DPWG recommendations
- Targeted to specific therapeutics (e.g., psychotropics)
- Exemplars
  - Myriad (GeneSight)

**Cons**
- Proprietary algorithm that interprets test results
  - Not transparent
- Comparative effectiveness studies vs. non-proprietary panels are lacking
- Cost vs. non-proprietary panels
  - Thousands vs. hundreds
How to Order a PGx Test
PGx Decision Tree

- **# of Genes**
  - **Oligo (1-3)**
    - Local lab/approval
  - **Panel (>1)**
    - Proprietary
    - Nonproprietary
      - PHASER supported site
        - Sanford/Fulgent
      - Non PHASER supported sites
        - Other vendors -->
          - Local lab/approval
    - Local lab/approval
PHASER provides ‘end-to-end’ solution for implementing PGx in any VA health system

- **Provider-friendly summary** of PGx test results in VistA Imaging
- **Return of results** to patients is handled by the PHASER program
- **Educational materials** (TMS modules and written materials) to review testing and interpretation
- Pharmacogenomics trained **pharmacist** for post-testing consultation
- **EHR Templates** to facilitate documentation/ordering
- Automated **clinical decision support tools** for point-of-prescribing alerts for drug-gene interactions
- Learning **community of practice** with a PHASER listserv and monthly case conference
PHASER Site Implementation
PHASER-Supported laboratory Vendors

• NY State
  • Fulgent Focus PGx panel
  • 18-gene panel impacting 47 medications (SSRIs, TCAs and other non-psychotropics)

• Non NY-state
  • Sanford Imagenetics PGx panel
  • 11-gene panel impacting 44 medications (SSRIs, TCAs and other non-psychotropics)
Step 1: Check for Previous Testing at PHASER-Supported Sites

• Check the ‘Postings’*. Select "Pharmacogenomics Note" to open note, including results, if available

*Clinical Posting not installed at all PHASER Sites

• Start a new note using “Pharmacogenomics Note” template. If the patient had previously been consented, the following text would appear in the note template presented:
Step 2: Educate the Patient – VHA Guidelines Require Documentation of Oral Consent for all PGx Testing

- Patient educational brochure.
- YouTube video for providers (5:04)
Key Information to Convey in Consenting for Panel-Based PGx Testing at PHASER Sites

- VA offers genetic testing to Veterans
- Covers 40+ medications
- Aims to improve medication efficacy & reduce toxicity
- Results may identify increased risk for certain health conditions – will inform Veteran if this is the case
- 1x blood test, results back in 2 weeks
- NOT a research study but a clinical program

= new content as of 11/22
1. Click the **New Note** button on the **Notes** tab
2. Begin typing ‘**pharmacogenomics**’ in the **Progress Note Title** box
3. Choose **PHARMACOGENOMICS NOTE** (not the e-consult)
4. Follow the prompts to document attestation and patient agreement to testing
5. Click “Finish”
6. Accept order that pops up on following screen
Document the patient’s decision regarding PGx testing
Ordering PHASER PGx Testing in VistA: Order Automatically Launches

*Note: using the note template is the preferred way to access lab order*

*Set collection/ start date as desired*
PGx Care Pathway for PHASER-Supported Cerner Sites
All Other Panels or Non-PHASER Sites

- Step #1: Query local lab for which vendors have contract for send out laboratories (e.g., Labcorp, Quest, ARUP, Mayo)
- Step #2: Search vendor test menu by gene name
  - https://www.labcorp.com/test-menu/search?query
  - https://testdirectory.questdiagnostics.com/test/home
  - https://www.aruplab.com/testing
- Step #3: Seek local approval and procedure for ordering one or more genes or gene panels
What Happens Next?

- Most laboratories require blood sample
  - Some may support saliva collection (local workflow)
- Typical turnaround times are 7-10 business days
- Non-PHASER sites
  - Notification like other laboratory testing
- PHASER-supported sites
  - ‘Additional signer’ on Pharmacogenomics Results note in CPRS
  - Results message in Cerner
Interpreting a PGx Test Result
Interpreting PGx Test Result

• Individual gene results
  • Usually, a comment to a CPRS miscellaneous lab test
    • Not standardized/searchable
    • Typically, only genotype/phenotype transcribed/pasted into CPRS
      • Usually without drug implications/recommendations
Resources to Assist with Interpretation

- National Pharmacogenomics Program [SharePoint](#) for supported genes/drugs
  - Executive summary (1-page overview)
  - Dosing guidelines (CPIC)
  - Videos describing drug-gene interactions (PharmGKB)
  - Drug label information (FDA)
DIY PGx Interpretation – CYP2C19 and Citalopram Example

Phenotype for CYP2C19
Poor Metabolizer

Classification: Moderate

Recommendation
Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.

Implications for CYP2C19
Greatly reduced metabolism when compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects.

Comments
Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age. Percent dose adjustments corresponding to percent difference in oral clearances have been calculated/estimated by Stingl et al. (PMID 22665786).
Examples of Non-Proprietary Panel-Reports (Varying Levels of Interpretation/Utility)

Example A

Example B

Genotype-predicted interactions for medications

Allergy/Pulmonary

- Moderate drug interaction

- Limited pharmacogenomic impact

- Chromosomal

- Metabolic

- Normalized

Antihistamines

- Moderate drug interaction

- Limited pharmacogenomic impact

- Chromosomal

- Metabolic

- Normalized

Antibiotics/antimicrobials

- Moderate drug interaction

- Limited pharmacogenomic impact

- Chromosomal

- Metabolic

- Normalized
Example Proprietary PGx Panel Report

Example

Antidepressants

Use as Directed
- Desvenlafaxine (Venlafaxine®)
- Venlafaxine (Venlafaxine®)
- Venlafaxine (Effexor®)

Tricyclics (Dissolved)
- Nortriptyline (Pamelor®)
- Amitriptyline (Elavil®)
- Imipramine (Tofranil®)
- Trimipramine (Surmontil®)
- Desipramine (Norpramin®)
- Nefazodone (Serzone®)
- Duloxetine (Cymbalta®)
- Lithium Carbonate (Lithobid®)

Moderate Gene-drug Interaction

Significant Gene-drug Interaction

Clinical Considerations
1. Therapeutic index may be too high. Lower doses may be required.
2. Therapeutic index may be too low. Higher doses may be required.
3. Difficult to predict dose adjustments due to conflicting variations in metabolism.
4. Changes in drug may result in drug absorption and result in mild to moderate reduced efficacy.
5. Use of this drug may increase risk of side effects.
6. FDA label identifies a potential gene-drug interaction for this medication.

CONFIDENTIAL HEALTHCARE INFORMATION
Additional Resources

• VISN4 MIRECC YouTube video for interpreting GeneSight report (14:47).

• PHASER YouTube video for interpreting Sanford Imagenetics report (5:19)
• Always consider pharmacogenomics test results in the context of your patient

• PGx is one piece of the puzzle
How Do I Act on PGx Test Results?

• For **existing** medications that you prescribe: Ask if you and your patient are satisfied with medication response (efficacy or toxicity).
  - Review PDF for alternative therapies if **not** satisfied with current medications

• For **newly** prescribed medications (my approach):
  - Rank the medications you are considering based on non-genetic factors
  - Reference PDF report for recommendations & dosing information and re-rank your list
  - If the re-ranked list makes sense for you and your patient → write your prescription.
  - If not, that’s OK! Just document your rationale.
PGx Consultation Services at PHASER-Supported Sites

VistA
Pharmacogenomics interfacility e-consult for patient-specific, clinical questions:

- In general, Genomic Medicine Service, does not view PGx as within scope
- In FY24 new PGx trained local/VISN pharmacists will be available at selected sites.
- Non-PHASER sites
  - Email: phasertechsupport@va.gov to install IFC
Sharing PGx Results with Patients

• Return of PGx to patients – like all laboratory results - required by VHA
• Empowers patients to utilize their PGx test results
• Allows sharing with non VA providers
Resources to Support Sharing PGx Results

- PHASER-supported sites

- Provider video (15:01)

Return of PGx test result via mail

PGx Educational Video
PGx Care Coordination
Unique Features of PGx Testing

• Unlike other laboratory testing PGx testing has implications beyond the initial use case (i.e., new psychotropic prescription)
  • Additional considerations for medications impacted by PGx test result

• Heritable conditions

• The scope/scale of additional impact beyond use case depends on the type of PGx test selected
Impact of PGx Beyond Initial Use

• Relevant for single-gene and panel-based PGx testing
  • Examples:
    • $CYP2D6$ (SSRIs) $\rightarrow$ tramadol/codeine
    • Panel-based PGx tests can impact up to 100 additional medications

• Reports may not indicate additional implications

• Scope
  • Existing medications with drug-gene interactions
  • Future medications with drug-gene interactions
    • In/outside VA
### Clinical Decision Support Tools — STORM

**STORM Patient Detail Report**

**Stratification Tool for Opioid Risk Mitigation**

Data generated from a 1-day log from CMS entry. This report is to be used along with the electronic medical record and direct discussion with the patient to help facilitate decision making. STORM predicts risk of overdose or suicide-related health events or death. STORM should not be used for research, only for individual and quality improvement purposes. Warning: Discontinuing opioids does not necessarily reduce your patient’s risk and may actually increase their risk. Always discuss potential risks with patients and their caregivers.

If a patient is registered at a facility using the Comar EHR and/or scheduling system, some of the patient’s health, demographic, or appointment data may be coming from Comar Check-JUV to view records from both VistA and Comar. Notify helpdesk if any data appears to be inconsistent.

#### Patient Information

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Risk Mitigation Strategies (qu吃得 for very high risk)</th>
<th>Non-pharmacological Pain Tx</th>
<th>Care Providers</th>
<th>Recent Appointments</th>
<th>Upcoming Appointments</th>
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<tbody>
<tr>
<td>Substance use disorder</td>
<td>Yes</td>
<td>Active Therapies</td>
<td>MH Appointment</td>
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<tr>
<td>Alcohol Use Disorder (restricted definition)</td>
<td>Yes</td>
<td>Other Therapies</td>
<td>MH Appointment</td>
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<tr>
<td>Mental Health</td>
<td>Yes</td>
<td>Cognitive Therapies</td>
<td>MH Appointment</td>
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<tr>
<td>Blood Pressure</td>
<td>Yes</td>
<td>Occupational Therapy</td>
<td>MH Appointment</td>
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<tr>
<td>Depression</td>
<td>Yes</td>
<td>Physical Pain Clinic</td>
<td>MH Appointment</td>
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<td>Stress Disorders</td>
<td>Yes</td>
<td>Mental Health Therapy/Pain</td>
<td>MH Appointment</td>
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<tr>
<td>Other Major Medical Conditions</td>
<td>Yes</td>
<td>Specialty Therapy</td>
<td>MH Appointment</td>
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<td>Mental Health/Depression</td>
<td>Yes</td>
<td>Other Therapies</td>
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<td>Acute Pain</td>
<td>Yes</td>
<td>Current Pain</td>
<td>MH Appointment</td>
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<td>Chronic Pain</td>
<td>Yes</td>
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<tr>
<td>Chronic Pulmonary Disease</td>
<td>Yes</td>
<td>Medical Pain Clinic</td>
<td>MH Appointment</td>
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<tr>
<td>Congenital Heart Failure</td>
<td>Yes</td>
<td>Adult Services</td>
<td>MH Appointment</td>
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<td>Renal Disease</td>
<td>Yes</td>
<td>Spine Surgery</td>
<td>MH Appointment</td>
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<td>Diabetes</td>
<td>Yes</td>
<td>Trauma Care</td>
<td>MH Appointment</td>
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<td>Hypertension</td>
<td>Yes</td>
<td>Other Therapies</td>
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<td>Cardiac Arrest</td>
<td>Yes</td>
<td>Mental Health Therapy/Pain</td>
<td>MH Appointment</td>
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<td>Neurological disorders</td>
<td>Yes</td>
<td>Specialty Therapy</td>
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<td>Weight Loss</td>
<td>Yes</td>
<td>Other Therapies</td>
<td>MH Appointment</td>
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<td>Adverse Event</td>
<td>Yes</td>
<td>Cognitive Therapies</td>
<td>MH Appointment</td>
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<tr>
<td>Related to Falls</td>
<td>Yes</td>
<td>Occupational Therapy</td>
<td>MH Appointment</td>
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</tr>
</tbody>
</table>

**Patient: JZTTESTPATIENT, SPONGE JOHN**

**Age:** 62

**Gender:** M

**Who Contributed to my patient’s risk?**

- Substantial use disorder
- Alcohol Use Disorder (restricted definition)
- Mental Health
- Blood Pressure
- Depression
- Other Major Medical Conditions
- Acute Pain
- Chronic Pain
- Chronic Pulmonary Disease
- Congenital Heart Failure
- Renal Disease
- Diabetes
- Hypertension
- Cardiac Arrest
- Neurological disorders
- Weight Loss
- Adverse Event
  - Related to Falls
  - Opioid Antidepressants
  - Acetaminophen/Hydrocodone
  - Other Pain Medications
  - Other Pain Medications

**How can I follow-up with this patient?**

- 3/28/2022 MH Appointment
- Other Therapies
- 3/28/2022 MH Appointment
- Occupational Therapy
  - 3/28/2022 MH Appointment
  - Physical Therapy/Pain
  - 3/28/2022 MH Appointment
- Specialty Therapy
  - 3/28/2022 MH Appointment
- Other therapy
  - 3/28/2022 MH Appointment
- MH Appointment
  - 3/28/2022 MH Appointment

**Upcoming Appointments**

- 3/28/2022 MH Appointment
- 3/28/2022 MH Appointment
- 3/28/2022 MH Appointment
- 3/28/2022 MH Appointment

**Current Health Status**

- High Risk for suicide: No
- Current Health Status: MH Appointment
- MH Appointment

**Past Medical History**

- MH Appointment
- MH Appointment
- MH Appointment
- MH Appointment

**Contact Information**

- Phone: 555-555-5555
- Email: info@storm.com

**Patient Contact Information**

- Last Four: 5555
- Age: 62
- Gender: M
- Vital Signs: 120/80, 98, 120"/98"
Pharmacogenomics Warning - Consider Alternative Agent

**ACTION:** Strongly consider removing tramadol order. Patient at increased risk of toxicity from tramadol based on pharmacogenomics (PGx) results.

**ALTERNATIVES:**
- Non-pharmacological treatments
- Non-opioid analgesics (e.g., NSAIDS)
- If an Opioid is indicated, do NOT use:
  - Codeine
  - Hydrocodone
  - Oxycodone

**RATIONALE:** Patient is an ultrarapid metabolizer of CYP2D6. Higher levels of tramadol active metabolite occur than expected. Possible toxicity includes:
- Life-threatening respiratory depression
- Increased fall risk
- Increased sedation

**RESOURCES:**
- Clinical assistance: order local or interfacility pharmacogenomics consult
- Information on testing: go to https://bit.ly/PHASERhome
- Feedback on this alert: email PHASER-CROC@va.gov
- Non-clinical support: IM or email PHASERtechsupport@va.gov

- CROCs fire for prescriber and pharmacist
- CROCs fire for CITC prescriptions filled at VA
- CROCs currently available at PHASER supported CPRS sites
- CROCs currently only recognize PHASER supported vendors (>90% of current PGx testing)
Inherited Conditions Implications of PGx Testing

• Genes on the panel may identify increased risk for certain health conditions beyond medications (health/family/reproductive planning)
  • Sanford panel: G6PD deficiency, Gilbert syndrome
  • Fulgent panel: G6PD deficiency, Gilbert syndrome, Malignant hyperthermia

• For PHASER panels
  • Providers & patients will be notified by PHASER and supported through next steps
  • Resources can be found on PHASER SharePoint

• For non PHASER panels → Refer to genetic counseling if actionable findings for these genes (examples, not exhaustive):
  • $G6PD$, $MTHFR$, $F_5$, $UGT1A1$, $RYR1$, $CACNA1S$, $APOE$
  • If unsure CPIC provides guidance for certain genes within its guidelines for certain genes
Future Directions
VA National Pharmacogenomics Program

Specialty Care Services

National Oncology Program Office

National Pharmacogenomics Program

PHASER
- Fulgent Panel
- Sanford Panel

EXCLAIM

TelePGx

SME Workgroups
- Cardiology
- Mental Health
- Primary Care
- Oncology
Initial NPP Goals

• Enterprise-wide access to VA approved PGx testing
  • VA customized genes, drugs, reporting

• Develop standardized, high-quality processes to support PGx at any site of care by training and supporting pharmacists
  • Models
    • Local
    • Regional
    • Remote, telehealth
  • Clinical, Education, Population Health strategies

• Integration of PGx support in EHR

• Centralized repository of all PGx test results to support clinical decision support
Summary

- PGx testing - at some level – is available to all VA sites of care to support psychotropic medication prescribing
- Current state is somewhat heterogeneous
  - Gene, drug, reports, implications
- PHASER is the VA’s clinical infrastructure that aims to standardize access to, interpretation of, and support for integrating PGx testing into routine clinical care
- The VA National Pharmacogenomics Program aims to provide standardized, high-quality, evidenced based access to PGx testing and integration of PGx to all aspects of Veterans care.
Resources

- **VA Precision Medicine in Mental Health (PRIME) Care website** (Veteran and clinician educational resources, publications)
- **VA Pharmacogenomic Testing for Veterans (PHASER) website** (Veteran information)
- **VA PHASER Sharepoint** [VA intranet only] (clinician resources, resources for Veteran outreach, information for leadership, educational event announcements)
- **Clinical Pharmacogenetics Implementation Consortium (CPIC) website** (treatment guidelines for pharmacogenomics)
- **PharmGKB website** (genes, alleles, and drug prescribing info)
- **FDA Table of Pharmacogenetic Associations**
- **University of Florida CYP2D6 Phenoconversion Calculator**
Q&A Panel