To Swab or Not to Swab?

Clinical Applications of Pharmacogenomics in Psychiatry
What? Why? When?

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What Are The Objectives?

- Identify factors that are driving pharmacogenomic (PGx) testing in clinical psychiatry
- Review examples of genetic variants affecting pharmacokinetics of psychotropics
- Introduce pharmacodynamic genetic variants that modulate outcome, tolerability, and safety of commonly prescribed psychotropics
- Reveal the factors fueling the debate regarding reliance on PGx outside of clinical trials

What Are Predictors of an Individual’s Response to Specific Psychotropics?

- Pharmacokinetics (PK)
  - Effect of the body on the psychotropic drug
  - Absorption, distribution, metabolism, and excretion of psychotropic medications
- Pharmacodynamics (PD)
  - Effect of the specific psychotropic drug on the body
  - Receptors, enzymes, ion channels, and immune system
- Often ethnic groups have variation in drug response, remission, and safety of due to genetic variants affecting PK and PD

What Are Critical Factors for Psychotropic Selection?

- Comorbid Medical Conditions, Substance Abuse, Psychiatric Diagnoses
- Concomitant Medications & OTCs, Smoking status
- Food and beverage preferences
- Frequency of dosing
- Laboratory monitoring requirements
- Liver Function/ Kidney Function
- Formulary & Co-pay fees
- Formulation

Pharmacogenomics Glossary

- A gene is a unit of heredity transferred from a parent to offspring, made up of a sequence of nucleotides (DNA)
- "Instructions" written in DNA, for building protein molecules
- Genome: the complete set of genes that is unique to an individual
- Different people can have different versions (a slightly different nucleotide sequence) of the same gene = variant
- Allele: any of several forms of a gene, usually arising through mutation that is responsible for hereditary variation
- Individuals inherit maternal and paternal star-alleles referred to as a diploidy (e.g., CYP2D6*1/*2, CYP2C19*1/*1)
What is the Difference Between Pharmacogenetics (PGt) & Pharmacogenomics (PGx)?

- Pharmacogenetics (PGt) field of science that seeks to identify specific genetic variants in or near the coding region of genes that encode for protein structures with which a drug interacts (i.e., an enzyme, a transporter, binding to a receptor).

- Pharmacogenomics (PGx) is the study of how a person’s genome affects his or her response to certain medications.

What is The Role of The NIH Regarding Pharmacogenomics?

- NIH funded scientists have studied the effects of genes on medications relevant to a wide range of conditions including depression, through the Pharmacogenomics Research Network (PGRN).

- The NIH funded PGRN findings are collected in an online resource called PharmGKB.

- A shared partnership between the PGRN and PharmGKB is the Clinical Pharmacogenetics Implementation Consortium (CPIC).

- CPIC is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.

- CPIC guidelines follow standardized formats, are regularly updated, and are posted to cpicpgx.org.

What Are Examples of PGx and PGt Research?

- Genome Wide Association Studies (GWAS): Assay sample populations seeking a genetic variant (polymorphism) that may have a putative role in the observed individual variability in the clinical profile of certain psychotropic drugs.

- Automated laboratory machines search for genetic variants that occur significantly more often in a large group of people with a particular outcome of medication treatment.

- The genetic polymorphisms identified by GWAS are then studied as candidate genes in randomized clinical trials to verify them as evidenced-based biomarkers.

- The goal of clinical trials is to verify that the variants identified in GWAS are indeed clinically useful in medication selection.

- Whole Exome Sequencing Studies (WES): A genomic technique for sequencing only the subset of DNA that encodes proteins in a genome (known as the exome).

- The goal of WES is to identify genetic variants that alter protein sequencing at a much lower cost than GWAS.

What is Commercial Pharmacogenomic Testing?

- Laboratory: Assay: computerized analysis of a patient’s DNA sequencing to identify the patient’s genotype (2 alleles for a specific gene) for a select panel of PK and PD genes that code for proteins that affect drug absorption and drug action (e.g., enzymes, receptors, transporters).

- Goal is to match the patient’s genotype, using a proprietary, computerized, data base, of well designed, peer reviewed, published research on clinically meaningful polymorphisms linked to drug response, to designate a phenotype (the observable characteristic of an individual due to their genotype) for each PK and PD genes in their panel.

- Customise a report that matches the patient’s genetic findings with known pharmacogenetics to determine a phenotype for pre-selected list of psychotropic medications.

- Report identifies moderate and severe gene-drug interactions that affect psychotropic safety and efficacy.

- Advises psychotropic selection and dosing parameters based on their phenotype.

Which Polymorphisms Can Pharmacogenomic Testing (PGx) Identify?

- Single nucleotide polymorphisms (SNPs)

- Variability of short sequence repeats

- Haplotypes

- Specific set/combination of allele or DNA sequence variations observed on a single chromosome

- DNA modifications, e.g., methylation

- Insertions or deletions of single nucleotide(s)

- Copy number variations

- Cyto genetic rearrangements, e.g., translocations, duplications, deletions, or inversions

What are Single Nucleotide Polymorphisms (SNPs)?

- Polymorphism: “having multiple forms,” patterns, or profiles of changes in DNA sequencing

- Single Nucleotide Polymorphisms (SNPs) are the simplest and most common genetic variation.

- A sequence of DNA that differs between members of the same genome.

- Variations of a single nucleotide in a DNA sequence (e.g., A to G).

- SNPs cause the formation of different alleles for the same gene which can affect how that gene functions (determine a phenotype).
What Role Does the FDA Have in the Clinical Utilization of PGx Testing?

- FDA monitors drug safety in the US
- "Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose."  
- FDA includes pharmacogenomic information on the labels of approximately 200 medications

Table of Pharmacogenomic Biomarkers in Drug Labeling Available at: https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm Accessed: February 2019

What FDA Directed Genomic Information is Included in Drug Labeling?

- Includes specific actions to be taken based on the genomic biomarker information
- Guidance on dose (PK)
- Possible side effects (PK/PD)
- Warn of differences in effectiveness for people with certain gene variants (PD)
- FDA pharmacogenomic information can help tailor drug prescriptions for individual patients

What Are the Factors Propelling Pharmacogenomic Testing (PGx) in Psychiatry?

- Prototype pharmacogenomic examples in other disciplines of clinical medicine
- Some PGx laboratory tests have been approved by the FDA
- Federal Drug Administration (FDA) language in package inserts of 30+ psychotropic medications
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for SSRIs and TCAs
- Expanding number of commercially available PGx testing and commercial PGx drug outcome studies
- Some labs are accredited by Clinical Laboratory Improvement Amendments (CLIA), and the College of American Pathologists (CAP)
- CLIA program is to ensure quality laboratory testing
- PGx lab must be properly certified to receive Medicare or Medicare Payments

Examples of Pharmacogenomic Decision Support Tools in Psychiatry

<table>
<thead>
<tr>
<th>Test</th>
<th>Gene/Geneset</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Cytochrome 2D6 Efficiency</td>
<td>CYP2D6</td>
<td>Determines efficiency of metabolism of drugs like antidepressants and antipsychotics</td>
</tr>
<tr>
<td>Cytochrome 2C19 Efficiency</td>
<td>CYP2C19</td>
<td>Determines efficiency of metabolism of drugs like antipsychotics and antidepressants</td>
</tr>
<tr>
<td>Cytochrome 2C19 Capacity</td>
<td>CYP2C19</td>
<td>Determines capacity of metabolism of drugs like antipsychotics and antidepressants</td>
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<td>UGT1A4 Activity</td>
<td>UGT1A4</td>
<td>Determines activity of metabolism of drugs like antidepressants</td>
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<tr>
<td>UGT2B15 Activity</td>
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<td>Methylenetetrahydrofolate Reductase</td>
<td>MTHFR</td>
<td>Determines activity of metabolism of drugs like antidepressants</td>
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<tr>
<td>Transporter</td>
<td>SLC6A4</td>
<td>Determines activity of metabolism of drugs like antidepressants</td>
</tr>
<tr>
<td>Human Leukocyte Antigens</td>
<td>HLA-B, HLA-A</td>
<td>Determines activity of metabolism of drugs like antidepressants</td>
</tr>
</tbody>
</table>

What Are Some of the Findings of Pharmacogenomic Research?

- Variants of genes that code for PK and PD proteins:
  - PK: Cytochrome P450 isoenzymes: 2D6, 2C19
  - PK: UGT1A4, UGT2B15
  - PK: MTHFR
  - PD: Solute Carrier Transporters SLC6A4
  - PD: Human Leukocyte Antigens HLA-B, HLA-A
What Is the Cytochrome P(CYP)450 System?

The CYP450 system is a family of about 58 enzymes responsible for drug metabolism in the liver. Most drug-drug interactions of psychotropics occur at the metabolic level involving the hepatic CYP450 enzyme system. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity. CYP enzyme activity may differ between individuals, and does differ between ethnic groups.

How Do SNPs in Cytochrome P450 (CYP) Isoenzymes Influence Psychotropic Medications?

- Antidepressant, antipsychotic, amphetamine, hypnotic and most benzodiazepines are mainly metabolized through the CYP450 superfamily.
- GWAS have revealed SNPs in CYP isoenzymes that are associated with interpersonal variability in medication drug levels.
- SNPs in the isoenzyme pathways involved in the metabolism of psychotropic drugs may effect their efficacy and tolerability.

How Are The CYP Isoenzyme Genotypes Categorized?

Selecting a psychotropic based on PGx identified genotype is promulgated on replicated, well designed, large clinical trials studying how accurately specific gene variations can predict the variability in the effect of specific psychotropic medications. E.G. assign a phenotype

- Poor (PM) = no function/inactivity due to amino acid or gene deletions in both inherited alleles
- Intermediate (IM) = decreased rate of activity (due to a deletion or inactive or deficient allele) in one inherited allele and one functional allele
- Extensive (EM) = inherited "equivalent" of two functional alleles = expected rate of activity
- Ultra Rapid (UM) = increased rate of activity due to gene duplications and multiplications in the alleles of one or both parents.

How Is The Activity Status of CYP2D6* Alleles?

<table>
<thead>
<tr>
<th>Allele type</th>
<th>Alleles</th>
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<tbody>
<tr>
<td>Active</td>
<td>*1, *2, *3, *33</td>
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What Is The Prevalence of CYP 2D6 Phenotypes In Different Ethnic Groups?

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<thead>
<tr>
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<th>Asian</th>
<th>African American</th>
<th>PDX Database</th>
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<tr>
<td>IM</td>
<td>2.11%</td>
<td>60%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>7.10%</td>
<td>1.2%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>UM</td>
<td>4.3%</td>
<td>&lt;1%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>77.92%</td>
<td>58%</td>
<td>58%</td>
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</tr>
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</table>

Why Do SNPs in CYP2D6 Alleles Affect Antidepressant & Antipsychotic Outcomes?

- CYP2D6 is highly polymorphic >160 known allelic variants (CYP2D6*x) and subvariants
- CYP2D6 low capacity/ high affinity i.e. preferentially metabolizes drugs at lower levels
- Poor Metabolizer status at CYP2D6 phenotype → high concentrations of a drug
  - Divert to CYP3A4 and CYP1A2 isoenzymes (high capacity/low affinity)
  - Delaying metabolism of the drug

What Are Examples of SSRI CYP450 Involvement?

- Citalopram: CYP2C19, CYP2D6, CYP3A4
- Escitalopram: CYP2C19, CYP2D6, CYP3A4
- Fluoxetine: CYP2C9, CYP2C19, CYP2D6, CYP3A4
- Fluvoxamine: CYP1A2, CYP2D6
- Paroxetine: CYP2D6, CYP3A4
- Sertraline: CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4

What Are Examples of CYP450 Involvement for TCAs?

- Desipramine: CYP2D6
- Nortriptyline: CYP2D6
- Amitriptyline: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A4
- Doxepin: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A4
- Imipramine: CYP1A2, CYP2C19, CYP2D6, CYP3A4

CYP2D6 Phenotypes and Nortriptyline

Number of functional CYP2D6 genes

Plasma concentration/25 mg dose (nmol/L)


What is an Example of FDA Pharmacogenomic Biomarker Drug Labeling?

Aripiprazole relies primarily on CYP2D6
- CYP3A4: dehydro-aripiprazole (an active metabolite)

FDA labeling under: Dosage and Administration, Use in Specific Populations, Clinical Pharmacology

FDA language for Dosage Adjustments for Phenotype
- Known CYP2D6 PM administer half of usual dose
- Known CYP2D6 PM and strong CYP3A4 inhibitors, administer a quarter of usual dose

FDA Language for Dose Adjustments for Drug Drug Interactions
- Strong CYP2D6 or CYP3A4 inhibitors administer half of usual dose
- Strong CYP2D6 and CYP3A4 inhibitors administer a quarter of usual dose
- Strong CYP3A4 inducers double usual dose over 1 to 2 weeks

Biomarkers in FDA Drug Labeling

<table>
<thead>
<tr>
<th>Medication</th>
<th>Gene</th>
<th>Phenotype</th>
<th>Labeling Section A</th>
<th>Labeling Section B</th>
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<td>Aripiprazole</td>
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<td>Dosage &amp; administration</td>
<td>Clinical Pharmacology</td>
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<tr>
<td>Atomoxetine</td>
<td>CYP3D6</td>
<td>Poor metabolizer</td>
<td>Dosage &amp; administration</td>
<td>Clinical Pharmacology</td>
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<td>Citalopram</td>
<td>CYP2C19</td>
<td>Poor metabolizer</td>
<td>Dosage &amp; administration</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td></td>
<td>CYP2D6</td>
<td>Poor metabolizer</td>
<td>Dosage &amp; administration</td>
<td>Clinical Pharmacology</td>
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<http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021436s028,021713s020,021729s013,021866s014lbl.pdf>
Biomarkers in FDA Drug Labeling

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<td>Dosage &amp; Administration</td>
<td>Specific Populations, Clinical Pharmacology</td>
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<tr>
<td>doxepin</td>
<td>2D6</td>
<td>Poor metabolizer</td>
<td>Clinical Pharmacology</td>
<td></td>
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<tr>
<td></td>
<td>2C19</td>
<td>Poor metabolizer</td>
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<td></td>
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<tr>
<td>escitalopram</td>
<td>2D6</td>
<td>Poor metabolizer</td>
<td>Drug Interactions</td>
<td></td>
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<tr>
<td>metoprolol</td>
<td>2D6</td>
<td>Poor metabolizer</td>
<td>Clinical Pharmacology</td>
<td></td>
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</table>

What Do We Know About CYP2C19 Alleles Variants?
- Highly polymorphic, over 30 allelic variants and subvariants
- CYP2C19 is involved in metabolizing atomoxetine, bupropion/noradrenaline, fluoxetine, escitalopram, citalopram, paroxetine, imipramine, diazepam, selegiline, sertraline, vilabazon, vorlafaxine
- Common variants of the CYP2C19 gene are associated with impaired drug metabolism
- CYP2C19P2 and CYP2C19P3 were identified in individuals who exhibited a reduced capability for metabolizing drug substrates
- Variant CYP2C19P17 is associated with ultra-rapid metabolism of CYP2C19 substrates

What is The Impact of CYP2C19 Genotype on Escitalopram?
Highly polymorphic CYP2C19 enzyme is responsible for the initial biotransformation of escitalopram. Compared with the CYP2C19*1/*1 (extensive) serum concentrations were:
- Significantly increased 3.3x in the CYP2C19*1/*1 group and 1.6x in the CYP2C19*1/*17 group
- Significantly decreased by 20% in the CYP2C19*17/*17 group and by 10% CYP2C19*1/*17 group

Antidepressant switches within 1 year = therapeutic failure compared with the CYP2C19*1/*1:
- 3.3 x more often in the CYP2C19Null/Null
- Increased 1.6x in the CYP2C19 Null/*1 group and 1.4x in the CYP2C19Null/*17 group
- Significantly decreased by 20% in the CYP2C19*17/*17 group and by 10% CYP2C19*1/*17 group

Why Test for Polymorphisms of UGT1A4?
- UGT genes encode for enzymes involved in the glucuronidation pathway
- UGT1A4 codes for the enzyme involved in metabolism of:
  - Amitriptyline, doxepin, haloperidol, asenapine, clozapine, olanzapine, lamotrigine, valproic acid
  - More than 100 UGT1A4 polymorphisms identified
- UGT1A4 phenotypes include EM & UM
- UM due to a SNP (leucine to valine change, caused by single T-->G substitution)
- UGT1A4*4 variants (GT + GG) associated with higher enzyme activity
- Three in vivo studies GT + GG → reduced lamotrigine concentrations vs. TT
- Carriers of UGT1A4*3 variant had reduced therapeutic efficacy when exposed to drugs for which UGT1A4 is the major elimination route for lamotrigine (lamotrigine is metabolized by UGT, no CYP450 enzymes)
Genotyping is reliable when performed in qualified clinical laboratories, but as with any laboratory test, an error can occur. Any errors in genotyping or phenotype prediction, along with the presence of a rare phenotype from some genetic test results, can lead to a misinterpretation of the test results. Based on genetic testing alone, CPIC recommends that:

- Adjustments can be made or an alternative agent selected.
- The drug dose may have already been adjusted based on plasma concentrations, response, or side effects.
- Dose adjustments guide dose adjustments.
- Ultrafast metabolizers of citalopram or escitalopram, are considered candidates for a non-CYP2D6 enzyme was strongly recommended (non CYP2D6).
- CYP2D6 PM greatly reduced metabolism of tertiary amines compared to normal metabolizers; decreased conversion of tertiary amines to secondary amines may affect response or side effects.
- Reduced metabolism of TCAs to less active compounds compared to normal metabolizers and higher plasma concentrations of active drug will increase the probability of side effects.
- Consider a 50% reduction of recommended starting dose and utilize therapeutic drug monitoring to guide dose adjustments.

CPIC translates genetic laboratory testing results into actionable prescribing decisions for affected drugs.

Why Should You Visit the CPIC Site?

- CPIC creates, curates, and posts freely available, peer-reviewed, evidence-based, updatable, and detailed gene-drug clinical practice guidelines to help clinicians optimize their medication recommendations.
- The level of evidence supporting drug–gene interactions is graded A–D based on study size, replication, and level of statistical significance of the findings.
- CPIC translates genetic laboratory testing results into actionable prescribing decisions for affected drugs.
- Addresses barriers to implementation of pharmacogenetic testing in the clinic.

What Are CPIC Dosing Guidelines for UM & PM Phenotypes for CYP2D6 & CYP2C19 Re: SSRIs?

- Ultrafast Metabolizers patient may experience lack of efficacy despite good adherence to maximal recommended dosing.
- Poor metabolizers phenotype for CYP2C19: CPIC guidelines recommend a non-CYP2C19 drug or reducing the starting dose by 50%.

What is MTHFR?

- Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism is one of the known associations in treatment-resistant depressed patients. 
- L-methylfolate is the only form of folate that crosses the blood–brain barrier and is immediately available for neurotransmitter synthesis.
- L-methylfolate is an important precursor to neurotransmitter synthesis.
- The MTHFR gene is a single nucleotide polymorphism that causes an alanine to valine amino acid change at position 677 of the MTHFR protein.
- Individuals who carry this mutation will have a reduced capacity to create L-methylfolate.

Why Test for Polymorphisms of UGT2B15?

- UGT2B15 gene codes for the enzyme involved in metabolism of:
  - Chlordiazepoxide, clorazepate, diazepam, lorazepam, oxazepam, & temazepam
  - Oxazepam is an active metabolite of chlordiazepoxide, clorazepate, diazepam & temazepam
- UGT2B15 phenotypes include EM and IM.
- Most studied polymorphism (G>T) UGT2B15*2 variant, lower doses may be required.
- Associated with decreased glucuronidation—inter-individual variability in the clearance of oxazepam & lorazepam
- TT: >40-50% lower metabolic activity/systemic clearance of oxazepam vs. GG
- IM UGTB15:
  - 50% Caucasians
  - 36-49% Hispanic, African American, Chinese, Japanese, & Korean populations

What Can We Learn From The CPIC Guidelines for TCAs?

Patients who have existing CYP2D6 and CYP2C19 genotyping test results, the potential benefit is identifying those patients who are at an elevated risk of unexpected, side effects or therapeutic failure. 

- The application of genotype-based dosing is most appropriate when initiating therapy with a tricyclic. 
- Obtaining a pharmacogenetic test after months of drug therapy may be less helpful in some instances, as the drug dose may have already been adjusted based on plasma concentrations, response, or side effects.
- Similar to diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy.
- A limitation inherent to most commercially available genotyping tests is that rare or de novo variants are not detected.
- Additionally, some alleles are not well characterized, resulting in uncertainty when predicting the phenotype from some genetic test results.

- Genotyping is reliable when performed in qualified clinical laboratories, but as with any laboratory test, an error can occur. Any errors in genotyping or phenotype prediction, along with the presence of a rare phenotype from some genetic test results, could potentially have lifelong implications for the patient’s drug therapy.
MTHFR appears to affect the metabolism & efficacy of medications including antidepressants and anti-psychotics.

The MTHFR enzyme converts synthetic folic acid & dietary folate into its active form, L-methylfolate. It manipulates the synthesis of monomamines: serotonin, norepinephrine, dopamine in a 2-step process.

- L-methylfolate acts as an important regulator of a critical neurotransmitter known as tetrahydrobiopterin (BH4), which is necessary for the synthesis of neurotransmitters.
- BH4 is critical for converting the enzyme, seroconversion hydroxylase (SHTP) & tyrosine hydroxylase. (for DA & NE synthesis)

Depressed patients who are homozygous (T/T) or heterozygous (C/T) for the MTHFR variant allele have a greater improvement in their Hamilton Depression Rating Scale scores after taking adjunctive L-methylfolate compared to placebo.

L-methylfolate may be particularly effective in patients with a C667T homozygous mutation for MTHFR.

L-methylfolate as a trimonoamine modulator & indirect regulator of trimonoamine neurotransmitter synthesis & monoamine concentrations, presents a therapeutic option in the management of treatment-resistant depression by enhancing BH4 to increase monoamine synthesis.

Some of the discoveries regarding the functional consequences of SLC6A4 variants are differentiated by a 44 base pair insertion/deletion.

The short allele (S) results in lower transcription rates, providing less active sites for SSRI.

The serotonin transporter gene (SLC6A4) regulates the pace of reuptake of serotonin into the presynaptic neuron.

SLC6A4 has two main variants: short (S) and long (L) (all is the wild genotype).

Some of the discoveries regarding the functional consequences of SLC6A4 variants have pharmacogenomic relevance for antidepressants (SSRIs).
What Is The Genotypic Variance Amongst Ethnicities For The SLC6A4 Gene?

<table>
<thead>
<tr>
<th>Geographic Ancestry</th>
<th>Long Allele Frequency %</th>
<th>Short Allele Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>European American</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Han Chinese</td>
<td>26</td>
<td>74</td>
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<tr>
<td>Korean</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>Japanese</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>

Estimated that 50% to 60% of Caucasians are carriers of the l allele
25% to 40% of Asians are carriers of the l allele

1 Lotrich et al. 2003  2 Gelernter et al. 1997  3 Kim et al. 2006  4 Mrazek 2010

Variants in Genes that Code for Solute Carrier (SLC) Transporters

SLC6A4
- Genetic variants of the serotonin transporter gene (5-HTTLPR, rs4795641) have been shown to determine varying rates of response and remission to selective serotonin reuptake inhibitors (SSRIs)1,2.
- Based on the presence of either a long (l) or short (s) allele, the patient may have improved or worse response to SSRIs, respectively, owing to twice the expression of the serotonin transporter among those with the long (l) allele.
- Ethnicity seems to be a modifying factor since response and remission to antidepressants have been shown to differ in certain ethnic groups.

What Are HLA Genes?
- The human Major Histocompatibility Complex plays a critical role in immunity, and is encoded by the Human Leukocyte Antigen Complex (HLA gene family) located on chromosome 6.
- HLA proteins are located on the surface of most cells, and help the immune system recognize foreign substances.
- HLA genes are the most polymorphic genes in the human genome.
- HLA-A*3101 and HLA-B*1502 are two alleles that have been associated with severe cutaneous drug reactions (cADRs) including Steven Johnson Syndrome (SJS) & toxic epidermal necrolysis (TEN)
- Caution should be exercised in prescribing carbamazepine/oxcarbazepine for patients carrying the HLA-B*1502 allele or HLA-A*3101 allele.

What Is The Risk of HLA-A*3101 Allele With Carbamazepine?

- A JAMA Neurology 2018 study showed that preemptive HLA-A*3101 genetic screening significantly decreased the incidence of carbamazepine-induced cutaneous ADRs among Japanese patients.
- Neuropsychiatrists were asked to Rx alternate drugs for the 198/1130 who tested positive for HLA-A*3101.
- Carbamazepine use in HLA-A*3101 allele carriers patients of non-Asian descent increased risk of cADRs.
- Northern Europeans HLA-A*3101 allele carriers increased risk from 5.0% to 26.0%.
- The package insert discourages the use of carbamazepine in HLA-A*3101 positive patients.

What Is The HLA-B*1502 Frequency?

<table>
<thead>
<tr>
<th>Continent</th>
<th>Population/ethnicity</th>
<th>Allele Frequency (%)</th>
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<tbody>
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<td>North America</td>
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<tr>
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<td>African</td>
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<td>India Khandesh Pawra</td>
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Why Does Carbamazepine Have HLA Related Black Box Warning?
- The FDA added a boxed warning requiring that people of Asian descent be screened for HLA-B*1502 before starting carbamazepine.
- If positive for HLA-B*1502 carbamazepine should be avoided unless benefits clearly outweigh the risk.
- The association between HLA-B*1502 allele and carbamazepine induced SJS/TEN has been extensively studied.
- HLA-B*1502 allele frequency highest in some Asian populations: Chinese, Thai, Malaysian, Vietnamese & Indian descent: 7-14%.
- HLA-B*1502 allele much less frequent in Japanese & Caucasian <1%.
- The FDA approved package insert for oxcarbazepine, a structural derivative of carbamazepine, warns against use of oxcarbazepine in patients positive for HLA-B*1502.

What is the HLA-B*1502 Frequency?

<table>
<thead>
<tr>
<th>Country</th>
<th>HLA-B*1502 Allele Frequency (%)</th>
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<tr>
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</tr>
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</tr>
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<td>China</td>
<td>3.5</td>
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<td>Singapore</td>
<td>2.4</td>
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<td>Thailand</td>
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What is the HLA-B*1502 Frequency?
Mr. A is a 24 y/o male c/o refractory depressive symptoms

Presented with symptoms of Major Depression including: feeling pessimistic, social isolation, no motivation, no drive, very low esteem, reduced libido, no energy, irritable, poor sleep, reduced appetite for 6 months.

- Been feeling hopeless & helpless, now on medical leave from grad school as his symptoms did not improve with full dose citalopram for 12 weeks followed by escitalopram for 12 weeks
- Chronic history of co-morbid “social anxiety disorder” (SAD) (met criteria for Generalized Anxiety Disorder (GAD))
- Smoked TPDD, no THC, no alcohol abuse
- Not taking any other medications or OTC’s
- Suffered a history of MDD, her MDD responded to sertraline

Discussing: starting fluvoxamine, paroxetine or sertraline as all are indicated in MDD

Non SSRI may be more effective- Skip sertraline, paroxetine, fluvoxamine

Recommend: augment venlafaxine XR 150mg qPM with 15mg l methylfolate qd

SNRI, less impact of the SLC6A4 phenotype, no special dosing instructions

Recommended: venlafaxine XR, indicated in MDD, GAD, and SAD (titrated to 150mg qPM)

Mirtazapine, doxepin, clomipramine, and imipramine (off label for SAD and GAD) may require higher doses

Duloxetine (SNRI) would require higher dosing, as serum level would be reduced by smoking

Inability to concentrate/ worrying all day, won’t sleep at night/ worrying something is wrong with his heart/ “doom and gloom”

Reduced appetite/ 8 pound weight loss/ not feeling healthy enough to play tennis or run/pacing and restless

Past History was consistent with periods of hypomania (shared by nephew)

PGx Results for Mr. A

PK Genes:
- CYP2D6 phenotype EM genotype *1/*41
- CYP2C19 phenotype EM genotype *1/*17
- CYP2C9 phenotype EM genotype *1/*1
- CYP3A4 phenotype EM genotype *1/*1
- UGT1A1 phenotype EM genotype *1

PD Gene:
- SLC6A4 L/S
- L/S phenotype associated with lower than expected response rates to SSRI’s, explain lack of response to full dose citalopram and escitalopram for 12 weeks.

PGx Guided Psychotropic Selection for Mr. A

- SLC6A4 phenotype explain lack of response to full dose citalopram and escitalopram
- Non SSRI may be more effective- 5-10 sertraline, paroxetine, fluvoxamine
- CYP2D6 (EM) would require higher dosing, as serum level would be reduced by smoking and 5HT phenotype of CYP2D2
- Aminophylline, doxepin, clomipramine, and imipramine (off label for SAD and GAD) may require higher doses
- CYP2D6 (EM)
  - Recommended venlafaxine XR, indicated in MDD, GAD, and SAD [titrated to 150mg qAM]
  - SNP, less impact of the SLC6A4 phenotype, no special dosing instructions
- MTHFR (L/S)
  - Recommend: augment venlafaxine XR 150mg qPM with 15mg l methylfolate qd

Mr. B, Presented Anxious & Sleepless

62 year old male felt very anxious, nearly medical concerns, racing thoughts–can’t get to sleep requesting “sleeping pills”

Hypomania, hypercortisolism, hypoglycemia, glaucoma, heart murmur

Reduction of appetite/ weight loss/ not feeling healthy enough to play tennis or run/pacing and restless

Past History was consistent with periods of hypomania (shared by nephew)
### Mr. B’s PGx Results

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Metabolizer</th>
<th>Poor Metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
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<td>Poor Metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*2</td>
<td>Intermediate Metabolizer</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Extensive Metabolizer</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*2</td>
<td>Intermediate Metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*17</td>
<td>Extensive Metabolizer</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*1/*6</td>
<td>Intermediate Metabolizer</td>
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<tr>
<td>CYP1A2</td>
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<tr>
<td>SLC6A4</td>
<td>-2467T&gt;DELTA – T/DELTA, -739T&gt;G – T/G, -163C&gt;A – A/A, 5347C&gt;T – C/T</td>
<td>Ultra rapid Metabolizer</td>
</tr>
<tr>
<td>*L/S</td>
<td></td>
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<tr>
<td>UGT1A4</td>
<td>*!/*3</td>
<td>Ultra rapid Metabolizer</td>
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<td>UGT2B15</td>
<td>*1/*2</td>
<td>Extensive Metabolizer</td>
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<tr>
<td>HLA-B*1502</td>
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<td>Low Risk</td>
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<tr>
<td>HLA-A*3101</td>
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<td>Low Risk</td>
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</tbody>
</table>

### PGx Guided Psychotropic Selection for Mr. B

- **History of hypomania**: Explained bipolar II vs. Classic Unipolar Depression. D/C citalopram (risk of QTc prolongation with age > 60 yo, = cardiac murmur, = EtOH use)
- Reviewed mood stabilizers including lamotrigine. Mr. B was extremely hesitant to increase the dosage of lamotrigine above the starting dose for fear of fatal rash, yet he needed to achieve a therapeutic dose and PGx revealed UGT1A4 ultrarapid metabolizer phenotype
- Selected oxcarbazepine (HLA*1502/HLA*3101) low risk cADR, avoid lab-work (vs. carbamazepine) no hematopoietic AEs, no drug interactions with his statin/alprazolam with oxcarbazepine, Mr. B is not on a diuretic = less concern re: low Na+ level
- Advised slow taper off alprazolam, not helping target symptoms, added risk with alcohol, more stage 2 sleep vs. stage 3 and 4, increased risk over age 60
- Began and maintained low dose Seroquel (PGx PM) FDA indicated in bipolar II depression, HS dosing helped with sleep as well as depressed/anxious mood, advised monitoring labs & HbA1c, caution re: orthostasis
- PGx was a valuable tool to educate, select and reassure patient about mood stabilizer selections
- PGx did not address the diagnosis of Bipolar II depression vs. Unipolar MDD, i.e. reason did not select an alternate ADR, rationale for taper of alprazolam, potential drug-drug interactions, age precautions, lifestyle (EtOH)

### Thank You!

- **Any questions?**