

Psychiatric Pharmacogenomics Testing

A. Introduction and background

- Few validated and clinically useful gene-response associations that can be used to reliably guide psychotropic medication choice
- Heterogeneity of psychiatric illnesses make disease biomarker validation challenging
- In comparison with genetic variation associated with adverse events or quantifiable biological processes (eg. rash, QTc prolongation), the evidence base for pharmacogenomics-based treatment recommendations is considerably smaller

B. Commercially available genetic tests that claim to guide psychotropic prescribing are now widely available (often advertised directly to consumers/patient driven), examples include: single-gene testing, vs multiple gene panels such as Genomind and GeneSight

Single Gene Testing:

- Several variants in human leukocyte antigen genes have been associated with CIAG (clozapine-induced agranulocytosis/granulocytopenia) indicating the importance of ethnic and population-level genetic differences in psychiatric pharmacogenomics
 - Presence of the genetic variant HLA-B*59:01 in patients of Japanese descent has been found to be associated with a tenfold increased risk of CIAG
 - Reduced risk of progressing from CIG to CIA on clozapine re-challenge if pts did not carry the HLA-B*59:01 variant
- All patients of Asian descent be tested for specific genetic variant HLA-B*1502 before initiating therapy to avoid carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis

Multiple Gene Testing: Genomind tests 20 genes, GeneSight tests 12 genes (55 FDA approved medications) in a “combinatorial” approach:

- Generally, patients are presented with a list of psychotropic drugs grouped into different categories that correspond to different prescription recommendations: use as normally prescribed, use with caution, or use with extreme caution
 - Recommendations are based on an integrated analysis of multiple genetic variants thought to affect the functioning of metabolizing enzymes. Patients are classified as poor, intermediate, extensive, or ultrarapid metabolizers
 - Slower metabolizers are more likely to benefit from lower doses to avoid toxicity
 - Rapid metabolizers may require higher doses to achieve therapeutic effect
 - Some tests also provide information about how a patient might respond to a medication based on genetic variants in receptors & transporters
- The adverse effect toxicity profile of antidepressants and their effectiveness for major depression and anxiety disorders vary among patients, genetic variation may contribute to this differential risk to benefit ratio
 - Revised max dose recommendations for citalopram – an example of regulatory revision of drug labeling associated with adverse event and genomic variation

- Citalopram has been associated with a dose-dependent QTc increase. An initial FDA recommendation to not prescribe doses greater than 40 mg/d was revised to greater than 20 mg/d, with identification of CYP 2C19 poor metabolizers or concomitant use of another CYP2C19 inhibitor
- Venlafaxine - CYP2D6 pharmacokinetic variation and treatment response
 - Review of 4 randomized, placebo-controlled studies (n=464 patients) indicates the extensive metabolizer phenotype in comparison to poor metabolizer phenotype and placebo was associated with a lower concentration of venlafaxine, a higher concentration of *O*-desmethylvenlafaxine, greater efficacy in MDD and no important tolerability differences
- Preliminary data from a nonrandomized open-label 8-week prospective study of patients with major depression revealed a significant reduction in depressive symptoms with antidepressant pharmacogenetics-guided treatment selection (n22 patients) compared to unguided treatment (22 patients)
 - This study was replicated with a larger cohort (72 patients with pharmacogenetics-guided treatment selection, 93 with unguided treatment) and found statistically significant reductions in depressive symptoms and remission rate
- However, the only double blind prospective randomized study to assess the clinical impact of integrated pharmacogenomics testing for MDD was underpowered to detect a statistically significant difference (Winner et al, 2013)

C. Evidence supporting the regular use of commercial panels has significant limitations

- Lack of oversight by an independent and qualified entity such as the FDA
 - Data collection and analysis may be solely done by an organization whose viability depends on the commercial success of the test
 - CLIA (Clinical Laboratory Improvement Amendments)-certified laboratories are required to document the analytic validity of tests. However, CLIA regulations allow the marketing of tests with no proven clinical validity/utility
- Many of the genetic variants that are commonly analyzed have not been found to have independent associations with treatment response or clinical outcome across multiple large studies
- A few studies have been conducted directly comparing clinical outcomes between patients who are treated with the help of pharmacogenomics information and those treated by standard approaches. The studies are small, limited by design/analysis flaws, absence of comparative data/generalizability, funded by industry, and need to be replicated

D. Future Studies that would help to use pharmacogenomics to enhance patient care

- Identifying genetic variants that are associated with adverse effects of psychotropic medications in contrast to those that try to predict therapeutic efficacy
 - The presence of a side effect is more easily defined and quantified than clinical efficacy. Clinicians need to first reduce adverse reactions before addressing targeted symptoms
- Cost-benefit ratio of pharmacogenomics in psychiatry
- Additional investigation/replication needed

- Effects of environmental exposures (e.g., diet, toxins) and demographic factors (eg. age and sex) on genetic predisposition and drug response
- With the continuous decrease in the cost of genetic testing, the willingness of insurance companies to cover such tests, and the increase in published data, CYP2D6/ CYP2C19 genotyping might become a routine test before prescribing relevant antidepressants

E. Recommendations

- Single gene testing is indicated for specific agents in specific situations such as Carbamazepine in Asian clients
- Some pharmacogenomics tests are useful in reducing risk of side effects in specific patients, but general use of pharmacogenomics panels is not well supported by the current literature. Consider pharmacogenomics recommendations by FDA (Package insert section 12 under Pharmacokinetics) and expert groups guidelines such as Clinical Pharmacogenetics Implementation Consortium for specific agents
- Large scale double-blind randomized clinical trials are needed to clarify the beneficial role of pharmacogenetic testing and its clinical utility in psychiatry, such trial is underway by Assurex/Myriad. Until such trials become available, BHRs cannot make definitive recommendations on combinatorial multigene pharmacogenomics testing for all clients
- However, GeneSight Assay may be of benefit for treatment resistant or treatment intolerant clients at net zero cost to the county at this time; P&T to recommend guidelines for use
- We anticipate that genetic testing will become more prevalent, and that providers will encounter pharmacogenetic tests even if they did not order them; therefore P&T committee will keep abreast of evolving literature on this topic, and update recommendations accordingly

F. Financial Considerations

Gene test	Retail Cost	Medicare coverage	MediCal coverage	Uninsured
HLA-B* by Labcorp	\$200-350	Yes	Yes	?
Genecept Assay by Genomind	\$1500	Yes	No	Financial assistance
GeneSight Assay by Assurex	\$1795	Yes	Company pays	Financial assistance

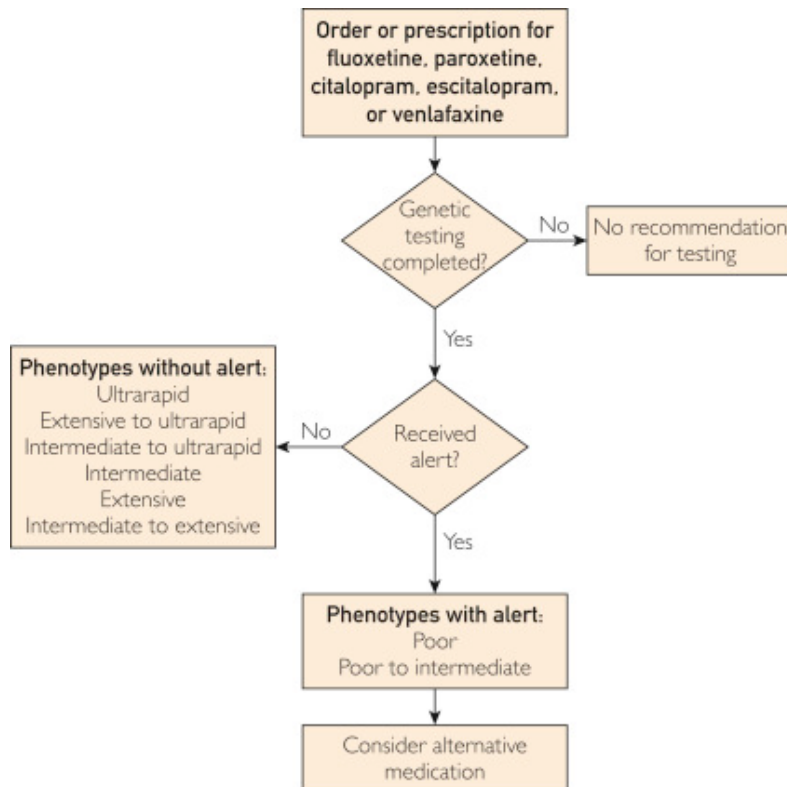
Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine (Nassan et al, 2016)

Authors maintain that the benefits of applying the recommendations below outweigh the risks and that waiting for stronger evidence is not in the best interest of patients. However, routine preemptive pharmacogenetic testing for antidepressant selection is not recommended due to lack of large-scale clinical trials, cost-effectiveness, and insurance coverage

TABLE 2. Method for Prediction of Drug Metabolizer Phenotype for CYP2D6 and CYP2C19^{a,b}

Predicted drug metabolizer phenotype	CYP2D6		CYP2C19
	Without gene duplication	With gene duplication	
UM	Two increased activity alleles	Three normal and/or increased activity alleles	Two increased activity alleles
EM to UM	A combination of 1 normal activity allele with 1 increased activity allele	A combination of 2 normal activity alleles with 1 decreased activity allele	A combination of 1 normal activity allele with 1 increased activity allele
EM	Two normal activity alleles; a combination of 1 increased activity allele with 1 decreased activity allele	A combination of 2 normal activity alleles with 1 null allele; a combination of 1 normal activity allele with 2 decreased activity alleles	Two normal activity alleles
IM to UM	NA	A combination of an increased activity allele and a null allele but the duplicated allele cannot yet be determined	NA
IM to EM	A combination of 1 normal activity allele with 1 decreased activity allele; a combination of 1 increased activity allele with 1 null allele	One increased activity allele with 2 null alleles; 3 decreased activity alleles	A combination of 1 increased activity allele with 1 null allele; a combination of 1 normal activity allele and a decreased activity allele
IM	One normal activity allele with 1 null activity allele; 2 decreased activity alleles	One normal allele with 2 or more null alleles; 2 decreased activity alleles with 1 null allele	Two decreased activity alleles; a combination of 1 normal activity allele with a null allele
PM to IM	A combination of 1 decreased activity allele with 1 null allele	One decreased activity allele with 2 null alleles	A combination of 1 decreased activity allele with 1 null allele
PM	Only null alleles detected		Two null alleles

^aEM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer.
^bSee Table 1 for individual allele functions for these genes.



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GeneSight® Psychotropic Results



Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9299
Report Date: 6/13/2013

Antidepressants

USE AS DIRECTED

- bupropion (Wellbutrin®)
- desvenlafaxine (Pristiq®)
- selegiline (Emsam®)
- vilazodone (Viibryd®)

USE WITH CAUTION

- amitriptyline (Elavil®) [2]
- citalopram (Celexa®) [3]
- clomipramine (Anafranil®) [2,7]
- doxepin (Sinequan®) [2]
- escitalopram (Lexapro®) [3]
- imipramine (Tofranil®) [3]
- sertraline (Zoloft®) [3]
- trazodone (Desyre®) [2]

USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

- desipramine (Norpramin®) [2]
- duloxetine (Cymbalta®) [2,7]
- fluoxetine (Prozac®) [2]
- fluvoxamine (Luvox®) [2,7]
- mirtazapine (Remeron®) [2,7]
- nortriptyline (Pamelor®) [2]
- paroxetine (Paxil®) [2,4,6]
- venlafaxine (Effexor®) [3]

Antipsychotics

USE AS DIRECTED

- fluphenazine (Prolixin®)
- lurasidone (Latuda®)
- paliperidone (Invega®)
- ziprasidone (Geodon®)

USE WITH CAUTION

- asenapine (Saphris®) [2,7]
- quetiapine (Seroquel®) [2]
- thiothixene (Navane®) [2,7]

USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

- aripiprazole (Abilify®) [2]
- chlorpromazine (Thorazine®) [2,7]
- clozapine (Clozaril®) [2,7]
- haloperidol (Haldol®) [2]
- iloperidone (Fanapt®) [2]
- olanzapine (Zyprexa®) [2,7]
- perphenazine (Trilafon®) [2,7]
- risperidone (Risperdal®) [2]
- thioridazine (Mellaril®) [2,7]

[2]: Serum level may be too low, higher doses may be required.
 [3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
 [4]: Genotype may impact drug mechanism of action and result in reduced efficacy.

[6]: Use of this drug may increase risk of side effects.
 [7]: Serum level may be too low in smokers.

All psychotropic medications require clinical monitoring.

Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

Patient Genotypes and Phenotypes		
CYP2D6	Ultrarapid Metabolizer	*2A/*2A
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Extensive Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163C>A - A/A
SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

Figure 2. Example of a GeneSight report for one individual subject. The green-yellow-red bin placements for medications are determined by the individual's genotype results.