JOHNS HOPKINS
MEDICINE

Pharmacogenomic Testing for Psychiatrists: An Introduction

Francis M. Mondimore, M.D.

November 6, 2018

Disclosure:

- Co-investigator for a multi-site clinical study of the ***GeneSight*** test in depression from Assurex Health.

Objectives:

- Introduction: Concept of personalized medicine in psychiatry
- Discovery versus translational studies
- Oversight of pharmacogenetic tests
- Latest evidence for available pharmacogenetic tests

Personalized Medicine

What is “personalized medicine” (precision medicine or individualized medicine)?

- A new approach to health care that uses information about individual differences in genes, environment and lifestyle to tailor prevention and treatment to the needs of the individual patient.
- This is in contrast to the traditional “one-size-fits-all” approach in which prevention/treatment is directed to the “average patient”

Definition adapted from President Obama’s “Precision Medicine Initiative” unveiled on 1/30/2015 that will provide $215 million to NIH, FDA and Office of Health Information Technology to advance “personalized medicine”

Possible Treatment Predictors for Individuals:

- Clinical features
- Family history
- Neuropsychological features
- Genetic markers
- Gene expression
- Epigenetic effects
- Serum/plasma analytes
- Neuroimaging
- Induced pluripotent stem cell (iPSc) markers

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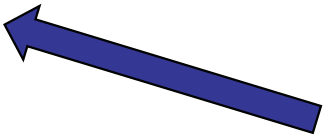
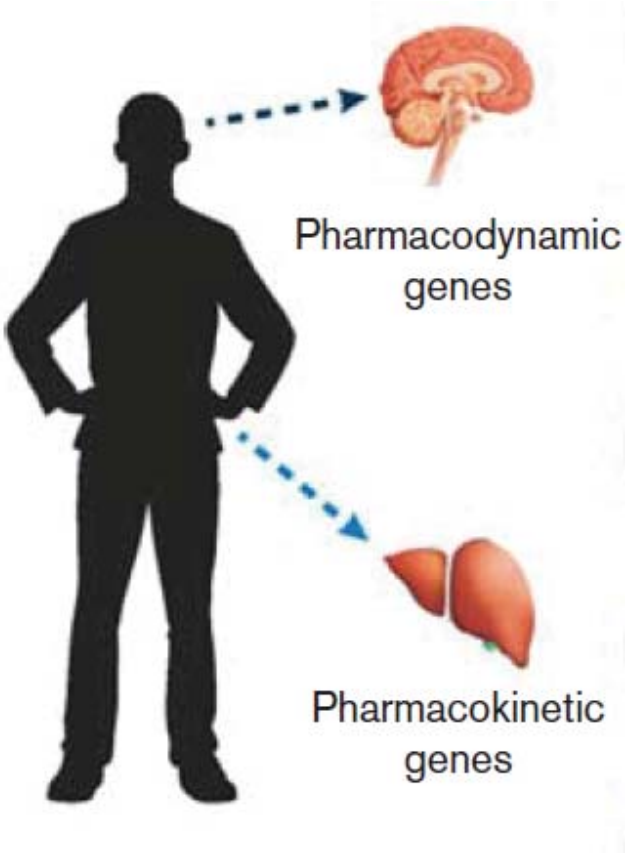


Pharmacogenomic Testing

Pharmacogenetics (PGx)

PGx- Identifying genetic markers that help predict efficacy or side-effect responses to drug treatments



Genes encoding proteins that mediate drug's **mechanisms of action:**

- Receptors
- G-couple proteins
- Ion Channels
- Transporters
- Etc.

Genes encoding proteins that mediate **metabolism** of drug:

- CYP450 (cytochromes)
- UGT, NAT

PGx – Discovery Studies

Discovery studies: Identify genetic markers* that predict drug efficacy/side-effect responses:

- Candidate gene study vs GWAS/WGS
- Retrospective vs prospective
- Observational vs randomized trial

* Drug-gene interaction: goal is to identify genetic markers that predict response to different drugs.

PGx Lithium Response

- Retrospective Study : ConLiGen
  - Consortium of 22 sites around the world
  - Retrospective assessment of lithium response
  - Genome-wide Association Study (GWAS) of lithium response (n=2,563)
  - Found a variant in a non-coding (possibly regulatory) area on Ch 21 associated with lithium response.
- Prospective Study: PGBD
  - 11 site study (n=600)
  - Sought genetic markers for response to lithium monotherapy (2 year prospective study)
  - Tested top findings from ConLiGen w/ time to relapse

Challenges with Discovery

- Measurement of treatment response
  - Retrospective assessment: Recall bias
  - Prospective assessment: How to define good response
- Trx response is a complex phenotype
  - Many factors contribute to response (multiple genes, nutrition, smoking, life stressors, etc.)
  - Requires large sample sizes to identify predictors
- Adherence
  - Can't determine response if not taking drug
- Polypharmacy
  - Drug-drug interactions
  - Difficult to associate response with single drug

PGx – Translational Studies

Translational studies: Studies of PGx tests in clinical practice to improve treatment outcomes

- **Analytic Validity**
  - How well the test measures what it is supposed to measure (e.g., Does it accurately genotype the marker(s)?)
- **Clinical Validity**
  - How well the test predicts who will respond to the treatment
- **Clinical Utility**
  - How useful the test is in improving the care given to a patient and patient outcomes

FDA - Labeling

- PGx information in drug labeling
  - May be informational or actionable recommendations

Tegretol®-XR

(carbamazepine extended-release tablets)

100 mg, 200 mg, 400 mg

Rx only

Prescribing Information

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF

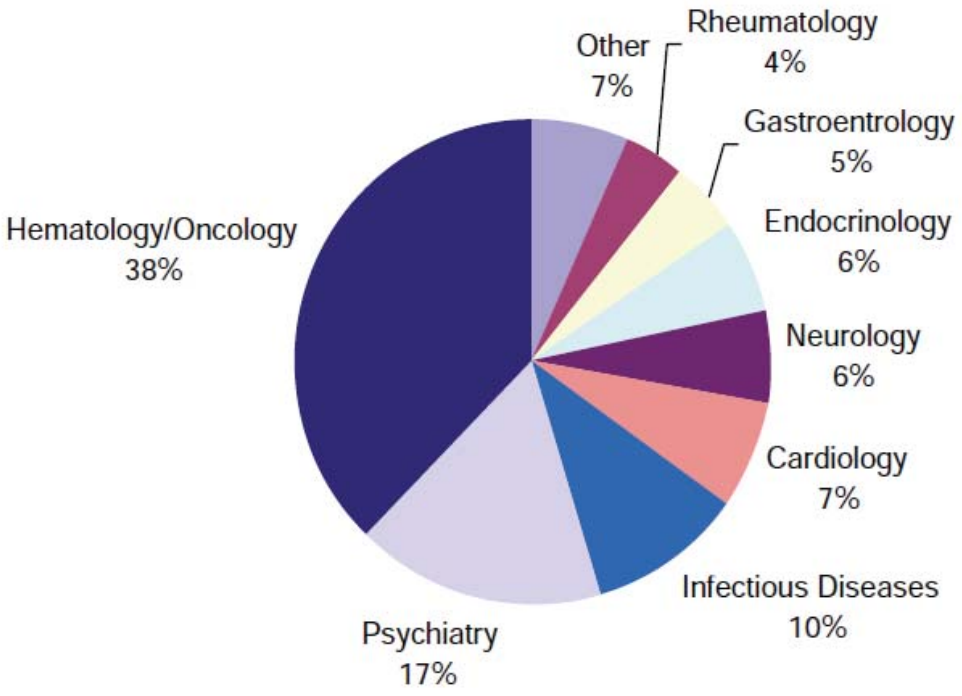
FDA - Labeling

285 FDA approved PGx drug-gene labels; 52 (18%) approved for neuropsychiatric drugs

- 45 involve CYP450 genes (CYP2D6, CYP2C19)
- Carbamazepine: HLA-B/A locus and dermatologic reactions
- Valproic acid: POLG mutations and liver failure
- Valproic acid: Urea cycle genetic disorders and hyperamonemia

https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

FDA Labeling

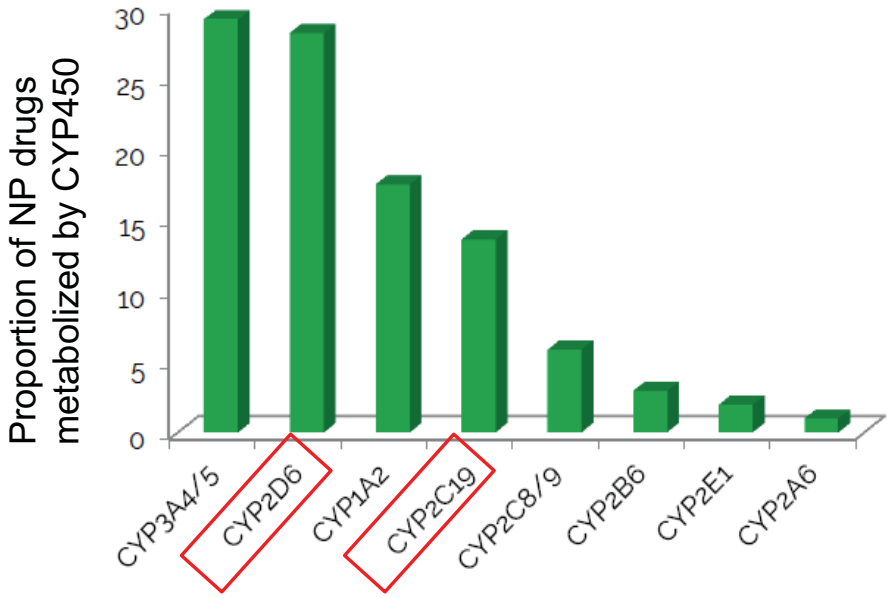


- Of the 135 drugs with approved PGx labeling the majority are oncology drugs
- Approximately 17% of these (n > 20) are for neuro-psychiatric drugs

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

FDA Labeling

- Almost all PGx indications for neuro-psychiatric drugs involve variants in CYP450 system (~57 enzymes responsible for drug metabolism in liver)



- Carbamazepine: HLA-B/A locus and dermatologic reactions
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http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

The FDA considers a pharmacogenomic test a **Medical Device**

- In-vitro diagnostic test (IVD): test developed by manufacturer and sold for use by labs, hospitals, offices
  - Classification: Class I, Class II, Class III (highest risk)
  - Regulation: Registration, PM Notification, PM Approval, Reporting
  - PM Approval requires evidence of analytic and clinical validity
  - **Roche AmpliChip**
- Laboratory developed test (LDT): test designed, manufactured, and used by single laboratory
  - FDA did not regulate and left oversight to CLIA
  - October 2014 issued draft guidance for LDT oversight (risk-based)
  - January 2017 issued discussion paper but no implementation
  - **Assurex GeneSight**

Important Distinction: PGx *TEST* versus *CLINICAL DECISION-SUPPORT TOOL*

- TEST:
  - Provides patient's genotype and predicted phenotype (eg, poor drug metaboliser) do not provide clinical interpretation
  - **Roche AmpliChip**

- PHARMACOGENETIC DECISION-SUPPORT TOOL:
  - Provides genotype, phenotype and information relevant for drug selection or dosing decisions and can also flag potential drug–drug interactions
  - **Assurex GeneSight**

AmpliChip

An In-vitro Diagnostic Test

CYP2D6: 33 alleles
CYP2C19: 3 alleles

FDA Approved (2004)
- Analytical validity: Yes
- Clinical validity: Marginal
- Clinical utility: No

Reduced efficacy

Increased toxicity

Ultrarapid (UM): Rapid rate of metabolism

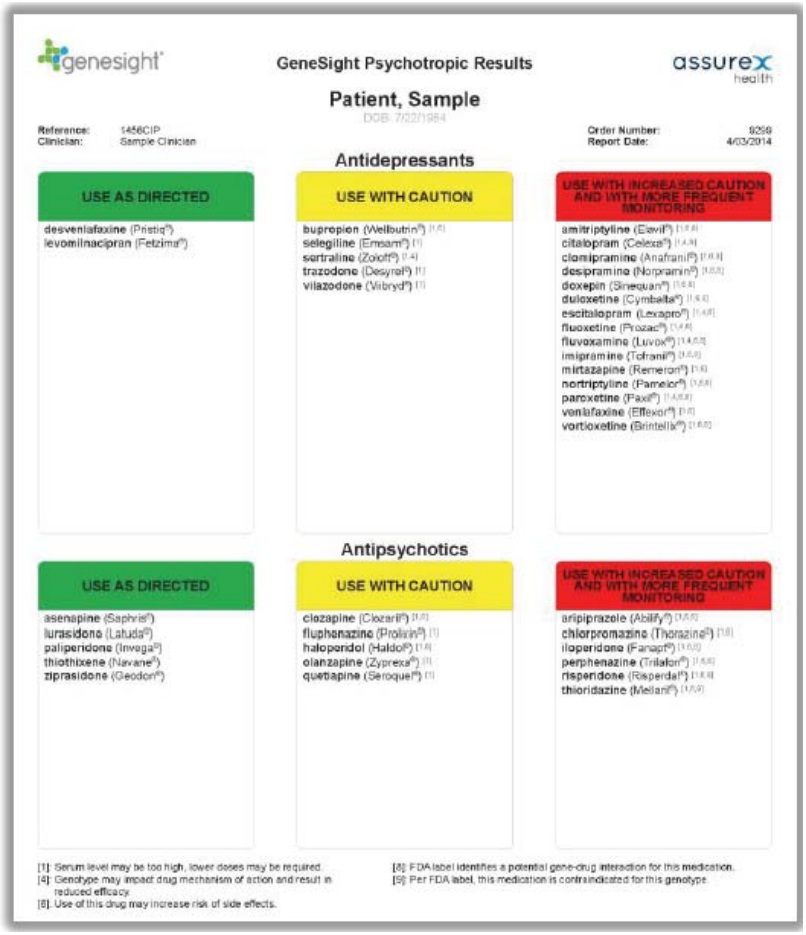
Extensive (EM): Normal metabolism

Intermediate (IM): Reduced rate of metabolism

Poor (PM): Slow rate of metabolism

Assurex GeneSight

SLC6A4*
5HTR2A*
HLA-A
HLA-B
CYP2D6
CYP2C19
CYP2C9
CYP1A2
CYP2B6
CYP3A4
UGT1A4
UGT2B15



genesight

GeneSight Psychotropic Results

assurex health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9259
Report Date: 4/03/2014

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®) levomilnacipran (Fetzima®)	bupropion (Wellbutrin®) [1,6] selegiline (Emsam®) [1] sertraline (Zoloft®) [1,4] trazodone (Desyrel®) [1] vilazodone (Viibryd®) [1]	amitriptyline (Elavil®) [1,6,8] citalopram (Celexa®) [1,4,9] clomipramine (Anafranil®) [1,6,9] desipramine (Norpramin®) [1,6,9] doxepin (Sinequan®) [1,6,8] duloxetine (Cymbalta®) [1,4,6] escitalopram (Lexapro®) [1,4,6] fluoxetine (Prozac®) [1,4,6] fluvoxamine (Luvox®) [1,4,6,9] imipramine (Tofranil®) [1,6,9] mirtazapine (Remeron®) [1,6] nortriptyline (Pamelor®) [1,6,8] paroxetine (Paxil®) [1,4,6,8] venlafaxine (Effexor®) [1,6] vortioxetine (Brintellix®) [1,6,9]

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
asenapine (Saphris®) lurasidone (Latuda®) paliperidone (Invega®) thiothixene (Navane®) ziprasidone (Geodon®)	clozapine (Clozaril®) [1,6] fluphenazine (Prolixin®) [1] haloperidol (Haldol®) [1,6] olanzapine (Zyprexa®) [1] quetiapine (Seroquel®) [1]	aripiprazole (Abilify®) [1,6,8] chlorpromazine (Thorazine®) [1,6] iloperidone (Fanapt®) [1,6,9] perphenazine (Trilafon®) [1,6,8] risperidone (Risperdal®) [1,6,8] thioridazine (Mellaril®) [1,6,9]

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

Clinical Decision Support Tool: 72 variants in 12 genes: 55 medications

Commercial PGx Tests*

Of 23 PGx Tests, Five have supporting peer-reviewed published clinical evidence

PGx Test	Genes Tested	Clinical Evidence
GeneSight	* Previous slide	2 Open-label non-randomized 2 Cost savings 1 Small RCT (n=51) 1 Large RCT (n=1,167)
Genecept	CYP2C19, CYP2D6, CYP3A4, ANK3, CACNA1C, COMT, DRD2, HTR2C, MTHFR, SLCA4	1 Open-label cohort (no comparator) 1 Cost savings
CNSDose	CYP2D6, CYP2C19, UGT1A1, ABCB1, ABCC1	1 Open-label non-randomized 1 RCT (n=148)

Bousman & Hopwood, *Lancet Psychiatry*, 2016

Commercial PGx Tests*

PGx Test	Genes Tested	Clinical Evidence
Neuropharm	CYP2C19, CYP2D6, CYP1A2, CYP2B6, CYP2C9, EPHX1, BDNF, CACNG2, COMT, DRD3, GRIA3, HTR2A, LPHN3, AKT1, DDIT4, FHSD1, RPTOR	1 RCT (n=316)
IDgentix: Neuropsychiatric Panel	CYP2C19, CYP2D6, CYP1A2, CYP2B6, CYP2C9, CYP3A4, CYP3A5, SLC6A4, COMT, H2RA, MTHFR	1 RCT (n=685)

Bousman & Hopwood, *Lancet Psychiatry*, 2016

Commercial PGx Tests: Genecept (Genomind)

RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) S/S [Higher risk of non-response]	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs • Potential for increased cortisol release in response to stress in S/S, L(G)/S or L(G)/L(G) patients • Therapeutic options such as SNRIs or other non-SSRI antidepressants may be used if clinically indicated		**Use caution** with SSRIs **Therapeutic options: SNRIs** or **non-SSRI antidepressants** may be used if clinically indicated
Calcium Channel (CACNA1C) A/A [Increased risk of altered neuronal signaling]	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Altered calcium signaling may be clinically associated with impairment of mood or cognition		**Therapeutic options: atypical antipsychotics, mood stabilizers** and/or **omega-3 fatty acids** may be used if clinically indicated
Serotonin Receptor 2C (5HT2C) C/C [Weight gain risk]	*5HT2C is a receptor involved in the regulation of satiety* • Atypical antipsychotics act by blocking this receptor • Patients with the C/C genotype have risk of weight gain with atypical antipsychotics, however, this is the most common genotype • Metformin, lorcaserin or other anti-obesity interventions may be beneficial to mitigate weight gain		**Use caution** with atypical antipsychotics **Therapeutic options: metformin, lorcaserin** or other **anti-obesity interventions** may be used if clinically indicated
Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk]	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics • Metformin, lorcaserin or other anti-obesity interventions may be beneficial to mitigate weight gain **High risk**: Clozapine; Olanzapine **Medium risk**: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone **Lower risk**: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone		**Use caution** with atypical antipsychotics **Therapeutic Options: metformin, lorcaserin** or other **anti-obesity interventions** may be used if clinically indicated

Commercial PGx Tests: IDgenetix:Neuro (AltheaDx)

IDgenetix
MAKING PERSONALIZED MEDICINE POSSIBLE™

Laboratory Test Report

Patient Name:	Patient ID:	Age:	Gender:	DOB:
Test, Test	FC571-B	66	Male	12/31/1950

Sample Type:	Date Collected:	Date Received:	Ordering Physician:	Client/Account #:
Buccal Swab	03/08/2017	03/09/2017	Cullors Ali	CAli910

Test Ordered:	Indication:	Report Date:	Report Status:
Depression 201	Depression	03/10/2017	Draft

PHARMACOGENETIC TESTING BASED TREATMENT GUIDANCE

Depression Drug Therapy Selection & Dosing Guidance

Use as Directed
Drug
fluoxetine (SSRI)
fluvoxamine (SSRI)
paroxetine (SSRI) [1]
desvenlafaxine (SNRI)
duloxetine (SNRI)
levomilnacipran (SNRI)
venlafaxine (SNRI)
bupropion (NDRI) [1]
mirtazapine (NaSSA) [1]
trazodone (SARI)
vilazodone (SRI)
vortioxetine (Serotonin Modulator and Stimulator)
desipramine (TCA) [1]
nortriptyline (TCA) [1]
aripiprazole (SGA) [1]
brexpiprazole (SGA)
quetiapine (SGA) [1]

Use With Caution and/or Increased Monitoring	
Drug	Dosing
citalopram	Consider dose adjustment or alternate drug. A 50% starting dose reduction is recommended by CPIC with titration to response (CYP2C19 PM), which may be delayed due to COMT variant. Note: drug label advises 20mg/day maximum for PMs given increased QT prolongation risk. PubMedID: 25974703
escitalopram	Consider dose adjustment or alternate drug. Per CPIC guideline, consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 (CYP2C19 PM). Greatly reduced metabolism, higher plasma concentrations may increase the probability of side effects. PubMedID: 25974703
sertraline	Consider dose adjustment or alternate drug. Per CPIC guideline, consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. (CYP2C19 PM) Greatly reduced metabolism, higher plasma concentrations may increase the probability of side effects. PubMedID: 25974703
amitriptyline [1]	Consider dose adjustment or alternate drug. Consider 50% reduction of recommended starting dose (CYP2C19 PM). Utilize therapeutic drug monitoring to guide dose adjustments. CPIC Guideline PubMedID: 23486447
doxepin [1]	Consider dose adjustment or alternate drug. Consider 50% reduction of recommended starting dose (CYP2C19 PM). Utilize therapeutic drug monitoring to guide dose adjustments. CPIC Guideline PubMedID: 23486447
imipramine [1]	Consider dose adjustment or alternate drug. Consider 50% reduction of recommended starting dose (CYP2C19 PM). Utilize therapeutic drug monitoring to guide dose adjustments. CPIC Guideline PubMedID:

Commercial PGx Tests: GeneSight (Assurex)

genesight

GeneSight® Psychotropic Results

assurex health

Patient Genotypes and Phenotypes

CYP2D6	Ultrarapid Metabolizer	*1/*1 (DUPLICATION)

CYP2D6 *1: This allele produces normal enzyme activity.
CYP2D6 *1: This allele produces normal enzyme activity.

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

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

CYP2C19	Extensive Metabolizer	*1/*1

CYP2C19 *1: This allele produces normal enzyme activity.
CYP2C19 *1: This allele produces normal enzyme activity.

Similar report for each gene tested

Commercial PGx Tests: GeneSight (Assurex)

genesight

GeneSight® Psychotropic Results

assurex health

[redacted]

DOB: 8/20/1945

Reference:
Clinician: Francis Mondimore MD

Order Number: 156695
Report Date: 3/12/2015

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**citalopram** (Celexa®) [2,4]	**amitriptyline** (Elavil®) [2,7]
desvenlafaxine (Pristiq®)	**escitalopram** (Lexapro®) [2,4]	**clomipramine** (Anafranil®) [2,7]
levomilnacipran (Fetzima®)	**sertraline** (Zoloft®) [4]	**desipramine** (Norpramin®) [2]
selegiline (Emsam®)	**venlafaxine** (Effexor®) [2]	**doxepin** (Sinequan®) [2,7]
vilazodone (Viibryd®)		**duloxetine** (Cymbalta®) [2,7]
		fluoxetine (Prozac®) [2,4]
		fluvoxamine (Luvox®) [2,4,7]
		imipramine (Tofranil®) [2,7]
		mirtazapine (Remeron®) [2,7]
		nortriptyline (Pamelor®) [2]
		paroxetine (Paxil®) [2,4,6]
		trazodone (Desyrel®) [2,7]
		vortioxetine (Brintellix®) [2]

[2]: Serum level may be too low, higher doses may be required.
[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.

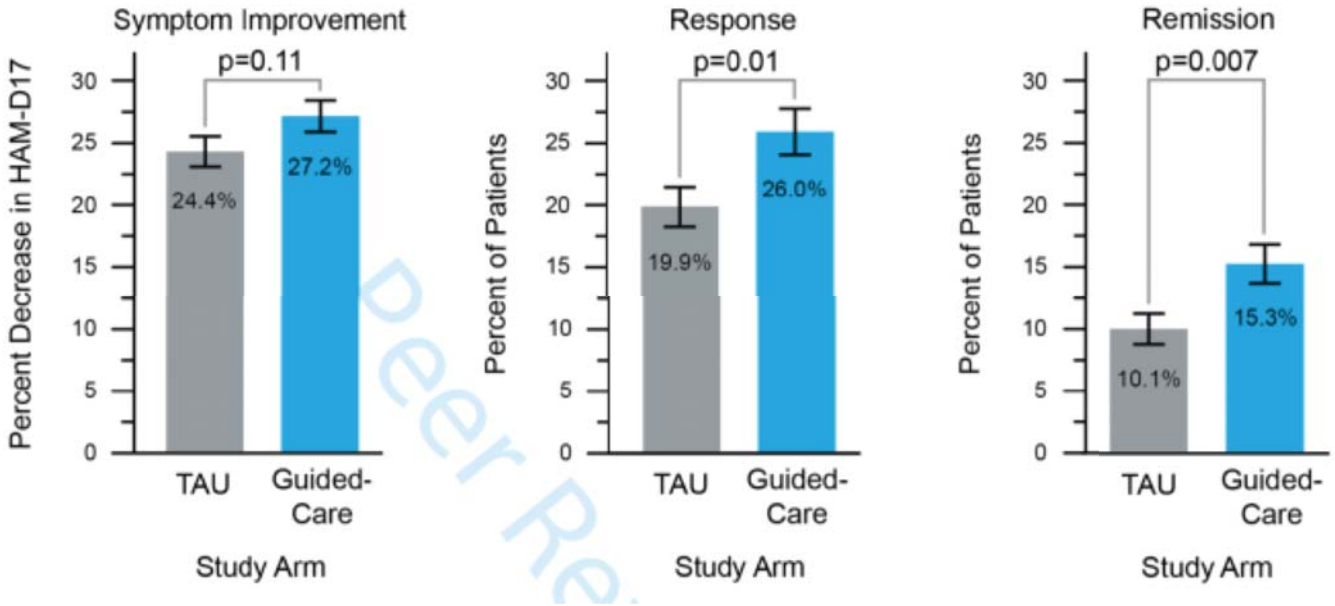
GeneSight RCT - Design

STUDY PROTOCOL

PROTOCOL NUMBER:	**ARX 1006**
PROTOCOL TITLE:	A 12-Week, Randomized, Double-Blind, Controlled Evaluation Followed by an Open-Label 12-Week Follow-up Period of the Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering from a Major Depressive Disorder (MDD) and Having Had – Within the Current Episode - an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic
TEST ARTICLE:	GeneSight Psychotropic
SPONSOR:	AssureRx Health, Inc. (Assurex)

- NNDC led study with 30 active sites
- Currently depressed MDD outpatients (n=1,167) with inadequate response to ≥1 treatment
- PGx guided arm (n=560) versus TAU (n=607)

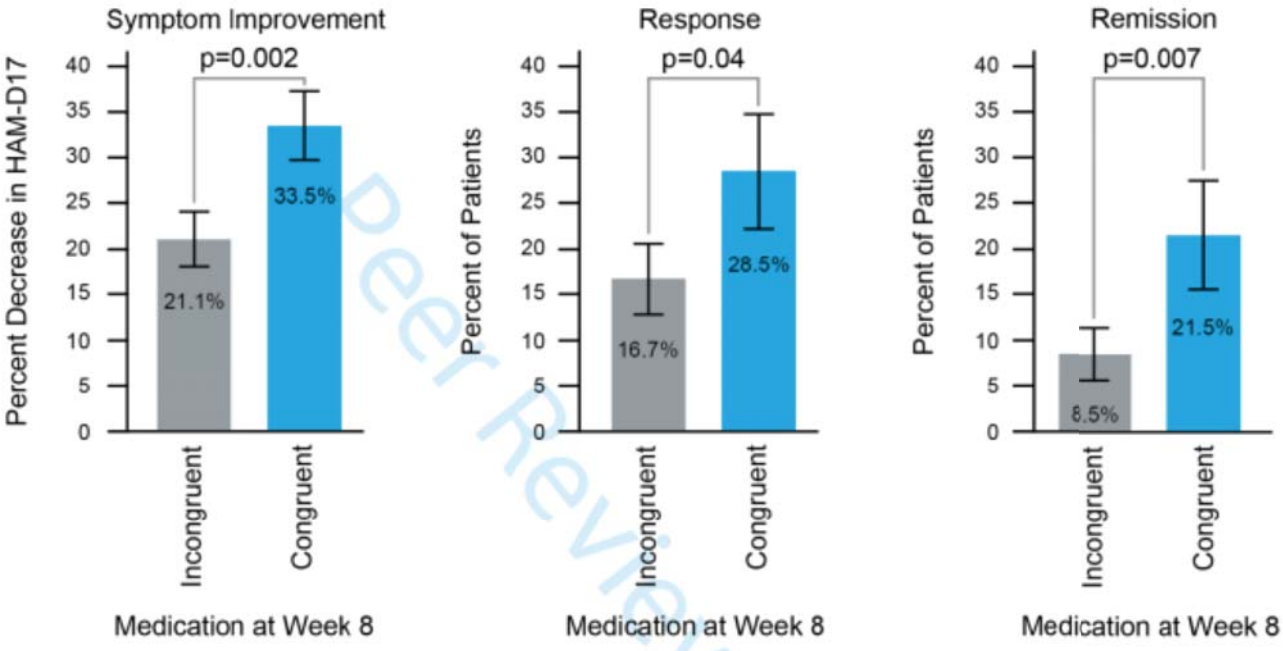
GeneSight RCT – Results (1)



- Primary outcome: Symptom improvement on HAMD at 8 weeks: *Benefit did not reach statistical significance.*
- Secondary outcomes: response (>50% decrease) & remission (HAMD<7); total of 25 secondary outcomes listed on ClinTrials.Gov

Courtesy of J. Raymond DePaulo, NNDC Chair

GeneSight RCT – Results (2)

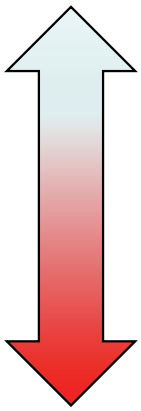


- Sub-group analysis in patients from both arms who were incongruent at baseline (n=213): *Significant benefit on all outcome measures*

Courtesy of J. Raymond DePaulo, NNDC Chair

GeneSight RCT - Conclusion

Assurex Press Release: “Landmark Study Shows GeneSight® Test Led to Significant Improvement in Mental Health Outcomes for Patients with Major Depressive Disorder”



Strict Intepretation: “Large Randomized Trial of GeneSight® Test Does Not Show Improvement in Mental Health Outcomes for Patients with Major Depressive Disorder,

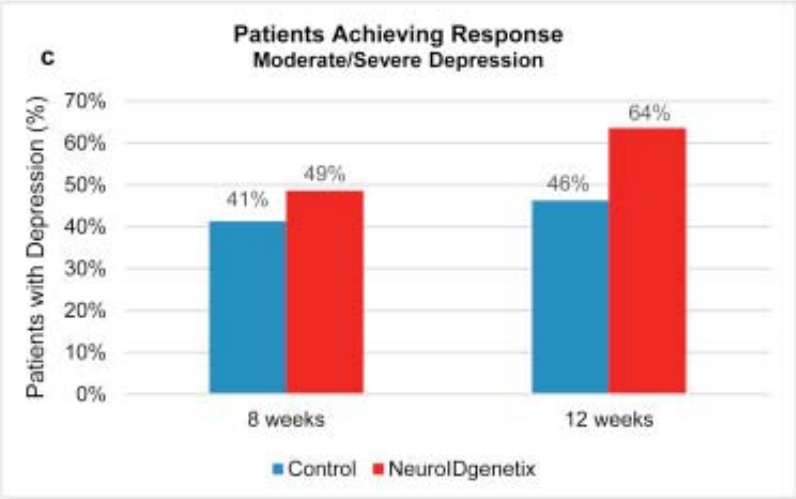
IDgenetix: Neuro RCT - Design

Study Protocol

Protocol Title:	A Prospective, Multi-Center, Randomized Clinical Study to Evaluate the Clinical Impact of Pharmacogenetic-Guided Treatment for Depression & Anxiety
Test Article:	IDgenetix Neuropsychiatric Test Panel
Sponsor:	AltheaDx

- 20 sites, incl. Psych., Internal.Med., OB-GYN, Family Med.
- Currently depressed (moderate or severe) or and/or anxious outpatients (n=685), “new to treatment” or with inadequate response to treatment.
- PGx guided arm (n=352) versus TAU (n=333)

IDgenetix: Neuro RCT – Results (1)

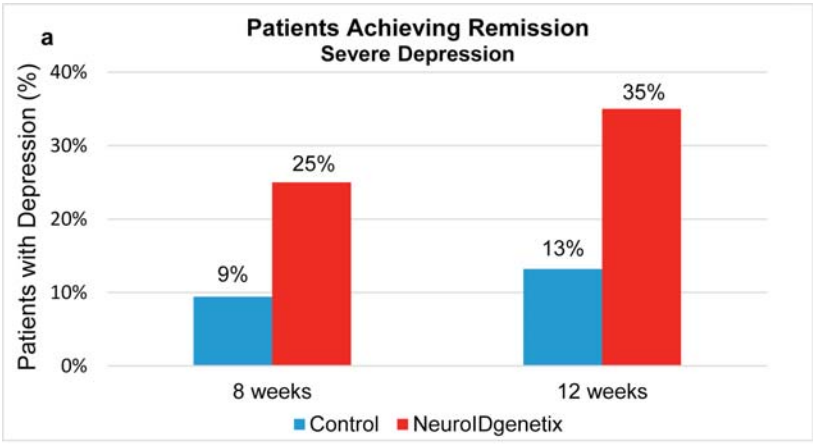


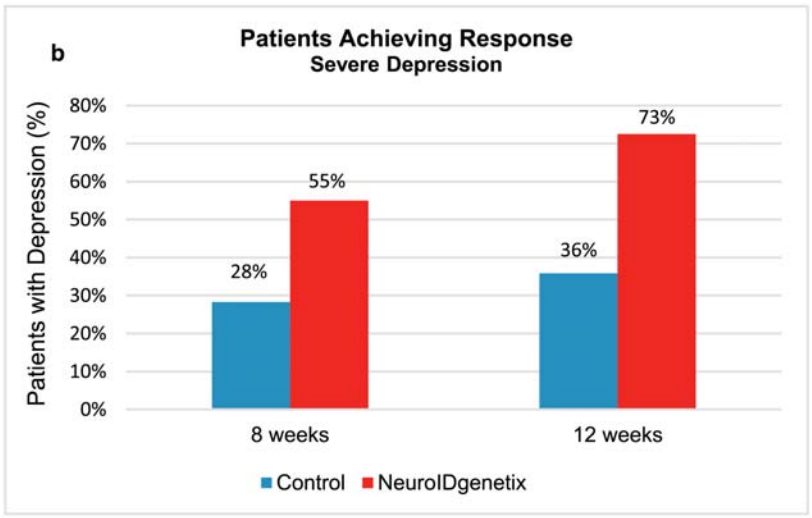
- Primary outcome: The reduction of adverse drug events in pharmacogenetics-guided treatment versus TAU: *Not significant*

- Secondary outcomes: Differences in HAM-D, HAM-A Scores. Differences in Response (>50% decrease) & Remission rates (HAMD<7): *Only response/remiss. rate differences reported for depressed patients.*

Courtesy of J. Raymond DePaulo, NNDC Chair

IDgenetix: Neuro RCT – Results (1)





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Courtesy of J. Raymond DePaulo, NNDC Chair

Final Assessment

Personalized medicine in psychiatry – Are we there yet?

PGx Resources

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
  (www.cdc.gov/egappreviews/)
- Pharmacogenomics Knowledge Base (PharmGKB)
  (www.pharmgkb.org)
- The Clinical Pharmacogenetics Implementation Consortium (CPIC)
  (www.cpicpgx.org)
- The Food and Drug Administration (FDA)
  (www.fda.gov)