Genetic Testing in Psychiatry: Ready for Prime-time?

Matthew Macaluso, DO
Bee McWane Reid Endowed Professor
Clinical Director, UAB Depression and Suicide Center

Disclosure

Dr. Macaluso has received grant/research support from the following commercial entities in the last year:

Alkermes, Allergan, AssureRx/Myriad, Eisai, Forum, Liva Nova, Lundbeck, Janssen, Naurex/Aptinyx, Otsuka.

All clinical trial and study contracts were with and payments made to either the University of Alabama at Birmingham or the Kansas University Medical Center Research Institute.

Dr. Macaluso has also received royalties from Springer Nature for his work as editor of the textbook *Antidepressants: from Biogenic Amines to New Mechanisms of Action.*

An ideal lab test in psychiatry

- **Have diagnostic sensitivity and specificity**
- **Determine diagnosis**
- **Predict course of illness**
- **Predict drug response**
- **Predict drug tolerability**

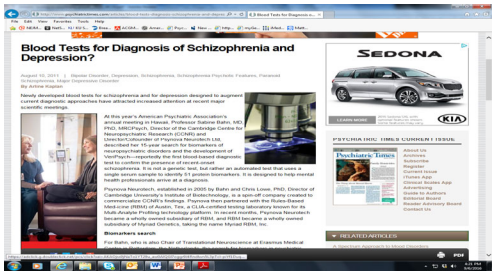
Failed lab tests in psychiatry

- Tests to distinguish serotonergic versus noradrenergic forms of depression in the 1970's
- Dexamethasone suppression test in the 1980's

Maas JW. Biogenic amines and depression. Arch Gen Psychiatry. 1975;32:1357–1361.

Carroll BJ, Feinberg M, Greden JF, et al. Arch Gen Psychiatry. 1981;38:15–22.

Recently a test for schizophrenia was marketed….



What types of tests are being developed?

- ***Pharmacogenomic based lab tests***
  - Genes coding for pharmacokineteic mechanisms (eg CYP 450)
  - Genes coding for pharmacodynamic mechanisms (serotonin transporter)
- ***Immunoassay based tests***
  - Measure proteins including inflammatory cytokines (eg IL-6)

What does it take to market these tests?

- Lab must meet CLIA standards
- Demonstrate analytical validity
- No requirement for clinical validity

http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm

What about the FDA?

- Currently only "high risk" tests (eg detecting malignancy) require FDA approval
- FDA requires proof of clinical validity and utility

What is clinical validity?

- **A clinically meaningful measure (eg response)**
- **An adverse effect**
- **A biologically meaningful measure (eg drug level)**

What is clinical utility?

- proof that the test can:
  - reliably be used to guide clinical management
  - Meaningfully improve outcomes (eg dose selection)

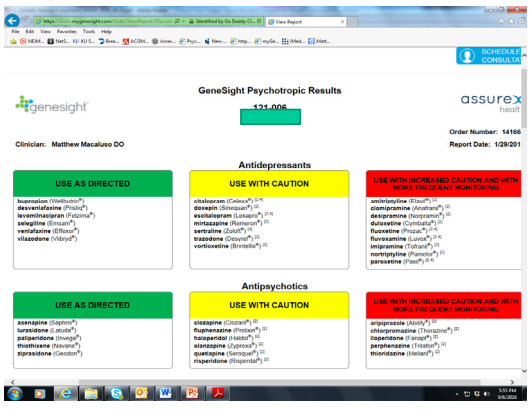
Several companies have marketed pharmacogenetic "decision support tools"

What are these decision support tools?

- Examine pharmacokinetic and pharmacodynamic genes that affect a patient's ability to tolerate or respond to medications

How are PG tests unique?

- PG tests are trait, rather than state characteristics
- PG tests could influence the prescribing of non-psychotropic medications



Is your functional status at a given moment the same as your PG trait?

What objective evidence supports the use of these tests in clinical practice?

Pharmacogenetics and Genomics:
October 2013 - Volume 23 - Issue 10 - p 535–548
doi: 10.1097/FPC.0b013e3283648b9a
Original Articles

Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting

Hall-Flavin, Daniel K.*; Winner, Joel G.*,†; Allen, Josiah D.‡; Carhart, Joseph M.‡; Proctor, Brian‡; Snyder, Karen A.*; Drews, Maureen S.*; Eisterhold, Linda L.*; Geske, Jennifer*; Mrazek, David A.*

Abstract

Objective: The objective was to evaluate the potential benefit of an integrated, five-gene pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications used to treat major depression in an outpatient psychiatric practice.

Methods: The open-label study was divided into two groups. In the first (unguided) group (n=113), pharmacogenomic information was not shared until all participants completed the study. In the second (guided) group (n=114), the pharmacogenomic report was provided to physicians for clinical use. Three depression ratings, the 17-item Hamilton Rating Scale for Depression (HAMD-17), the Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C16), and the Patient Health Questionnaire (PHQ-9), were collected at baseline, and at 2, 4, and 8 weeks.

Results: The guided group experienced greater percent improvement in depression scores from baseline on all three depression instruments (HAMD-17, $P<0.0001$; QIDS-C16, $P<0.0001$; PHQ-9, $P<0.0001$) compared with the unguided group. Eight-week response rates were higher in the guided group than in the unguided group on all three measurements (HAMD-17, $P=0.03$; QIDS-C16, $P=0.005$; PHQ-9, $P=0.01$). Eight-week QIDS-C16 remission rates were higher in the guided group ($P=0.03$). Participants in the unguided group who at baseline were prescribed a medication that was most discordant with their genotype experienced the least improvement compared with other unguided participants (HAMD-17, $P=0.007$). Participants in the guided group and on a baseline medication most discordant with their genotype showed the greatest improvement compared with the unguided cohort participants (HAMD-17, $P<0.01$).

Conclusion: These findings replicate previous studies and demonstrate significantly improved depression outcomes with use of GeneSight, an integrated, multigenetic pharmacogenomic testing platform.

© 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

Article Level Metrics

See more details

Picked up by 2 news outlets
Tweeted by 10
Highlighted by 1 platforms
51 readers on Mendeley

Keywords
antidepressant, genomics, pharmacogenomic, translational medicine, treatment-resistant depression

Search for Similar Articles
You may search for similar articles that contain these same keywords or you may modify the keyword list to augment your search.

antidepressant, genomics, pharmacogenomic, translational medicine,

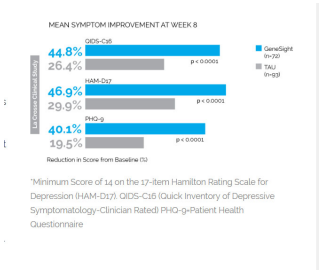
Search | Restore Keywords

Related Links

- Articles in PubMed by Daniel K. Hall-Flavin
- This article in PubMed
- Articles in Google Scholar by Daniel K. Hall-Flavin
- Other articles in this journal by Daniel K. Hall-Flavin

Readers Of this Article Also Read

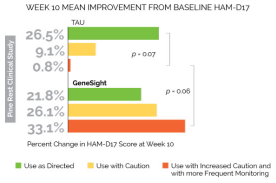
Hall-Flavin, et al results



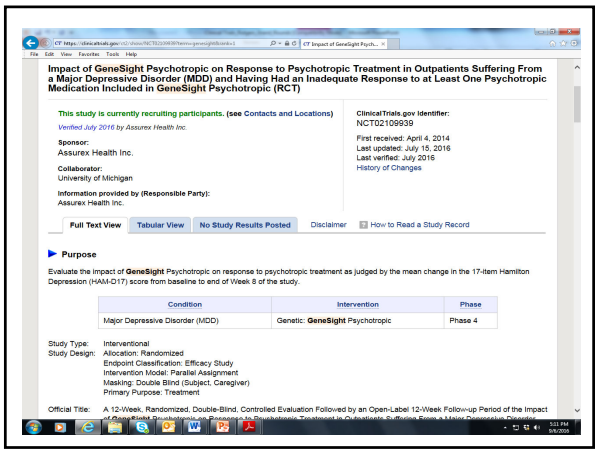
*Minimum Score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). QIDS-C16 (Quick Inventory of Depressive Symptomatology–Clinician Rated) PHQ-9-Patient Health Questionnaire

https://genesight.com/education/clinical-studies/

Winner, et al results



*Minimum Score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17).



Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic (RCT)

This study is currently recruiting participants. (see Contacts and Locations)
Verified July 2016 by Assurex Health Inc.

Sponsor:
Assurex Health Inc.

Collaborator:
University of Michigan

Information provided by (Responsible Party):
Assurex Health Inc.

ClinicalTrials.gov Identifier:
NCT02109939

First received: April 4, 2014
Last updated: July 15, 2016
Last verified: July 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

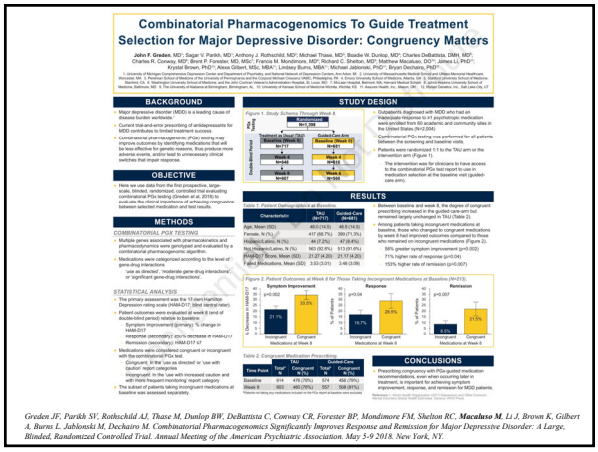
Purpose

Evaluate the impact of **GeneSight** Psychotropic on response to psychotropic treatment as judged by the mean change in the 17-item Hamilton Depression (HAM-D17) score from baseline to end of Week 8 of the study.

Condition	Intervention	Phase
Major Depressive Disorder (MDD)	Genetic: **GeneSight** Psychotropic	Phase 4

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver)
Primary Purpose: Treatment

Official 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



Combinatorial Pharmacogenomics To Guide Treatment Selection for Major Depressive Disorder: Congruency Matters

BACKGROUND

OBJECTIVE

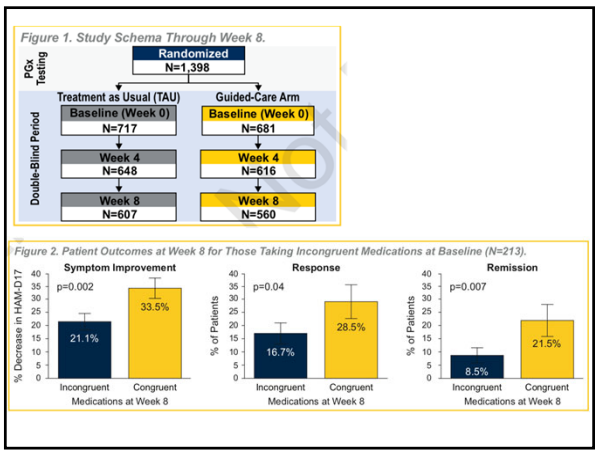
METHODS

STUDY DESIGN

RESULTS

CONCLUSIONS

*Greden JF, Parikh SV, Rothschild AJ, Thase M, Dunlop BW, DeBattista C, Conway CR, Forester BP, Mondimore FM, Shelton RC, **Macaluso M**, Li J, Brown K, Gilbert A, Burns L, Jablonski M, Dechairo M. Combinatorial Pharmacogenomics Significantly Improves Response and Remission for Major Depressive Disorder: A Large, Blinded, Randomized Controlled Trial. Annual Meeting of the American Psychiatric Association. May 5-9 2018. New York, NY.*



Dunlop et al. BMC Psychiatry (2019) 19:420
https://doi.org/10.1186/s12888-019-2410-2

BMC Psychiatry

RESEARCH ARTICLE Open Access

Comparing sensitivity to change using the 6-item versus the 17-item Hamilton depression rating scale in the GUIDED randomized controlled trial

Boadie W. Dunlop[1], Sagar V. Parikh[2], Anthony J. Rothschild[3], Michael E. Thase[4], Charles DeBattista[5], Charles R. Conway[6], Brent P. Forester[7], Francis M. Mondimore[8], Richard C. Shelton[9], Matthew Macaluso[10], Jennifer Logan[10], Paul Traxler[11], James Li[11], Holly Johnson[11] and John F. Greden[2]

Abstract

Background: Previous research suggests that the 17-item Hamilton Depression Rating Scale (HAM-D17) is less sensitive in detecting differences between active treatment and placebo for major depressive disorder (MDD) than is the HAM-D6 scale, which focuses on six core depression symptoms. Whether HAM-D6 shows greater sensitivity when comparing two active MDD treatment arms is unknown.

Methods: This post hoc analysis used data from the intent-to-treat (ITT) cohort ($N = 1541$) of the Genomics Used to Improve DEpression Decisions (GUIDED) trial, a rater- and patient-blinded randomized controlled trial. GUIDED compared combinatorial pharmacogenomics-guided care with treatment as usual (TAU) in patients with MDD. Percent of symptom improvement, response rate and remission rate from baseline to week 8 were evaluated using both scales. Analyses were performed for the full cohort and for the subset of patients who at baseline were taking medications predicted by the test to have moderate or significant gene-drug interactions. A Mokken scale analysis was conducted to compare the homogeneity of HAM-D17 with that of HAM-D6.

Results: At week 8, the guided-care arm demonstrated statistically significant benefit over TAU when the HAM-D6 ($\Delta = 4.4\%$, $p = 0.023$) was used as the continuous measure of symptom improvement, but not when using the HAM-D17 ($\Delta = 3.2\%$, $p = 0.069$). Response rates increased significantly for guided-care compared with TAU when evaluated using both HAM-D6 ($\Delta = 7.0\%$, $p = 0.004$) and HAM-D17 ($\Delta = 6.3\%$, $p = 0.007$). Remission rates also were significantly greater for guided-care versus TAU using both measures (HAM-D6 $\Delta = 4.6\%$, $p = 0.031$; HAM-D17 $\Delta = 5.5\%$, $p = 0.005$). Patients in the guided-care arm who at baseline were taking medications predicted to have gene-drug interactions showed further increased benefit over TAU at week 8 for symptom improvement ($\Delta = 7.3\%$, $p = 0.004$) response ($\Delta = 10.8\%$, $p = 0.001$) and remission ($\Delta = 7.9\%$, $p = 0.005$) using HAM-D6. All outcomes showed continued improvement through week 24. Mokken scale analysis demonstrated the homogeneity and unidimensionality of HAM-D6, but not of HAM-D17, across treatment arms.

Conclusions: The HAM-D6 scale identified a statistically significant difference in symptom improvement between combinatorial pharmacogenomics-guided care and TAU, whereas the HAM-D17 did not. The demonstrated utility of pharmacogenomics-guided treatment over TAU as detected by the HAM-D6 highlights its value for future biomarker-

Knowledge of the Pharmacology of Antidepressants and Antipsychotics Yields Results Comparable With Pharmacogenetic Testing

MATTHEW MACALUSO, DO
SHELDON H. PRESKORN, MD

Several companies offer pharmacogenetic testing for psychiatry on the basis of the claim that the outcome of drug selection is better when guided by such testing than when such testing is not used. This column examines the results of the GeneSight Psychotropic Test which groups various antidepressants and antipsychotics into 3 bins: green ("use as directed"), yellow ("use with caution"), and red ("use with increased caution and more frequent monitoring"). The authors examined how frequently the same drugs appeared in these different bins in 19 patients. They found that of the 22 antidepressants evaluated, 2 were virtually always (> 90%) in the green bin: desvenlafaxine and levomilnacipran; and 8 were almost never (≤ 10.5%) in the green bin: citalopram, duloxetine, escitalopram, fluoxetine,

antipsychotic medications in clinical practice.[1] These pharmacogenetic tests provide data principally on patient genotype relative to cytochrome P450 (CYP) enzymes and, to a lesser extent, relevant to pharmacodynamic targets (eg, the serotonin transporter). These "decision support tools" can advise when a specific patient will have faster or slower clearance of a drug. This information can be used to predict when a patient will have a higher or lower blood level of a specific medication relative to the dose prescribed and compared with the usual patient population. Such predictions are based on genotypic expression of specific CYP enzymes and the known metabolic pathways of specific drugs.[1]

Different companies marketing genetic tests use different formats for presenting the findings

Macaluso and Preskorn. Journal of Psychiatric Practice Vol. 24, No. 6

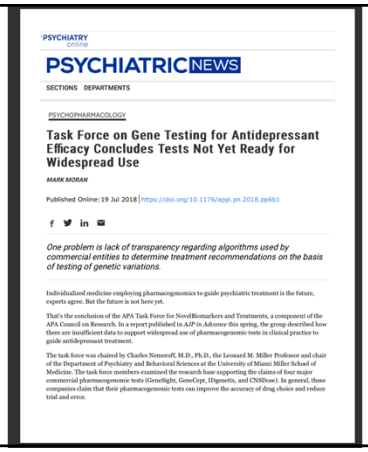
TABLE 1. Antidepressants*

	Green [n (%)]	*Yellow [n (%)]*	*Red [n (%)]*
Amitriptyline	5 (26.3)	5 (26.3)	9 (47.4)
Bupropion	7 (36.8)	10 (52.6)	2 (10.5)
Citalopram	0 (0.0)	17 (89.5)	2 (10.5)
Clomipramine	6 (31.6)	6 (31.6)	7 (36.8)
Desipramine	6 (31.6)	6 (31.6)	7 (36.8)
Desvenlafaxine	19 (100.0)	0 (0.0)	0 (0.0)
Doxepin	5 (26.3)	8 (42.1)	6 (31.6)
Duloxetine	2 (10.5)	8 (42.1)	9 (47.4)
Escitalopram	0 (0.0)	17 (89.5)	2 (10.5)
Fluoxetine	2 (10.5)	10 (52.6)	7 (36.8)
Fluvoxamine	0 (0.0)	10 (52.6)	9 (47.4)
Imipramine	5 (26.3)	7 (36.8)	7 (36.8)
Levomilnacipran	18 (94.7)	1 (5.3)	0 (0.0)
Mirtazapine	2 (10.5)	10 (52.6)	7 (36.8)
Nortriptyline	6 (31.6)	6 (31.6)	7 (36.8)
Paroxetine	0 (0.0)	6 (31.6)	13 (68.4)
Selegeline	11 (57.9)	4 (21.1)	4 (21.1)
Sertraline	2 (10.5)	17 (89.5)	0 (0.0)
Trazodone	6 (31.6)	12 (63.2)	1 (5.3)
Venlafaxine	8 (42.1)	6 (31.6)	5 (26.3)
Vilazodone	16 (84.2)	3 (15.8)	0 (0.0)
Vortioxetine	6 (31.6)	9 (47.4)	4 (21.1)

*Based on GeneSight testing for 19 patients. Green indicates "use as directed"; yellow, "use with caution"; red, "use with increased caution and more frequent monitoring".

Macaluso and Preskorn. Journal of Psychiatric Practice Vol. 24, No. 6

When is pharmacogenomic testing recommended?



PSYCHIATRY online

PSYCHIATRIC NEWS

SECTIONS DEPARTMENTS

PSYCHOPHARMACOLOGY

Task Force on Gene Testing for Antidepressant Efficacy Concludes Tests Not Yet Ready for Widespread Use

MARK MORAN

Published Online: 19 Jul 2018 | https://doi.org/10.1176/appi.pn.2018.pp6b1

One problem is lack of transparency regarding algorithms used by commercial entities to determine treatment recommendations on the basis of testing of genetic variations.

Individualized medicine employing pharmacogenomics to guide psychiatric treatment is the future, experts agree. But the future is not here yet.

That's the conclusion of the APA Task Force for NovelBiomarkers and Treatments, a component of the APA Council on Research. In a report published in *AJP in Advance* this spring, the group described how there are insufficient data to support widespread use of pharmacogenomic tests in clinical practice to guide antidepressant treatment.

The task force was chaired by Charles Nemeroff, M.D., Ph.D., the Leonard M. Miller Professor and chair of the Department of Psychiatry and Behavioral Sciences at the University of Miami Miller School of Medicine. The task force members examined the research base supporting the claims of four major commercial pharmacogenomic tests (GeneSight, GeneCrpt, IDgenetix, and CNSDose). In general, these companies claim that their pharmacogenomic tests can improve the accuracy of drug choice and reduce trial and error.

Psychiatry Research 290 (2020) 113017

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder

Richard C. Shelton (MD)[a,*], Sagar V. Parikh (MD)[b], Rebecca A. Law (MS)[c], Anthony J. Rothschild (MD)[d], Michael E. Thase (MD)[e], Boadie W. Dunlop (MD)[f], Charles DeBattista (DMHMD)[g], Charles R. Conway (MD)[h], Brent P. Forester (MDMSc)[i], Matthew Macaluso (DO)[j], Daniel T. Hain[c], Aime Lopez Aguilar (PhD)[c], Krystal Brown (PhD)[k], David J. Lewis (MS)[c], Michael R. Jablonski (PhD)[c], John F. Greden (MD)[b]

[a] Department of Psychiatry and School of Medicine, The University of Alabama at Birmingham, Birmingham, AL
[b] University of Michigan Comprehensive Depression Center and Department of Psychiatry, and National Network of Depression Centers, Ann Arbor, MI
[c] Myriad Neuroscience, Mason, OH
[d] University of Massachusetts Medical School and UMass Memorial Healthcare, Worcester, MA
[e] Perelman School of Medicine of the University of Pennsylvania and the Corporal Michael Crescenz VAMC, Philadelphia, PA
[f] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
[g] Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Stanford, CA
[h] Department of Psychiatry, Washington University School of Medicine, and the John Cochran Veteran's Administration Hospital, St. Louis, MO
[i] McLean Hospital, Division of Geriatric Psychiatry, Belmont, MA; Harvard Medical School
[j] Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, Wichita, KS
[k] Myriad Genetics, Inc., Salt Lake City, UT

ARTICLE INFO

Keywords:
GeneSight
Pharmacokinetics
Medication Blood Levels
Depression
Citalopram
Escitalopram

ABSTRACT

Pharmacogenomic tests used to guide clinical treatment for major depressive disorder (MDD) must be thoroughly validated. One important assessment of validity is the ability to predict medication blood levels, which reflect altered metabolism. Historically, the metabolic impact of individual genes has been evaluated; however, we now know that multiple genes are often involved in medication metabolism. Here, we evaluated the ability of individual pharmacokinetic genes (*CYP2C19*, *CYP2D6*, *CYP3A4*) and a combinatorial pharmacogenomic test (GeneSight Psychotropic®; weighted assessment of all three genes) to predict citalopram/escitalopram blood levels in patients with MDD. Patients from the Genomics Used to Improve **D**epression **D**ecisions (GUIDED) trial who were taking citalopram/escitalopram at screening and had available blood level data were included (N = 191). In multivariate analysis of the individual genes and combinatorial pharmacogenomic test separately (adjusted for age, smoking status), the F statistic for the combinatorial pharmacogenomic test was 1.7 to 2.9-times higher than the individual genes, showing that it explained more variance in citalopram/escitalopram blood levels. In multivariate analysis of the individual genes and combinatorial pharmacogenomic test together, only the combinatorial pharmacogenomic test remained significant. Overall, this demonstrates that the combinatorial pharmacogenomic test was a superior predictor of citalopram/escitalopram blood levels compared to individual genes.

Back to our question: when is pharmacogenomic testing recommended?

FDA Recommends Specific Types of Genetic Tests

- **More than 30 drugs have PG testing incorporated into their package labeling**
- **Some recommend testing at certain dose levels, others prior to starting certain medications**

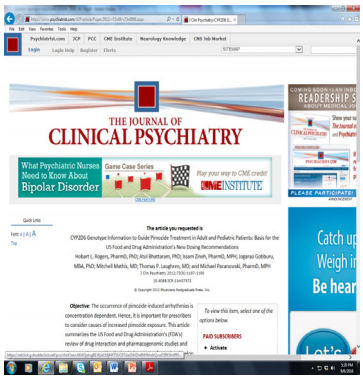
Table 1. Therapeutic areas in which pharmacogenomic information (PGI) is being incorporated into product labels as well as influencing the development of new designer drugs

Biomarker	*Therapeutic area*	*Biomarker*	*Therapeutic area*
ALK	Oncology	G6PD	Oncology, dermatology & dental, antiinfectives
Antithrombin III deficiency (SERPINC1)	Hematology	HGPRT	Transplantation
APOE2	Cardiovascular, metabolic & endocrinology	HLA-B*1502	Neurology
BRAF	Oncology	HLA-B*5701	Antivirals
CCR5	Antivirals	IL28B	Antivirals
CD20 antigen	Oncology	KRAS	Oncology
CD25	Oncology	LDL receptor	Metabolic & endocrinology
CD30	Oncology	NAT1; NAT2	Antiinfectives, cardiovascular
CFTR (G551D)	Pulmonary	PDGFR	Oncology
Chromosome 5q	Hematology	Ph Chromosome	Oncology
C-Kit	Oncology	PML/ RARα	Dermatology & dental, oncology
CYP1A2	Gastroenterology	Prothrombin mutations (F2)	Oncology
CYP2C19	Antifungals, cardiovascular, gastroenterology, reproductive, psychiatry, musculoskeletal, neurology	Rh genotype	Reproductive & urologic
CYP2C9	Hematology, rheumatology	TPMT	Rheumatology, oncology
CYP2D6	Psychiatry, analgesics, reproductive and urologic, neurology, antifungals, antiarrhythmic/cardiovascular, dermatology & dental	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Gastroenterology, psychiatry
		UGT1A1	Oncology, pulmonary
		VKORC1	Hematology
DPD	Dermatology & dental, oncology		
EGFR	Oncology		
ER & PGR	Oncology		
ERBB2 (HER2)	Oncology		
Factor V Leiden (FV)	Hematology		
FIP1L1-PDGFRα	Oncology		

This table is adapted from the Table Pharmacogenomic Biomarkers in Drug Labels on the FDA website www.fda.gov /DrugsScienceResearch/ResearchAreas/Pharmacogenetics/ucm 083378.htm.

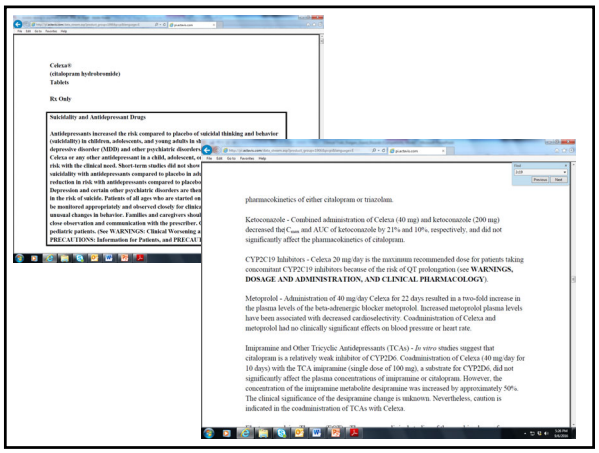
Commonly accepted abbreviations for biomarkers are shown in the Table in the interest of space, but full names of most, if not, all of these biomarkers can be readily located via an Internet search. Note that, in some cases, two therapeutic areas are listed together (e.g.,metabolic & endocrinology, dermatology & dental) because these are therapeutic groupings for FDA review and approval, with specific advisory committees with these names.

Preskorn, et al J Psychiatr Pract. 2013 Mar;19(2):142-9. doi: 10.1097/01.pra.0000428559.01953.73.



Conclusions: Given the risk of increased pimozide concentrations and longer time to steady state in CYP2D6 poor metabolizers, the FDA has revised the pimozide label to provide clinicians with clearer dosing, titration, and genotype testing recommendations. The new information is intended to enhance therapeutic individualization of pimozide in pediatric and adult patients.
J Clin Psychiatry 2012;73(9):1187–1190

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism *[see Drug Interactions (7.1)]*, and in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3)]*.



Celexa®
(citalopram hydrobromide)
Tablets

Rx Only

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in sh depressive disorder (MDD) and other psychiatric disorders Celexa or any other antidepressant in a child, adolescent, o risk with the clinical need. Short-term studies did not show suicidality with antidepressants compared to placebo in ad reduction in risk with antidepressants compared to placebo Depression and certain other psychiatric disorders are ther in the risk of suicide. Patients of all ages who are started on be monitored appropriately and observed closely for clinic unusual changes in behavior. Families and caregivers shoul close observation and communication with the prescriber. pediatric patients. (See WARNINGS: Clinical Worsening a PRECAUTIONS: Information for Patients, and PRECAU

pharmacokinetics of either citalopram or triazolam.

Ketoconazole - Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP2C19 Inhibitors - Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant CYP2C19 inhibitors because of the risk of QT prolongation (see **WARNINGS, DOSAGE AND ADMINISTRATION, AND CLINICAL PHARMACOLOGY**).

Metoprolol - Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs) - *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the TCA imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCAs with Celexa.

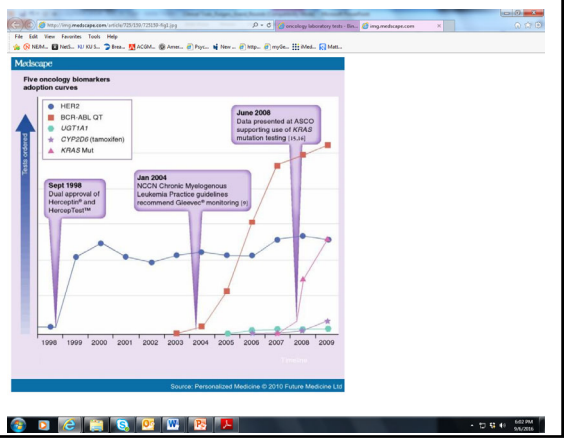
Example: venlafaxine

- **Examined data from 4 RCT's of venlafaxine**
- **Examined ODV/VEN ratio and EM/PM status**
- **ODV/VEN ratio and EM status predicted response and remission**

J Clin Psychiatry 2010;71(11):1482-1487 10.4088/JCP.08m04773blu

What does the future hold?

- **In oncology lab tests are used to understand how cancer tissue differs genetically from normal tissue**
- **There continues an unmet need for clinically meaningful tests to aid in patient care in psychiatry**



AS GENETIC TESTS ARE INCREASINGLY USED IN CLINICAL TRIALS, DRUGS APPROVED IN THE FUTURE WILL REQUIRE GENETIC TESTING IN CLINICAL PRACTICE

What does the future hold?

- **Personalized medicine**
- **The end of one size fits all prescribing both for type of drug and dosing**
- **Understand how individuals with the same disease have differing biology**

Could psychiatry follow a similar path?

- ***Stay tuned…….***

The End

Thank You