Precision Medicine:

Therapeutic Management

and

Clinical Utility

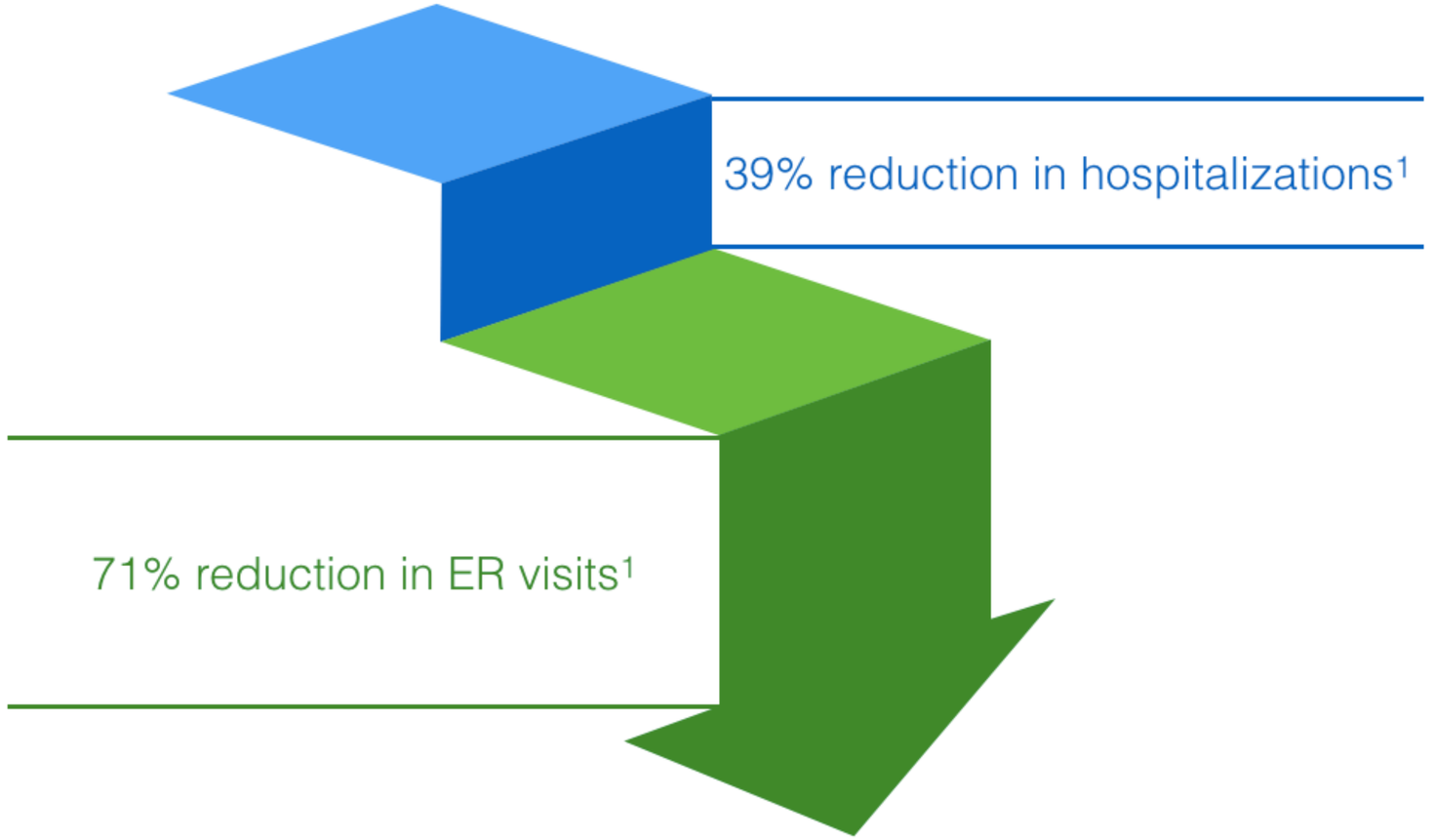
Using the P3 Report

Proving Clinical Utility

The use of pharmacogenomic testing and clinical decision support software reduced:

- **Hospitalizations by 39%**
- **ER visits by 71%**

in elderly patients taking multiple medications in just 4-months[1]



1 – The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. D. Brixner , E. Biltaji , A. Bress , S. Unni , X. Ye , T. Mamiya , K. Ashcraft , J. Biskupiak. Journal of Medical Economics. Vol. 19, Iss. 3, 2016.

Clinical Studies in Pharmacogenetics

Objectives:

Three separate studies compared medication management guided by pharmacogenetic testing to trial-and-error (treatment as usual) in patients with depression

Outcomes:

Prescribing guided by PGx testing demonstrated a statistically significant improvement in patient outcomes by:

(1)Reducing depression symptoms[1]

(2)Decreasing time to symptom relief[2]

(3)Increasing patient satisfaction with their medication[3]

An additional study by the same group also proved that healthcare costs decreased by $5,188 on average per patient when prescribed genetically optimal medications[4]

1Hall-Flavin DK, Winner, JG, Allen JD, Jordan JJ, Nesheim RS, Snyder KA, Drews MS, Eisterhold LL, Biernacka JM, Mrazek DA. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2:e 172.

2Hall-Flavin DK, Winner JG, Allen JD, Carhart JM, Proctor B, Snyder KA, Drews MS, Eisterhold LL, Geske J, Mrazek DA. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics and Genomics. 2013;23(10):535-548.

3Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discovery Med. 2013;16(89): 219-227.

4Winner JG, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013;3:e300. doi:10. 1038/tp.2013.2.

Accurate and Actionable- It's What P-3 Does!

"**Multigenic combinatorial testing** discriminates and predicts the poorer antidepressant outcomes and **greater health-care utilizations** by depressed subjects better than do phenotypes derived from single genes. **This clinical validity is likely to contribute to the clinical utility reported for combinatorial pharmacogenomic decision support.**"

The Pharmacogenomics Journal (2015) 15, 443–451

www.nature.com/tpj

ORIGINAL ARTICLE

Clinical validity: Combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes

CA Altar[1], JM Carhart[1], JD Allen[1], DK Hall-Flavin[2], BM Dechairo[1] and JG Winner[1]

In four previous studies, a combinatorial multigene pharmacogenomic test (GeneSight) predicted those patients whose antidepressant treatment for major depressive disorder resulted in poorer efficacy and increased health-care resource utilizations. Here, we extended the analysis of clinical validity to the combined data from these studies. We also compared the outcome predictions of the combinatorial use of allelic variations in genes for four cytochrome *P*450 (CYP) enzymes (*CYP2D6, CYP2C19, CYP2C9* and *CYP1A2*), the serotonin transporter (*SLC6A4*) and serotonin 2A receptor (*HTR2A*) with the outcome predictions for the very same subjects using traditional, single-gene analysis. Depression scores were measured at baseline and 8–10 weeks later for the 119 fully blinded subjects who received treatment as usual (TAU) with antidepressant standard of care, without the benefit of pharmacogenomic medication guidance. For another 96 TAU subjects, health-care utilizations were recorded in a 1-year, retrospective chart review. All subjects were genotyped after the clinical study period, and phenotype subgroups were created among those who had been prescribed a GeneSight panel medication that is a substrate for either CYP enzyme or serotonin effector protein. On the basis of medications prescribed for each subject at baseline, the combinatorial pharmacogenomic (CPGx™) GeneSight method categorized each subject into either a green ('use as directed'), yellow ('use with caution') or red category ('use with increased caution and with more frequent monitoring') phenotype, whereas the single-gene method categorized the same subjects with the traditional phenotype (for example, poor, intermediate, extensive or ultrarapid CYP metabolizer). The GeneSight combinatorial categorization approach discriminated and predicted poorer outcomes for red category patients prescribed medications metabolized by *CYP2D6*, *CYP2C19* and *CYP1A2* ($P = 0.0034$, $P = 0.04$ and $P = 0.03$, respectively), whereas the single-gene phenotypes failed to discriminate patient outcomes. The GeneSight CPGx process also discriminated health-care utilization and disability claims for these same three CYP-defined medication subgroups. The *CYP2C19* phenotype was the only single-gene approach to predict health-care outcomes. Multigenic combinatorial testing discriminates and predicts the poorer antidepressant outcomes and greater health-care utilizations by depressed subjects better than do phenotypes derived from single genes. This clinical validity is likely to contribute to the clinical utility reported for combinatorial pharmacogenomic decision support.

The Pharmacogenomics Journal (2015) **15,** 443–451; doi:10.1038/tpj.2014.85; published online 17 February 2015

INTRODUCTION

Psychiatric clinics are increasingly using pharmacogenomic information to tailor medications to each patient's genetic makeup. Nucleotide polymorphisms within multiple genes can alter the metabolism, efficacy and adverse events of psychiatric drugs,[1–3] including antidepressant medications.[4–6] Most psychiatric medications are metabolized through the cytochrome *P*450 (CYP) system. These pharmacokinetic-based gene–drug interactions have important clinical implications on medication prescribing. For a given CYP gene, a patient may possess functionally important polymorphisms that alter the corresponding *P*450 enzyme activity within a phenotypic continuum from poor metabolism (PM) to ultrarapid metabolism (UM). For UMs, typical medication dosing may be inadequate for clinical response; conversely for PMs, typical dosing may result in increased blood levels and side effects. Owing to these known gene–drug interactions, the Food and Drug Administration (FDA) has made a number of gene–drug-specific medication recommendations for psychiatric medications, such as a 20 mg daily maximum dose of citalopram for patients who are *CYP2C19* PMs.[7,8] In addition, pharmacodynamic genes such as those for the serotonin transporter whose variants potentially alter medication response[6] may also have a role with variants in pharmacokinetic genes.

Inadequate translation of pharmacogenomic information has become a major limitation to transforming psychiatric treatment and improving clinical outcomes.[9,10] Even if a clinician is aware of which medications are primarily metabolized by a specific CYP enzyme and knows all of the FDA recommendations relating pharmacokinetic genetics to the use and dosing of medications, the integration of this information may remain convoluted. This is because most psychiatric medications are metabolized through multiple pathways and utilize multiple effector proteins to attain therapeutic responses, which create many possible gene–drug interactions, some of which may compensate for other interactions.

Some medications are metabolized principally by one CYP enzyme (for example, nortriptyline by CYP2D6), which makes the interpretation of *CYP2D6* pharmacogenomic information fairly

[1]Assurex Health, Inc., Mason, OH, USA and [2]Mayo Clinic, Departments of Psychiatry and Psychology, Rochester, MN, USA. Correspondence: Dr CA Altar, Assurex Health, Inc., 6030 S. Mason Montgomery Road, Mason, OH 45040, USA.
E-mail: taltar@assurexhealth.com
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DRUG SENSITIVITY REPORT

Our Genetic Drug Sensitivity Report looks at 12 genes and how particular variants of those genes can impact your ability to respond to the most commonly prescribed medications.

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125 MEDS

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Pharmacogenetics, the science of how genes affect responses to many commonly prescribed medicines, allows physicians to make a quick and more informed treatment decisions.

Drug Guide

Customer Name: John Doe III
Test ID: XXXXXXXXX

These lists of drugs are color-coded to reflect whether a genetic predisposition indicates that there may be issues with regard to drug response or adverse effects.

Normal	Increased Risk	Extreme Risk
A drug in GREEN font indicates that no genetic issues of clinical relevance were found for this drug among the genes tested.	A drug in YELLOW FONT indicates that genetic issues of clinical relevance were found for this drug. Extra caution should be observed when considering this drug for this patient.	A drug in RED FONT Indicates that serious genetic issues of clinical relevance were found for this drug and extreme caution or avoidance of this drug should be observed when considering this drug for this patient.

Antipsychotic

aripiprazole (Abilify)
asenapine (Saphris)
chlorpromazine (Thorazine)
clozapine (Clozaril)
haloperidol (Haldol)
Iloperidine (Fanapt)
lurasidone (Latuda)
olanzapine (Zyprexa)
perphenazine (Trilafon)
promazine (Sparine)
quetiapine (Seroquel)
risperidone (Risperdal)
thioridazine (Mellaril)
ziprasidone (Geodon)

Neuropsychiatric - Precognitive Drug

Neuropsychiatric - Antidepressant

amitriptyline (Elavil)
buproprion
citalopram (Celexa)
clomipramine (Anafranil)
desipramine (Norpramin)
desvenlafaxine (Pristiq)
doxepin (Sinequan, Silenor, Prudoxin, Zonalon)
escitalopram (Lexapro)
fluoxetine (Prozac)
imipramine (Tofranil)
mirtazapine (Remeron)
nefazodone (Serzone)
nortriptyline (Aventyl,Pamelor)
paroxetine (Paxil)

Pain Management

alfentanil (Alfenta)
carisoprodol++ (Soma)
celecoxib (Celebrex)
codeine++
cyclobenzaprine (Flexaril)
fentanyl (Actiq, Duragesic, Sublimaze)
hydrocodone++
ibuprofen (Advil, Motrin)
lidocaine (xylocaine, various brands)
meperidine (Demerol)
naproxen (Aleve)
oxycodone++ (Oxycontin)
ropivacaine (Naropin)
tapentadol (Nucynta)

Benefits of our

Drug Sensitivity Report

- **Combines pharmacology with genetics to determine safe medications tailored to an individual's DNA**
- **A key component to Precision Medicine, aimed at making drugs safer and more effective vs. the traditional "Take this medication and let's see how it works" approach**
- **Provides healthcare providers with likely responses to over 125 medication treatments based on a patient's own unique genetic makeup.**
- **Provides a tool for healthcare providers to select the right drug for the right patient the first time.**
- **By providing patients with a more accurate initial drug treatment selection, the Report may significantly increase the likelihood of patient adherence to treatment and successful patient outcomes.**
- **Simple to understand for both healthcare providers and their patients.**
- **Because your genes don't change, the results shown in the Drug Sensitivity Report are:**

GOOD FOR LIFE®.