Precision Medicine: Cost Effectiveness and Impact on Patient Care including Safety

Using genomics as a primary tool for individualizing patient care is the future of medicine. Genetic screening can offer a new level of confidence in medication efficacy and hereditary disease prevention, and a higher level of patient trust and comfort with treatment decisions. Understanding a patient's genetic variants helps to avoid unnecessary (and sometimes life-threatening) adverse reactions, ineffective medications, and can reduce costs. Hereditary risk screening adds to this value by giving providers and patients information on heightened germline disease risks. The cost savings comes not only from avoiding prescribing ineffective medications, but from decreased re-hospitalization rates, decreased ER visits, shortened hospitalization stays due to the avoidance of adverse reactions, and decreased treatment costs for serious illnesses that are caught early or prevented.

Introduction

About one in six US prescriptions by volume are for drugs with known drug-genomic interactions. Drug-genomic interactions can involve decreased efficacy, dosing changes, or increased risk of adverse reactions.

Current evidence suggests that for numerous drugs genetic factors account for 20% to 95% of patient variability in response.

In selected populations, pre-emptive pharmacogenomic screening can be a cost effective method to improve patient safety and care results. Once a patient's genomics are on file, each new prescription order can be screened automatically in the background (within normal Epic and Cerner workflow). Apart from saving the costs of prescribing ineffective medications, cost reductions occur from decreased re-hospitalization rates, decreased ER visits, shortened hospitalization stays due to the avoidance of adverse reactions**,** and decreased adverse reaction related patient visits. *(See below for a discussion of the evidence).*

The table below illustrates how common a major PGx risk is in patients from different groups.

4 year risk of first time exposure to a serious PGX risk due to a prescription				
	Private Ins. 14-39	Private Ins. 40-64	Medicaid 40-64	Medicare >64
n	22,824,848	26,561,525	1,130,797	5,429,266
≥1 drug exposure	30.4	42.2	55.5	50.6
≥2 drug exposure	9.1	17.8	32.8	27.5
≥3 drug exposure	3.1	7.5	18.5	13.8
≥4 drug exposure	1.1	3.1	9.9	6.4

Ref. PLOS One 2016 11 (10) e0164972, Samwald et al.

Recent studies show a clear trend in the reduction of re-hospitalization rates and ER visits in selected patient populations (such as older polypharmacy patients) who have received pharmacogenomic screening.

Medication adherence may also be improved by pharmacogenomics screening, as patients get greater confidence that they were given the correct medication.

Some examples of common medications impacted by genetic markers include: Patients with genetic variants in CYP2C9 and VKORC1 require lower doses of Warfarin or they risk excessive anticoagulation. Ultra-rapid metabolizers of CYP2C19 see up to a 40% failure rate due to low blood concentration levels of the common proton pump inhibitor, Omeprazole. About 30% of Caucasian patients have an inadequate response to clopidogrel as measured with platelet-function tests, due to loss-of-function alleles in CYP2C19. 5% – 10% of Northern European descent patients have genetic variants in CYP2D6 and receive little to no benefit from Codeine and its common alternatives, often requiring a non-opioid analgesic. 25% of patients carry variants in SLCO1B1, greatly increasing their risk for statin induced myopathy from Simvastatin. Stevens Johnson syndrome, a severe medication side effect, is genetically predictable for common medications like Carbamazepine or Allopurinol. Specific SSRI's can be ineffective for depression depending on the patient's genetics. Knowing about patients' genetic variants in advance of prescribing may help providers choose the right initial medication, with a better outcome and frequently at a less expensive price.

Many drug labels contain warnings about drug-genome interactions. See https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Using evidence-based research from CPIC (Clinical Pharmacogenomic Implementation Consortium), the Dutch Pharmacogenomic Working Group, the FDA and many other credible original sources, ActX currently reports on significant variants in 52 genes which impact more than 500 current medications.

Another large factor in cost effectiveness and patient safety is hereditary risk analysis. 3-4% of patients have an actionable, evidence based, serious risk and another 20% of patients have genomic risk factors, which are less serious. Shifting resources to prevention and early intervention can be cost effective.

Another added benefit for a healthcare system in implementing systematic genomic screening is the ability to attract and retain patients. Private marketing surveys (personal communication from a large healthcare system) have shown that patients are willing to change healthcare providers if they perceive that the new healthcare provider will take better care of them by using genetics to improve medication selection.

The evidence is growing in support of pre-emptive genomic screening for both PGx and hereditary risks, but it has yet to reach mainstream utilization. There are excerpts from a few different studies below that outline some of the key arguments for patient safety and cost-effectiveness. These studies have focused on either pharmacogenomics or genetic risks, but generally not both. ActX genetic screening brings both factors into play, at a low cost. There are substantial opportunities to improve care and patient safety in a cost effective manner.

Selected patient populations can benefit from pre-emptive pharmacogenomic testing

Patient populations can be selected for genetic testing based on immediate benefit such as patients with percutaneous cardiovascular intervention, refractory depression, thromboembolic risk, or extreme polypharmacy. However, if the pharmacogenomics test is the usual multi-gene test, then thereafter they will get pre-emptive pharmacogenomics screening in seconds with every new prescription.

The importance of PGX workflow integration

Traditionally, pharmacogenomics testing results have been delivered as large text files, usually PDF's. While this can work well for single medication-gene results, it is not practical for these results to be used in routine, daily practice across many medications. Physicians simply do not have time to find and consult a PDF before each prescription. The best practice is to integrate real time genomic decision support within medication ordering. This means that during normal prescription ordering (for example within Epic or Cerner), the medication is checked in the background against the patient's genetics, and the physician is alerted in their normal workflow about a drug-genomic interaction, prior to completing the medication order. No change in physician workflow or habits should be required.

Specialties where drug genomic interactions are common

ANESTHESIOLOGY
CARDIOLOGY
ENDOCRINOLOGY
FAMILY MEDICINE
GASTROENTEROLOGY
GYNECOLOGY
HEMATOLOGY
INTERNAL MEDICINE
INFECTIOUS DISEASE
NEUROLOGY
ONCOLOGY
PSYCHIATRY
PULMONARY
RHEUMATOLOGY
TRANSPLANTATION

Example high priced drugs where genomic testing can detect inefficacy in advance

Ineffective outcomes can be expensive. Pre-emptive pharmacogenomic screening can help to avoid spending large sums on ineffective and/or side effect-inducing drugs.

Some examples of high priced[1] drugs where drug genomic interactions affect efficacy:

- Aripiprazole (ABILIFY) 10 mg #30 = $831
- Atomoxetine (STRATTERA) 100 mg #30 = $308
- Eltrombopag (PROMACTA) 75 mg #30 = $9,041 *
- Iloperidone (FANAPT) 6 mg #60 = $820
- Nilotinib (TASIGNA) 150 mg #112 = $9,126 **
- Pimozide (ORAP) 2 mg #60 = $142 ***
- Tetrabenazine (XENAZINE) 12.5 mg #60 = $3,585 ****
- Tolteridone ER 4 mg (generic for Detrol LA) = $213
- Vortioxetine (BRINTELLIX) 20 MG #30 = $260

*eltrombopag is for idiopathic thrombocytopenic purpura, **nilotinib is for CML,***pimozide is for Tourette's syndrome, ****Tetrabenazine is for chorea caused by Huntington Disease [1]-Prices based on web results for patient drug store pricing.

Selected Research Excerpts

There are thousands of individual articles on genetic risk factors and drug genomic interactions in published peer reviewed literature. Below are a few selected articles. **For a more comprehensive survey of the pharmacogenomics literature see www.pharmgkb.org, a NIH sponsored site maintained by Stanford University. For risks and other genetic conditions, see NIH's Gene Reviews, https://www.ncbi.nlm.nih.gov/books/NBK1116/.**

PREVENTATIVE GENOMIC SCREENING FOR YOUNG ADULTS PROVED HIGHLY COST-EFFECTIVE

An Australian study found population screening for all adults 18-25 in a single-payer health care system for selected genetic conditions would substantially improve outcomes and be cost effective.

"Purpose: To consider the impact and cost-effectiveness of offering preventive population genomic screening to all young adults in a single-payer health-care system.
Methods: We modeled screening of 2,688,192 individuals, all adults aged 18–25 years in Australia, for pathogenic variants in *BRCA1/BRCA2/MLH1/MSH2* genes, and carrier screening for cystic fibrosis (CF), spinal muscular atrophy (SMA), and fragile X syndrome (FXS), at 71% testing uptake using per-test costs ranging from AUD$200 to $1200 (~USD$140 to $850). Investment costs included genetic counseling, surveillance, and interventions (reimbursed only) for at-risk individuals/couples. Cost-effectiveness was defined below AUD$50,000/DALY (disability-adjusted life year) prevented, using an incremental cost-effectiveness ratio (ICER), compared with current targeted testing. Outcomes were cancer incidence/mortality, disease cases, and treatment costs reduced.
Results: Population screening would reduce variant-attributable cancers by 28.8%, cancer deaths by 31.2%, and CF/SMA/FXS cases by 24.8%, compared with targeted testing. Assuming AUD$400 per test, investment required would be between 4 and 5 times higher than current expenditure. However, screening would lead to substantial savings in medical costs and DALYs prevented, at a highly cost-effective ICER of AUD$4038/DALY. At AUD$200 per test, screening would approach cost-saving for the health system (ICER = AUD$22/DALY).
Conclusion: Preventive genomic screening in early adulthood would be highly cost-effective in a single-payer health-care system, but ethical issues must be considered."

Bennette, C., Gallego, C. J., Burke, W., et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Genetics in medicine: official journal of the American College of Medical Genetics 2014; 17. DOI: 10.1038/gim.2014.156

ECONOMIC EVALUATION OF POPULATION SCREENING FOR BRCA1/BRCA2 ACROSS MULTIPLE COUNTRIES AND HEALTH SYSTEMS APPEARS HIGHLY COST-EFFECTIVE

A large proportion of BRCA carriers are missed by current clinical and history based screening. This analysis looks at the cost effectiveness of large scale population based genetic screening for BRCA1 and BRCA2.

"Abstract: Clinical criteria/Family history-based BRCA testing misses a large proportion of BRCA carriers who can benefit from screening/prevention. We estimate the cost effectiveness of population-based BRCA testing in general population women across different countries/health systems. A Markov model comparing the lifetime costs and effects of BRCA1/BRCA2 testing all general population women ≥30 years compared with clinical criteria/FH-based testing. Separate analyses are undertaken for the UK/USA/Netherlands (high-income countries/HIC), China/Brazil (upper–middle income countries/UMIC) and India (low–middle income countries/LMIC) using both health system/payer and societal perspectives. BRCA carriers undergo appropriate screening/prevention interventions to reduce breast cancer (BC) and ovarian cancer (OC) risk. Outcomes include OC, BC, and additional heart disease deaths and incremental cost-effectiveness ratio (ICER)/quality-adjusted life year (QALY). Probabilistic/one-way sensitivity analyses evaluate model uncertainty. For the base case, from a societal perspective, we found that population-based BRCA testing is cost-saving in HIC (UK-ICER = $-5639/QALY; USA-ICER = $-4018/QALY; Netherlands-ICER = $-11,433/QALY), and it appears cost-effective in UMIC (China-ICER = $18,066/QALY; Brazil-ICER = $13,579/QALY), but it is not cost-effective in LMIC (India-ICER = $23,031/QALY). From a payer perspective, population-based BRCA testing is highly cost-effective in HIC (UK-ICER = $21,191/QALY, USA-ICER = $16,552/QALY, Netherlands-ICER = $25,215/QALY), and it is cost-effective in UMIC (China-ICER = $23,485/QALY, Brazil-ICER = $20,995/QALY), but it is not cost-effective in LMIC (India-ICER = $32,217/QALY). BRCA testing costs below $172/test (ICER = $19,685/QALY), which makes it cost-effective (from a societal perspective) for LMIC/India. Population-based BRCA testing can prevent an additional 2319 to 2666 BC and 327 to 449 OC cases per million women than the current clinical strategy. Findings suggest that population-based BRCA testing for countries evaluated is extremely cost-effective across HIC/UMIC health systems, is cost-saving for HIC health systems from a societal perspective, and can prevent tens of thousands more BC/OC cases."

Manchanda, R., Sun, L., Patel, S., et al. Economic Evaluation of Population-Based BRCA1/BRCA2 Mutation Testing across Multiple Countries and Health Systems. MDPI: Cancers 2020; 12, 1929. DOI: 10.3390/cancers12071929

GENETIC TESTING FOR INHERITED CARDIOVASCULAR DISEASES & IDENTIFICATION OF UNIDENTIFIED MONOGENIC CARDIOVASCULAR DISORDERS

A look at two papers shows the impact genetic testing could have on diagnosing cardiovascular diseases early, and identifies the "missed opportunity" for providing better care to patients seeing cardiologists.

"**ABSTRACT (1)**
Advances in human genetics are improving the understanding of a variety of inherited cardiovascular diseases, including cardiomyopathies, arrhythmic disorders, vascular disorders, and lipid disorders such as familial hypercholesterolemia. However, not all cardiovascular practitioners are fully aware of the utility and potential pitfalls of incorporating genetic test results into the care of patients and their families."

"ABSTRACT (2)
BACKGROUND: Monogenic diseases are individually rare but collectively common, and are likely underdiagnosed.
OBJECTIVES: The purpose of this study was to estimate the prevalence of monogenic cardiovascular diseases (MCVDs) and potentially missed diagnoses in a cardiovascular cohort.

METHODS: Exomes from 8,574 individuals referred for cardiac catheterization were analyzed. Pathogenic/likely pathogenic (P/LP) variants associated with MCVD (cardiomyopathies, arrhythmias, connective tissue disorders, and familial hypercholesterolemia were identified. Electronic health records (EHRs) were reviewed for individuals harboring P/LP variants who were predicted to develop disease (Gþ). Gþ individuals who did not have a documented relevant diagnosis were classified into groups of whether they may represent missed diagnoses (unknown, unlikely, possible, probable, or definite) based on relevant diagnostic criteria/features for that disease.
RESULTS: In total, 159 P/LP variants were identified; 2,361 individuals harbored at least 1 P/LP variant, of whom 389 Gþ individuals (4.5% of total cohort) were predicted to have at least 1 MCVD. EHR review of 342 Gþ individuals predicted to have 1 MCVD with sufficient EHR data revealed that 52 had been given the relevant clinical diagnosis. The remaining 290 individuals were classified as potentially having an MCVD as follows: 193 unlikely (66.6%), 50 possible (17.2%), 30 probable (10.3%), and 17 definite (5.9%). Grouping possible, probable, definite, and known diagnoses, 149 were considered to have an MCVD. Novel MCVD pathogenic variants were identified in 16 individuals.
CONCLUSIONS: *Overall, 149 individuals (1.7% of cohort) had MCVDs, but only 35% were diagnosed. These patients represents a "missed opportunity," which could be addressed by greater use of genetic testing of patients seen by cardiologists."*

Musunuru, K., Hershberge, R.E., Day, S.M., et al. Genetic Testing for Inherited Cardiovascular Diseases. Circ Genom Precis Med. 2020; 13, e000067. DOI: 10.1161/HCG.0000000000000067

Abdulrahim, et al. Identifying Undetected MCVD. JACC. 2020; 76, 7. https://doi.org/10.1016/j.jacc.2020.06.037

NEXT-GENERATION GENOMIC SEQUENCING LOOKS COST-EFFECTIVE FOR CERTAIN PATIENT POPULATIONS

The American College of Medical Genetics and Genomics (ACMG) developed a decision-analytic policy model to find the QUALYS for 3 patient groups with genetic screening

"Purpose: ACMG recommended that clinical laboratories performing next-generation sequencing analyze and return pathogenic variants for 56 specific genes it considered medically actionable. Our objective was to evaluate the clinical and economic impact of returning these results.
Methods: We developed a decision-analytic policy model to project the quality-adjusted life-years and lifetime costs associated with returning ACMG-recommended incidental findings in three hypothetical cohorts of 10,000 patients.
Results: Returning incidental findings to cardiomyopathy patients, colorectal cancer patients, or healthy individuals would increase costs by $896,000, $2.9 million, respectively, and would increase quality-adjusted life-years by 20, 25.4, and 67 years, respectively, for incremental cost-effectiveness ratios of $44,800, $115,020, and $58,600, respectively. In probabilistic analyses, returning incidental findings cost less than $100,000/quality-adjusted life-year gained in 85, 28, and 91%, respectively, of simulations. Assuming next-generation sequencing costs $500, the incremental cost-effectiveness ratio for primary screening of health individuals was $133,400 (<$100,000/quality-adjusted life-year gained in 10% of simulations). Results were sensitive to the cohort age and assumptions about gene penetrance.
Conclusion: Returning incidental findings is likely cost-effective for certain patient populations. Screening of generally healthy individuals is likely not cost-effective based on current data, unless next-generation sequencing costs less than $500."

Bennette CS, Gallego CJ, Burke W, et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Genet Med 2015; 17(7):587-95. https://www.ncbi.nlm.nih.gov/pubmed/25394171

eMERGE III NETWORK FINDS ACTIONABLE INCIDENTAL FINDINGS IN 3% OF PATIENTS AS A RESULT OF GENOMIC TESTING ACROSS 21,915 INDIVIDUALS FROM EIGHT DIFFERENT INSTITUTIONS

Results showed a 3.02% overall frequency of secondary findings, most associated with cancer susceptibility, cardiovascular diseases, and lipid disorders

"Purpose: Discovering an incidental finding (IF) or secondary finding (SF) is a potential result of genomic testing, but few data exist describing types and frequencies of SFs likely to appear in broader clinical populations.
Methods: The Electronic Medical Records and Genomics Network Phase III (eMERGE III) developed a CLIA-compliant sequencing panel of 109 genes and 1551 variants of clinical relevance or research interest and deployed this panel at ten clinical sites. We evaluated medically actionable SFs across 67 genes and 14 single-nucleotide variants (SNVs) in a diverse cohort of 21,915 participants drawn from a variety of settings (e.g., primary care, biobanks, specialty clinics).
Results: Correcting for testing indication, we found a 3.02% overall frequency of SFs; 2.54% from 59 genes the American College of Medical Genetics and Genomics recommends for SF return, and 0.48% in other genes, primarily HFE and PALB2. SFs associated with cancer susceptibility were most frequent (1.38%), followed by cardiovascular diseases (0.87%), and lipid disorders (0.50%). After removing HFE, the frequency of SFs and proportion of pathogenic versus likely pathogenic SFs did not differ in those self-identifying as White versus others.
Conclusion: Here we present frequencies and types of medically actionable secondary findings to support informed decision making by patients, participants, and practitioners engaged in genomic medicine."
Gordon, A.S., Zouk, H., Venner, E. et al. Frequency of genomic secondary findings among 21,915 eMERGE network participants. Genet Med (2020). https://doi.org/10.1038/s41436-020-0810-9

ELDERLY EXPOSED TO POLYPHARMACY BENEFIT FROM GENETIC SCREENING

The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy

The University of Utah concluded there was a significant reduction in hospital admissions and ED visits after a 4 month trial with elder polypharmacy patients by implementing pharmacogenomics

"Results: There were 205 tested patients PS matched to 820 untested patients. Hospitalization rate was 9.8% in the tested group vs 16.1% in the untested group (RR¼0.61, 95% CI¼0.39–0.95, p¼0.027), ED visit rate was 4.4% in the tested group vs 15.4% in the untested group (RR¼0.29, 95% CI¼0.15–0.55, p¼0.0002) and outpatient visit rate was 71.7% in the tested group vs 36.5% in the untested group (RR¼1.97, 95% CI¼1.74–2.23, p50.0001). The rate of overall HRU was 72.2% in the tested group vs 49.0% in the untested group (RR¼1.47, 95% CI¼1.32–1.64, p50.0001). Potential cost savings were estimated at $218 (mean) in the tested group. The provider majority (95%) considered the test helpful and 46% followed CDST provided recommendations.
Conclusion: Patients CYP DNA tested and treated according to the personalized prescribing system had a significant decrease in hospitalizations and emergency department visits, resulting in potential cost savings. Providers had a high satisfaction rate with the clinical utility of the system and followed recommendations when appropriate."

Brixner D, Biltaji E, Bress A, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. J Med Econ 2016; 19(3):213-28. https://www.ncbi.nlm.nih.gov/pubmed/?term=26478982

CHRONICALLY ILL POLYPHARMACY PATIENTS HAD 40% DROP IN ER VISITS AFTER GENETIC TESTING

Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial.

According to a small study done by Harding University, healthcare providers who combine genetic testing with clinical decision support were able to reduce ER visits by 40% and admissions were halved.

Note: *While we believe that these numbers may be on the high side and actual reductions may be smaller, we do think that ER visits and admissions can be significantly reduced by avoiding ineffective medications and serious drug interactions.*

BACKGROUND:
"In polypharmacy patients under home health management, pharmacogenetic testing coupled with guidance from a clinical decision support tool (CDST) on reducing drug, gene, and cumulative interaction risk may provide valuable insights in prescription drug treatment, reducing re-hospitalization and emergency department (ED) visits. We assessed the clinical impact of pharmacogenetic profiling integrating binary and cumulative drug and gene interaction warnings on home health polypharmacy patients.

METHODS AND FINDINGS:
This prospective, open-label, randomized controlled trial was conducted at one hospital-based home health agency between February 2015 and February 2016. Recruitment came from patient referrals to home health at hospital discharge. Eligible patients were aged 50 years and older and taking or initiating treatment with medications with potential or significant drug-gene-based interactions. Subjects (n = 110) were randomized to pharmacogenetic profiling (n = 57). The study pharmacist reviewed drug-drug, drug-gene, and cumulative drug and/or gene interactions using the YouScript® CDST to provide drug therapy recommendations to clinicians. The control group (n = 53) received treatment as usual including pharmacist guided medication management using a standard drug information resource. The primary outcome measure was the number of re-hospitalizations and ED visits at 30 and 60 days after discharge from the hospital. The mean number of re-hospitalizations per patient in the tested vs. untested group was 0.25 vs. 0.38 at 30 days (relative risk (RR), 0.65; 95% confidence interval (CI), 0.32-1.28; P = 0.21) and 0.33 vs. 0.70 at 60 days following enrollment (RR, 0.48; 95% CI, 0.27-0.82; P = 0.007). The mean number of ED visits per patient in the tested vs. untested group was 0.25 vs. 0.40 at 30 days (RR, 0.62; 95% CI, 0.31-1.21; P = 0.16) and 0.39 vs. 0.66 at 60 days (RR, 0.58; 95% CI, 0.34-0.99; P = 0.045). Differences in composite outcomes at 60 days (exploratory endpoints) were also found. Of the total 124 drug therapy recommendations passed on to clinicians, 96 (77%) were followed. These findings should be verified with additional prospective confirmatory studies involving real-world applications in larger populations to broaden acceptance in routine clinical practice.

CONCLUSIONS:
Pharmacogenetic testing of polypharmacy patients aged 50 and older, supported by an appropriate CDST, considerably reduced re-hospitalizations and ED visits at 60 days following enrollment resulting in potential health resource utilization savings and improved healthcare."

Elliott LS, Henderson JC, Neradilek MB, et al. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS ONE 12(2): e0170905. https://doi.org/10.1371/journal.pone.0170905

FREQUENTLY HOSPITALIZED ADULTS WITH POLYPHARMACY SHOW CONSISTENT PHARMACOGENETIC POLYMORPHISMS

Pharmacogenetic polymorphism as an independent risk factor for frequent hospitalizations in older adults with polypharmacy: a pilot study

This Columbia University study hypothesized that frequently hospitalized older adults with polypharmacy have higher frequency of pharmacogenetic polymorphism as compared to older adults with polypharmacy who are rarely admitted to a hospital. In this study, frequently hospitalized older adults (≥65 years of age) with polypharmacy were matched with rarely hospitalized older adults with polypharmacy by age, gender, race, ethnicity, and chronic disease score. Average age and number of prescription drugs did not differ in cases and controls. At least one major pharmacogenetic polymorphism

defined as presence of at least one allelic combination resulting in poor or rapid metabolizer status was identified in all the cases. None were detected in controls. In 50% of cases, more than one major pharmacogenetic polymorphism was found. The frequency of CYP2C19 rapid metabolizer, CYP3A4/5 poor metabolizer, VKORC1 low sensitivity, and CYP2D6 rapid metabolizer status in cases was 67%, 33%, 33%, and 17%, respectively, which significantly exceeded respective prevalence in general population. The mean number of major gene–drug interactions found in cases was 2.8±2.2, whereas no major drug–gene interactions were identified in controls. The pilot data supported the hypothesis that pharmacogenetic polymorphism may represent an independent risk factor for frequent hospitalizations in older adults with polypharmacy.

Finkelstein J, Friedman C, Hripcsak G, et al. Pharmacogenetic polymorphism as an independent risk factor for frequent hospitalizations in older adults with polypharmacy: a pilot study. Pharmacogenomics and Personalized Medicine 2016; 9: 107-16. https://doi.org/10.2147/PGPM.S117014

CLOPIDOGREL PLUS PGX TESTING IS AS EFFECTIVE AND SIGNIFICANTLY LESS EXPENSIVE THAN PRASUGREL AND TICAGRELOR [FOR PERCUTANEOUS CORONARY INTERVENTION PATIENTS]

Cost effectiveness analysis of pharmacogenomics-guided clopidogrel treatment in patients undergoing percutaneous coronary intervention

Patients undergoing percutaneous coronary interventions are placed on anti-platelet therapy following the intervention. Many cardiologists routinely prescribe prasugrel (average cost $370 per month) or ticagrelor (average cost $250 per month) because of concerns about the efficacy of clopidogrel (average cost $10 per month). Using pharmacogenomics testing for therapy selection is a much less expensive alternative than placing all patients on prasugrel or ticagrelor. Clopidogrel is a pro-drug and 30% of patients have a loss of function (LOF) variant in the gene CP2C19, making the drug inefficacious. The 70% of patients with normal clopidogrel metabolism respond well to clopidogrel therapy as evidenced by the studies below.

If all patients undergoing percutaneous coronary intervention are genetically tested, the cost of testing will be recouped in less than two months, because 70% of patients can be safely placed on inexpensive clopidogrel. This will lead to thousands of dollars in savings per patient. In addition, each genetically tested patient can then benefit from pre-emptive pharmacogenomics testing across hundreds of medications.

Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther 2013; 94(3):317–23. http://www.ncbi.nlm.nih.gov/pubmed/23698643

Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite Investigation of Outcomes With Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC 2018; 11(2):181-91. https://doi.org/10.1016/j.jcin.2017.07.022

Fragoulakis V, Bartsakoulia M, Diaz-Villamarin X, et al. Cost effectiveness analysis of pharmacogenomics-guided clopidogrel treatment in Spanish patients undergoing percutaneous coronary intervention. The Pharmacogenomics J 2019. https://doi.org/10.1038/s41397-019-0069-1

IMPROVEMENTS IN THE TREATMENT OF DEPRESSION

Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists

"Failed medication trials are common in the treatment of major depressive disorder (MDD); however, the use of combinatorial pharmacogenomics to guide medication selection has been previously associated with improved outcomes in the psychiatric care setting. This study evaluated combinatorial pharmacogenomics in patients with MDD (N=1871). All patients had pharmacogenomic testing done and were evaluated at baseline and follow-up (8-12 weeks). Symptom improvement, response, and remission at follow-up were evaluated according to provider type and whether medications were genetically congruent (little/no gene-drug interactions).

There was a 27.9% reduction in depression symptoms at follow-up, as well as response and remission rates of 25.7% and 15.2%, respectively. Outcomes were significantly better among patients treated by primary care providers versus psychiatrists (symptom improvement 31.7% versus 24.9%, $p < 0.01$; response rate 30.1% versus 22.3%, $p < 0.01$; remission rate 19.5% versus 12.0%, $p < 0.01$). There was a 31% relative improvement in response rate among patients taking congruent versus incongruent medications, with slightly higher congruence among primary care providers (87.6%) versus psychiatrists (85.2%). Following combinatorial pharmacogenomic testing, outcomes were significantly improved among patients treated by primary care providers compared to psychiatrists, which supports the use of pharmacogenomics in broader treatment settings."

Tanner JA, Davies PE, Voudouris NC, et al. Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists. J Psychiatr Res 2018; 104: 157-62. https://www.ncbi.nlm.nih.gov/pubmed/30081389

See also:

Vilches S, Tuson M, Vieta E, et al. Effectiveness of a pharmacogenetic tool at improving treatment efficacy in major depressive disorder: a meta-analysis of three clinical studies. Pharmaceutics 2019; 11(9): E453. https://www.ncbi.nlm.nih.gov/pubmed/31480800

Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015; 98(2): 127-34. http://www.ncbi.nlm.nih.gov/pubmed/25974703

WARFARIN: DECREASE IN SEVERE ADVERSE REACTIONS FROM ANTI-COAGULATION, A RIGOROUS PROSPECTIVE RANDOMIZED TRIAL IN PERI-OPERATIVE PATIENTS

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty

While genetics clearly affect warfarin dosing (see the FDA label), given that INR is used to guide dosing, there has been some controversy over the real world benefits of using genetic testing in anti-coagulation therapy. A recent prospective, randomized trial in peri-operative patients has shown a decrease in severe adverse reactions, such as major bleeding, venous thromboembolism and death.

"Overview: Warfarin use accounts for more medication-related emergency department visits among older patients than any other drug. The objective of this study was to determine whether genotype-guided dosing improves the safety of warfarin initiation. The randomized clinical Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis included patients age 65 or older initiating warfarin for elective hip or knee arthroplasty and was conducted at 6 US medical centers.
Interventions: Patients were genotyped for the following polymorphisms: *VKORC1-1639G>A*, *CYP2C9*2, CYP2C9*3*, and *CYP4F2 V433M*. In a 2 × 2 factorial design, patients were randomized to genotype-guided (n = 831) or clinically guided (n = 819) warfarin dosing on days 1 through 11 of therapy and to a target international normalized ratio (INR) of either 1.8 or 2.5. The recommended doses of warfarin were open label, but the patients and clinicians were blinded to study group assignment.

Main Outcomes and Measures: The primary end point was the composite of major bleeding, INR of 4 or greater, venous thromboembolism, or death. Patients underwent a screening lower-extremity duplex ultrasound approximately 1 month after arthroplasty.
Results: Among 1650 randomized patients, 1597 (96.8%) received at least 1 dose of warfarin therapy and completed the trial (n = 808 in genotype-guided group vs n = 789 in clinically guided group). A total of 87 patients (10.8%) in the genotype-guided group vs 116 patients (14.7%) in the clinically guided warfarin dosing group met at least 1 of the end points (absolute difference, 3.9% [95% CI, 0.7%-7.2%], *P* = .02; relative rate [RR], 0.73 [95% CI, 0.56-0.95]). The numbers of individual events in the genotype-guided group vs the clinically guided group were 2 vs 8 for major bleeding (RR, 0.24; 95% CI, 0.05-1.15), 56 vs 77 for INR of 4 or greater (RR, 0.71; 95% CI, 0.51-0.99), 33 vs 38 for venous thromboembolism (RR, 0.85; 95% CI, 0.54-1.34), and there were no deaths.
Conclusions and Relevance: Among patients undergoing elective hip or knee arthroplasty and treated with perioperative warfarin, genotype-guided warfarin dosing, compared with clinically guided dosing, reduced the combined risk of major bleeding, INR of 4 or greater, venous thromboembolism, or death. Further research is needed to determine the cost-effectiveness of personalized warfarin dosing."

Gage BF, Bass AR, Lin H, et al. Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. JAMA 2017; 318(12): 1115-24. doi:10.1001/jama.2017.11469

INCREASE IN MEDICATION ADHERENCE

Patient perspectives following pharmacogenomics results disclosure in an integrated health system

Based on a study done at NorthShore University Health System, Mark Dunnenberger, Director of Pharmacogenomics, stated the following:

"Our recent study highlighted that more than 50 percent of patients were more confident in their medications after pharmacogenomics testing. Patients who are more confident in their treatments are more likely to have better outcomes. Pharmacogenomics offers a new data point for both patients and providers to use to better understand a patient's experience with medications, and this is incredibly powerful."

Quoted in https://www.beckershospitalreview.com/hospital-management-administration/patients-more-confident-in-their-medications-after-pharmacogenomics-testing-says-northshore-s-dr-mark-dunnenberger.html

Lemke AA, Hulick PJ, Wake DT, et al. Patient perspectives following pharmacogenomics results disclosure in an integrated health system. Epub 2018 19(4): 321-31. https://www.ncbi.nlm.nih.gov/pubmed/29469671

AN EXAMINATION AT THE GENOMIC EFFECTS ON THE METABOLIZATION OF CODEINE

Clinical pharmacogenetics implementation consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype

CYP2D6 is involved in the metabolism in up to 25% of all prescriptions. For example, if a patient is a CYP2D6 poor metabolizer they receive little to no benefit from **codeine** and many common alternatives. Review the table below for metabolizer rates in different ethnic groups.

INCIDENCE OF CYTOCHROME P450 METABOLIZER PHENOTYPES AMONG ETHNIC GROUPS				
ENZYME	**METABOLIZER PHENOTYPE**	**POPULATION FREQUENCY (%)**		
		ASIANS	**BLACKS**	**WHITES**
CYP2C9	Poor	0.4	0	1
	Intermediate	3.5	13	33
	Ultrarapid	-	-	-
CYP2C19	Poor	18 to 23	1.2 to 5.3	2.0 to 5.0
	Intermediate	30	29	18
	Ultrarapid	-	-	-
CYP2D6	Poor	1.0 to 4.8	1.9 to 7.3	7.0 to 10
	Intermediate	51	30	1.0 to 2.0
	Ultrarapid	0.9 to 21	4.9	1.0 to 5.0
Note: Poor metabolizers have markedly reduced or asent enzyme activity; intermediate metabolizers have reduce enzyme activity; and ultrarapid metabolizers have high enzyme activity.				
CYP = cytochrome P450				

Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6* (*CYP2D6*) Genotype. Clin Pharmacol Ther 2012, 91(2): 321-6. https://www.ncbi.nlm.nih.gov/pubmed/22205192

SUMMARY

Pre-emptive genetic testing accompanied by EHR integrated genomic decision support can improve patient outcomes and safety in a cost effective manner for selected patient populations. While there is still much research to be done, the existing evidence for both individual medications and many conditions is substantial. Understanding a patient's genetic variants can help avoid unnecessary adverse reactions, avoid ineffective medications, alert of disease risk, and reduce costs.