High-Evidence, Actionable Phenotype Gene Distribution in a Multispecialty, Tertiary Care Clinic: Potentially Actionable Genes and a Referring Department Profile

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Abstract

Background *There has been a trend in recent years toward individualized medicine. Pharmacogenomics (PGx) is the use of patient-specific genetic variations to guide medication selection and treatment.*

Objective: *The primary objective was to characterize the population of referring department patients and identify the number of high-evidence, actionable phenotype (HEAP) genes in this referred population to help guide marketing efforts to the most applicable patient populations and departments.*

Practice description: *Located in a destination, tertiary care clinic. Providers refer patients to a Pharmacogenomics (PGx) specialist for a comprehensive medication review using their pharmacogenomic results.*

Practice Innovation: *The practice is innovative because it has been using PGx in the pharmacy and medical practices since 2016 and has been routinely developing and incorporating PGx best practice alerts (BPAs) into the electronic medical record (EMR) since 2020.*

Evaluation Methods *Genetic results were analyzed from a 27-gene PGx panel test which tests for both pharmacokinetic and pharmacodynamic genes. High-Evidence Actionable Phenotypes (HEAP) are defined as phenotypes with guideline support that may suggest an action by healthcare provider. Low-Evidence Nonactionable Phenotypes (LENP) are defined as phenotypes that do not recommend action.*

Results *There were 1,236 atypical phenotypes identified in the 154 patients referred. Of the atypical genes, 39.97% were HEAP and 60.03% were LENP. Of the HEAP's identified, the majority came from CYP2D6, VKORC1, and UGT1A1. At least 1 HEAP was found in 98.7% of patients (n=152).*

Conclusion *There are a variety of High Evidence Actionable Phenotypes (HEAPs) with a high likelihood of at least one HEAP gene in every patient. These phenotypes can result in serious safety concerns when combined with a medication impacted by one of these HEAP genes. Thus, referral to a pharmacogenomics consultation service may lead to an overall decrease in morbidity and mortality with potential cost avoidance.*

Keywords: pharmacogenomics, PGx

What was already known

- Pharmacogenomics (PGx) may assist in current and future medication selection as well as identify past sensitivities and treatment failures
- PGx can be used clinically at the bedside
- PGx can decrease trial and error in medication selection, decrease health care costs and improve patient outcomes

What this quality project adds

- Increases the efficiency of identifying departments who refer the most patients and those patient populations with the most PGx actionable genes
- More evidence PGx can be used very broadly in many medical specialties since many patients in many specialties will have at least one HEAP gene
- Decrease institutional trial and error prescribing, directly decrease medication management and medical costs, improve patient outcomes and patient satisfaction

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Objective

The primary objective of this quality project was to characterize the population of referring department patients and identify the number of high-evidence, actionable phenotype (HEAP) genes in this referred population. Results will be used to target departments and patient populations who may benefit from Pharmacogenomic (PGx) testing and consultation.

Background

Pharmacogenomics (PGx) is the use of patient-specific genetic variations to guide medication selection and treatment. While individuals differ in genetic code, some share variations. The most common of these variations are known as single-nucleotide polymorphisms often referred to as "SNPs." A more relevant example, to PGx, are the splicing variants 12662A>G (rs12769205) and 19154G>A (rs4244285) that lead to the CYP2C19*2 allele. Individuals with the CYP2C19*2 allele may experience overall loss of function, as the *2 allele is associated with no CYP2C19 function.[1] Individuals receive one star allele (e.g., CYP2C19 *2) from each parent which makes up their genotype (e.g., CYP2C19 *2/*2). These genotypes can be converted to phenotypes using a translation table.[2] A patient with the genotype CYP2C19 *2/*2, for example, would be considered a poor metabolizer since they would have little-to-

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no CYP2C19 enzyme function. Genotype to phenotype translations vary from gene-to-gene.[2]

Little-to-no CYP2C19 function is associated with increased blood concentrations of selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), and a decrease in the active metabolite of the P2Y12 inhibitor clopidogrel. Because of these increases or decreases in therapeutic drug exposure, lack of efficacy or increased adverse drug reactions from these medications may occur.[1]

By increasing PGx testing and application at the bedside, medication related problems (MRPs) may be further minimized through predictive avoidance, current regimens may be adjusted for better efficacy, and past medication intolerances or inefficacy may be more specifically identified.

Objective

With limited resources, the primary objective of this quality project was to characterize the population of referring department patients and identify the number of high-evidence, actionable phenotype (HEAP) genes in this referred population. Results will be used to target departments and patient populations who may benefit most from Pharmacogenomic (PGx) testing and consultation. A secondary objective was to determine if current marketing efforts with existing departments was justified.

Practice Description

This clinical pharmacist practice is located in a destination, tertiary care facility located in Jacksonville, Florida. Medical specialties and subspecialties are many, as is expected in this type of medical facility. The practice is totally dependent on physician and other medical provider referrals for its patients so marketing to these referring departments is critical to the success of the practice.

The practice provides pharmacotherapy (PTx), primary care (PC), pharmacogenomics (PGx) and solid organ transplant as service lines. Patient and provider demand is high for transplant services and pharmacist involvement in all transplant departments is mandated for program certification, so garnering provider referrals is not difficult for transplant services. However, there is no such mandate for the other 20 to 25 departments referring patients to the PTx and PGx services. One must actively market these services to these departments to show the value of pharmacists in their patient's medication management. This is done through relationship marketing, where pharmacists actively provide interdepartmental in-services and seek collaborative research, education and quality projects with providers. The PC service is imbedded in the Family Medicine (FM) and Community Internal Medicine (CIM) practices so there is less of a need for marketing here since the pharmacist occupies a prominent location at the nursing station where many physicians dictate their patient documentation. In this location, physicians are constantly interacting with the pharmacist, so relationship marketing is already imbedded into the FAM and CIM practices by default.

Each pharmacist service line is structured as a physician office practice. Each service has its own patient schedule with designated patient slots. The PTx service functions as a pharmacology trouble shoot service. Any potential MRP, including supplements and cannabis, can be referred from any other department except PC. The PC pharmacist serves as the PTx pharmacist for FAM and CIM but is not currently trained in PGx. All departments can refer PGx patients since the PC pharmacist does not see PGx patients. The PGx pharmacist performs PTx services but adds the complexity of PGx assessment to the patient consult. Both PTx and PGx pharmacists are required to be trained in PGx so they can cross cover for one another. The PTx and PGx services are consult services and do not normally see patients longitudinally or long-term as the PC service does. The transplant services see patients longitudinally during the transplantation process and in the acute phase, post-transplant clinic only.

Practice Innovation

The practice is already innovative because it has been using PGx in the pharmacy and medical practices since 2016 and has been routinely developing and incorporating best practice alerts (BPAs) into the electronic medical record (EMR) since 2020. This project was to further apply PGx to a broader population of patients in departments who may need PGx services the most. BPAs are continuing to be developed and incorporated into the EMR and PGx is being applied to cannabis and supplement products in addition to prescription and over the counter medications. By applying this project to the practice, marketing efforts may be more efficient. This model of practice does not need to be an internal referral only model of practice. It may be incorporated anywhere. Depending on state laws, to incorporate PGx into a pharmacy ambulatory practice of any kind, all one needs is a trained PGx pharmacist and licensed health care provider who can order PGx testing in that state. The health care provider could be a pharmacist. This practice applies PGx principles to all medication management patients. If a MRP is identified on any non-PGx service that may need further PGx testing, patients are referred to the PGx service for a consult after a DNA buccal swab sample is ordered and processed. It is the view of this practice and its institution PGx will become a routine tool everywhere in the management of patient medication regimens, be used predictively to avoid MRPs before a medication is prescribed and provide evidence of why a medication was ineffective or may not have been tolerated by a patient in the past.

Evaluation Methods

This project analyzed results from a 27 gene PGx panel test (all genes tested are shown in Supplemental Table 1) which tests for both pharmacokinetic and pharmacodynamic genes to

determine where internal marketing efforts could be concentrated for best efficiency and patient efficacy for a pharmacy department with few resources. The phenotypes included are listed in Supplemental Table 2.

Because Mayo Clinic is a tertiary care, destination medical facility, a substantial number of patients do not live locally. Therefore, some medical departments are built around being a gateway department to the specialists and subspecialists one may only find in such a destination facility. Executive Medicine is such a gateway department that referred the most patients during the time selected for this project. The Executive Health Program (EXE) is a comprehensive, holistic preventive health evaluation provided by all three Mayo Clinic major sites. The program uses a thorough set of evidence-based assessments to develop a complete understanding of a patient's health status. After completing an in-depth meeting with the EXE physician, patients may be referred to pharmacy for medication therapy management. Services offered by Mayo Clinic pharmacy to EXE patients include pharmacotherapy review and pharmacogenomics consultation with PGx trained pharmacists.

A pharmacogenomics consultation begins with a comprehensive review of the patient's current medications, diet, allergies, family history, supplements, and social history. Next, PGx results are reported to the patient gene-by-gene, including application to current medications, past trials, and potential future use of medications impacted by their pharmacogenetic test results. Other referring department patients follow the same procedure as EXE.

The greatest potential benefit of genotyping to guide warfarin dosing would be early in therapy. CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the initial dose or loading dose of warfarin to help reach INR goal quickly and safely.[3-4] Patients with decreased CYP2C9 function (*2, *3, *4, *5, *6, *8 and *11) and increased VKORC1 expression (c.-1639G>A, rs9923231) may have an increased sensitivity to warfarin and thus may be at risk of over anti-coagulation when standard dosing is used. This risk is increased even more if the patient is taking other medications or supplements with antiplatelet or anticoagulant effect.[5] When pharmacogenetic results are used, there is a shorter time to stable dose, improved percent time in therapeutic range, and reduced number of episodes with an INR > 4 compared to standard dosing.[6] Major or fatal bleeding is a risk with warfarin and this risk may be exacerbated by high intensity anticoagulation.[4]

Clopidogrel is a commonly prescribed antiplatelet agent used to reduce the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndromes (ACS) and/or following percutaneous coronary intervention (PCI). Other indications include recent MI, recent stroke, or established peripheral arterial disease.[7] Patients with decreased CY2C19 function (*2, *3, *4, *10) are at risk for lack of efficacy as clopidogrel, a prodrug, is activated by CYP2C19.

Tamoxifen, a selective estrogen receptor modulator used for breast cancer treatment, is activated by CYP2D6 into its more active metabolites. Patients with decreased CYP2D6 function (poor or intermediate metabolizers) may be at risk for lack of efficacy with this medication. These patients with a higher risk of breast cancer recurrence and worse event free survival may be identified and alternative doses and agents administered.[8]

Patients with increased CYP2D6 function (ultrarapid metabolizers) may have higher concentrations of the active metabolite of codeine, morphine, and may be at risk for toxicity (e.g., respiratory depression). CYP2D6 poor or intermediate metabolizers are at risk of decreased analgesia due to lack of morphine concentrations.[9]

Patients who are HLA-A (*31:01, *31:03) or HLA-B (*15:02, *57:01, *58:01) positive are at risk for hypersensitivity, severe hepatotoxicity, or a life-threating severe cutaneous adverse reactions (SCAR). These reactions can occur when treated with a drug administered in a patient who is positive for one of these alleles. The associated gene-drug pairs are HLA-A:*31:01 with carbamazepine, HLA-B*15:02 with carbamazepine, oxcarbazepine, lamotrigine, and phenytoin; HLA-B*57:01 with abacavir, and HLA-B*58:01 with allopurinol. Patients treated with chemotherapeutics metabolized by TPMT or NUDT15 (e.g., azathioprine, mercaptopurine), DPYD (e.g., capecitabine, fluorouracil), or UGT1A1 (e.g., atazanavir) who have decreased function of one of these enzymes may be at risk of toxicity.[1]

Individuals with decreased to poor SLCO1B1 function may have increased blood levels of statins (e.g., atorvastatin, simvastatin) compared to those with normal activity and are at increased risk for Statin-Associated Myopathies (SAMs) or rhabdomyolysis.[10]

Coagulation Factor II (F2) and Coagulation Factor V (F5) Leiden, also known as thrombin and proaccelerin respectively, have been associated with an increased risk of clotting.[1] This risk is further increased by the use of an estrogen-containing combined oral contraceptives (COC) or hormonal replacement therapy (HRT).[11] Other factors that may increase risk of clotting include smoking and physical inactivity. Patients with known F5 positive status can benefit from education on these risks so they can instill proper lifestyle modifications to decrease the risk of clotting. Such modifications include smoking cessation, weighing risk vs benefits of using COC or HRT, as well as taking proper surgery and post-surgery precautions (e.g., DVT prophylaxis).

The above-mentioned phenotypes were chosen for this project because they may significantly impact therapy, either through toxicities needing dosing adjustments, possible fatal reactions

or ineffectiveness that may result in serious adverse drug reactions (ADRs) or fatality via clotting or other mechanism. The associated safety concerns with each phenotype can be found in Table 1**.**

High-Evidence Actionable Phenotypes (HEAP) are defined as phenotypes with guideline support that recommend an action (e.g., dose adjustment, drug avoidance) performed by a healthcare provider.[12] Low-Evidence Nonactionable Phenotypes (LENP) are defined as phenotypes that do not require action by the healthcare provider due to lack of guideline support. Table 2 shows the High-Evidence Actionable Phenotype (HEAP) genes that were included. Individual LENP's were excluded from data collection. These HEAP genes were included due to the safety concerns that arise when patients are treated with medications or supplements that are affected by these genes. While there are actionable guidelines available for rapid and ultrarapid CYP2C19 metabolizers, these phenotypes were excluded (classified as LENP) due to their lack of safety concern. Additionally, although there are currently no CPIC guidelines available for Factor II (F2) and Factor V (F5) Leiden, there is one planned.[12] While both F5 and combined oral contraceptives (COCs) have been found to independently increase the risk for thrombosis, with a cumulative effect on thrombosis risk, the evidence for F2 and COCs is not as established.[1] Regardless, both positive F2 and positive F5 phenotypes were included as a HEAP.

Results

The results of this study showed that among the 154 patients referred to the pharmacogenomics consultation service at the Mayo Clinic in Jacksonville, FL from December 2019 to December 2021, 1,236 atypical phenotypes were identified. The results are reported in Table 3. Of the atypical phenotypes identified, 40% were high-evidence actionable phenotypes (HEAP) and 60% were low-evidence nonactionable phenotypes (LENP). The majority of HEAPs identified were in the genes CYP2D6, VKORC1, and UGT1A1. HEAPs were found in 98.7% of patients. The breakdown of actionable phenotypes by patient is shown in Supplemental Table 3.

The referral departments with the highest number of patients were Executive Medicine and Hematology/Oncology, while the departments with the lowest number of patients were Allergy and Immunology, Pulmonology, Rheumatology, Sleep Medicine, Surgery, and Women's Health. The distribution of LENP and HEAP by department is shown in Figure 2. Among the atypical phenotypes identified, several had clinical implications for specific departments. For example, in Cardiology, CYP2C9, CYP2C19, F2, F5, SLCO1B1, and VKORC1 phenotypes had the potential to impact the effectiveness and toxicity of medications used to treat or prevent cardiovascular conditions. In Neurology, HLA-A and HLA-B phenotypes had associations with antiepileptic drugs and the risk of hypersensitivity reactions or severe cutaneous adverse reactions. In Hematology/Oncology, CYP2D6, DPYD, NUDT15, TPMT, and UGT1A1 phenotypes had clinical implications for the use of cancer drugs. Overall, these results highlight the importance of pharmacogenomic testing in informing personalized medicine and improving patient outcomes.

Practice Implications

A baseline belief in this practice and institution from previous experience is PGx testing and assessment improves medication management and patient outcomes.[13-17] Upon that base is desire to improve services by targeting them in the most efficient and effective way so limited resources, particularly labor, can be conserved to produce the most desired outcomes. An unexpected consequence of this project was that all of our referring departments had a substantial percentage of HEAP genes in their patient populations. This could be explained by an already tertiary, complex patient population who are already heavy users of prescription medications but also demonstrates broad applicability of PGx testing and services to many medical specialties.

Outside of this practice, implications are that the more medications a patient takes or is projected to take, the more relevance for PGx testing and services. However, since a high percentage of HEAP genes were found equally in referred patient populations with a low sample size, one could infer PGx testing and services may be useful and applicable more broadly than to select departments. PGx testing and services can be applied outside this institution to any medical or pharmacy practice that utilizes medications where PGx applies. This would be most practices since most practices in these fields use medications. In addition, our internal medicine department with many of the most complex patients and our executive medicine department with many of our least complex patients had a comparable percentage of HEAP genes. General implication from the above results is PGx testing and services likely would benefit most medical practices, regardless of population size, number of medications used, medical specialty, geographic location, number of disease states or patient disease acuity. The findings of this project add to existing literature by demonstrating broad application of PGx across a diverse patient population in multiple medical specialties.

Conclusion

There are a variety of High Evidence Actionable Phenotypes (HEAPs) with a high likelihood of at least one HEAP in at least a third of patients across all referring departments.. These phenotypes can result in safety concerns when combined with a medication impacted by one of these HEAPs. Thus, referral to a pharmacogenomics consultation service may lead to an overall decrease in morbidity and mortality with potential cost avoidance. Further investigation should be done to see if these potential benefits are realized in patients at other facilities. This project demonstrates a potential need for more PGx testing and

referral from most, if not all referring departments to the PGx service since the proportion (range 35-50%) of HEAP seems consistent in every department, regardless of number of patients referred. The data used from this project will be used as education to individual providers, departments, and patients to help enable the ability to expand services to existing and new medical departments.

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- Sheena Crosby, PharmD, BCGP
  Review and editing, project administration, resources
- Michael J. Schuh, PharmD, MBA, FAPhA, FFSHP
  Conceptualization, methodology, formal analysis, investigation, writing original draft

The opinions expressed in this paper are those of the author(s).

References

1. Whirl-Carrillo M, Huddart R, Gong L, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. *Clin Pharmacol Ther.* 09 2021;110(3):563-572.
2. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci.* 01 2020;13(1):116-124.
3. Johnson JA CK, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther* . 2017, doi:10.1002/cpt.668 -.
4. Bristol-Myers Squibb Company. Coumadin (warfarin) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Revised October 2011. Accessed September 20, 2022.
5. toddard GJ, Archer M, Shane-McWhorter L, Bray BE, Redd DF, Proulx J, Zeng-Treitler Q. Ginkgo and Warfarin Interaction in a Large Veterans Administration Population. AMIA Annu Symp Proc. 2015 Nov 5;2015:1174-83. PMID: 26958257; PMCID: PMC4765589.
6. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* Dec 12 2013;369(24):2294-2303.
7. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther.* Jan 16 2022.
8. Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clin Pharmacol Ther.* 05 2018;103(5):770-777.
9. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. *Clin Pharmacol Ther.* 10 2021;110(4):888-896.
10. Cooper-DeHoff RM, Niemi M, Ramsey LB, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clin Pharmacol Ther.* 05 2022;111(5):1007-1021.
11. Apil. Minastrin (TM) 24 Fe Oral Chewable Tablets (norethindrone acetate ethinyl estradiol ferrous fumarate oral chewable tablets) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204426s000lbl.pdf. Revised April 2013. Accessed September 20, 2022.
12. Prioritization of CPIC guidelines. CPIC. https://cpicpgx.org/prioritization-of-cpic-guidelines/. Accessed September 13, 2022.
13. Wang L, Scherer SE, Schuh M, Crosby S, Weinshilboum R, et al. Implementation of preemptive DNA sequence–based pharmacogenomics testing across a large academic medical center: The Mayo-Baylor RIGHT 10K Study. Genet Med. 2022 Mar. https://doi.org/10.1016/j.gim.2022.01.022.
14. Schuh MJ, Kaur JS. Pharmacogenomic (PGx) testing as a standard of clinical care. Biomed J Sci & Tech Res. 2020 Feb; 25(3): 19233-34.
15. Schuh MJ, Crosby S. Description of an established, fee-for-service, office-based, pharmacist-managed pharmacogenomics practice. Sr Care Pharm 2019 Dec;34(10):660-668.
16. Speicher L, Crosby S, Schuh M. Pharmacogenomics Testing Confirmation of Carbamazepine Induced DRESS Reaction of an HLA-A*31:01 Positive, Polypharmacy Patient. Inov Pharm. 2021 Dec;12(4). Art 20. https://doi.org/10.24926/iip.v12i4.4341.
17. Wieruszewski PM, Schuh MJ. Incorporation of herbal supplements into a pharmacogenomic medication therapy management practice. Consult Pharm 2017 Feb; 32(2): 99-104.

Table 1: Rational for Inclusion: Gene-Phenotype-Drug Safety Concerns

Gene	Phenotype(s)	Drug(s)	Safety Concern
CYP2C9	PM, IM	Warfarin	Increased risk of bleeding due to over anticoagulation with warfarin
CYP2C19	PM, PM-IM, IM, IM-NM	Clopidogrel	Increased risk of cardiovascular event due to reduced active antiplatelet metabolite
CYP2D6	PM, PM-IM, IM, IM-NM	Tamoxifen	Increased risk of breast cancer treatment failure
CYP2D6	UM	Codeine	Increased risk of respiratory depression due to increased concentrations of morphine
DPYD	Atypical	Capecitabine, 5-Fluorouracil	Increased risk of severe or fatal drug toxicity
F2	Positive	Combined Oral Contraceptives	Increased risk of clotting
F5	Positive	Combined Oral Contraceptives	Increased risk of clotting
HLA-A	*31:01 or *31:03 Positive	Carbamazepine	Increased risk of SCAR
HLA-B	*15:02, *57:01, or *58:01 Positive	Several Medications*	Increased risk of SCAR
TPMT	PM, IM	Azathioprine, Mercaptopurine	Increased risk of thiopurine-related leukopenia, neutropenia, and myelosuppression.
UGT1A1	*28 Carrier	Irinotecan	Increased risk of neutropenia
NUDT15	Reduced Function	Azathioprine, Mercaptopurine	Increased risk of thiopurine-related leukopenia, neutropenia, and myelosuppression.
SLCO1B1	Decreased or Poor Function	Statins	Increased risk of statin associated myopathy
VKORC1	Decreased or Poor Activity	Warfarin	Increased risk of bleeding due to over anticoagulation with warfarin

*Medications include: abacavir, allopurinol, carbamazepine, lamotrigine, oxcarbazepine, phenytoin

Table 2: Atypical Genes

Gene	Number (Genes)	% Total (Genes)	Number (Patients)	% Total (Patients)
High Evidence Actionable Genes	**494**	**40.0%**	**152**	**98.7%**
CYP2C9	52	4.2%	52	33.8%
CYP2C19	56	4.5%	56	36.4%
CYP2D6	101	8.2%	101	65.6%
DPYD	8	0.6%	8	5.2%
F2	5	0.4%	5	3.2%
F5	9	0.7%	9	5.8%
HLA-A	6	0.5%	6	3.9%
HLA-B	20	1.6%	20	13.0%
NUDT15	0	0.0%	0	9.7%
SLCO1B1	48	3.9%	48	49.4%
TPMT	15	1.2%	15	0.0%
UGT1A1	76	6.1%	76	31.2%
VKORC1	98	7.9%	98	63.6%
Low Evidence Nonactionable Genes	**742**	**60.0%**	**154**	**100%**
Total	**1236**	**100%**	**154**	**100%**

Table 3: Number of Patients, Atypical Phenotypes, LENP and HEAP, and Most Common HEAP by Department

Department	Patients, # (%)	Atypical Phenotypes, # (%)	LENP, # (%)	HEAP, # (%)
Allergy and Immunology	1 (0.6%)	5 (0.4%)	3 (0.4%)	2 (0.4%)
Anesthesiology	3 (1.9%)	20 (1.6%)	13 (1.8%)	7 (1.4%)
Cardiology	3 (1.9%)	26 (2.1%)	17 (2.3%)	9 (1.8%)
Endocrinology	4 (2.6%)	27 (2.2%)	17 (2.3%)	10 (2.0%)
Executive	34 (22.1%)	273 (22.1%)	161 (21.7%)	112 (22.7%)
Family Medicine	6 (3.9%)	47 (3.8%)	27 (3.6%)	20 (4.0%)
Gastroenterology	22 (14.3%)	183 (14.8%)	106 (14.3%)	77 (15.6%)
Genetics	8 (5.2%)	72 (5.8%)	46 (6.2%)	26 (5.3%)
Hematology and Oncology	9 (5.8%)	72 (5.8%)	45 (6.1%)	27 (5.5%)
Internal Medicine	30 (19.5%)	234 (18.9%)	144 (19.4%)	90 (18.2%)
Medallion	13 (8.4%)	108 (8.7%)	64 (8.6%)	44 (8.9%)
Neurology	12 (7.8%)	97 (7.8%)	60 (8.1%)	37 (7.5%)
Preventive Medicine	2 (1.3%)	10 (0.8%)	6 (0.8%)	4 (0.8%)
Psychiatry	2 (1.3%)	21 (1.7%)	11 (1.5%)	10 (2.0%)
Pulmonary	1 (0.6%)	12 (1.0%)	6 (0.8%)	6 (1.2%)
Rheumatology	1 (0.6%)	10 (0.8%)	6 (0.8%)	4 (0.8%)
Sleep Medicine	1 (0.6%)	5 (0.4%)	3 (0.4%)	2 (0.4%)
Surgery	1 (0.6%)	8 (0.6%)	4 (0.5%)	4 (0.8%)
Women's Health	1 (0.6%)	6 (0.5%)	3 (0.4%)	3 (0.6%)
Totals	**154**	**1236**	**742**	**494**

*Tie LENP = Low-Evidence Nonactionable Phenotypes
HEAP = High-Evidence Actionable Phenotypes

Figure 1: Percent of High Evidence Actionable Phenotypes by Gene

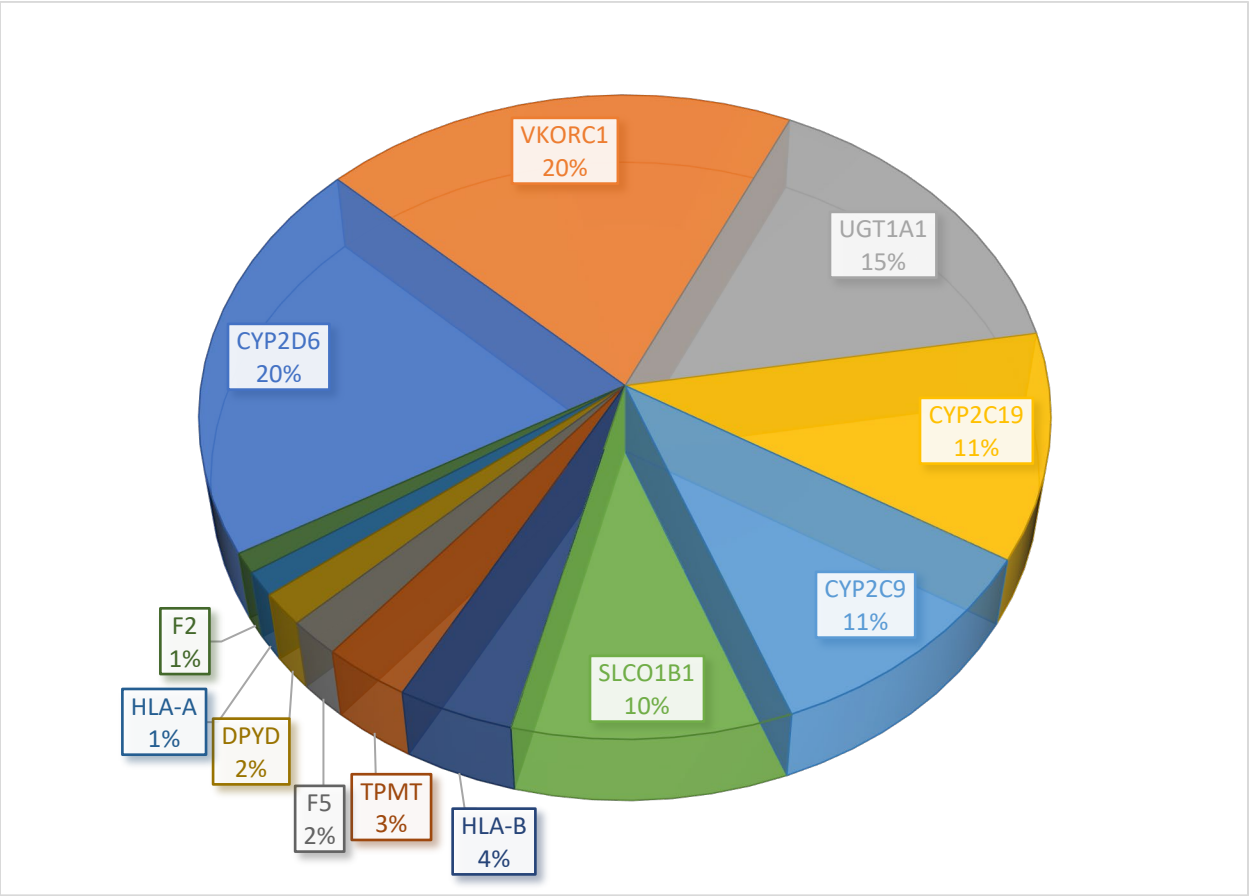
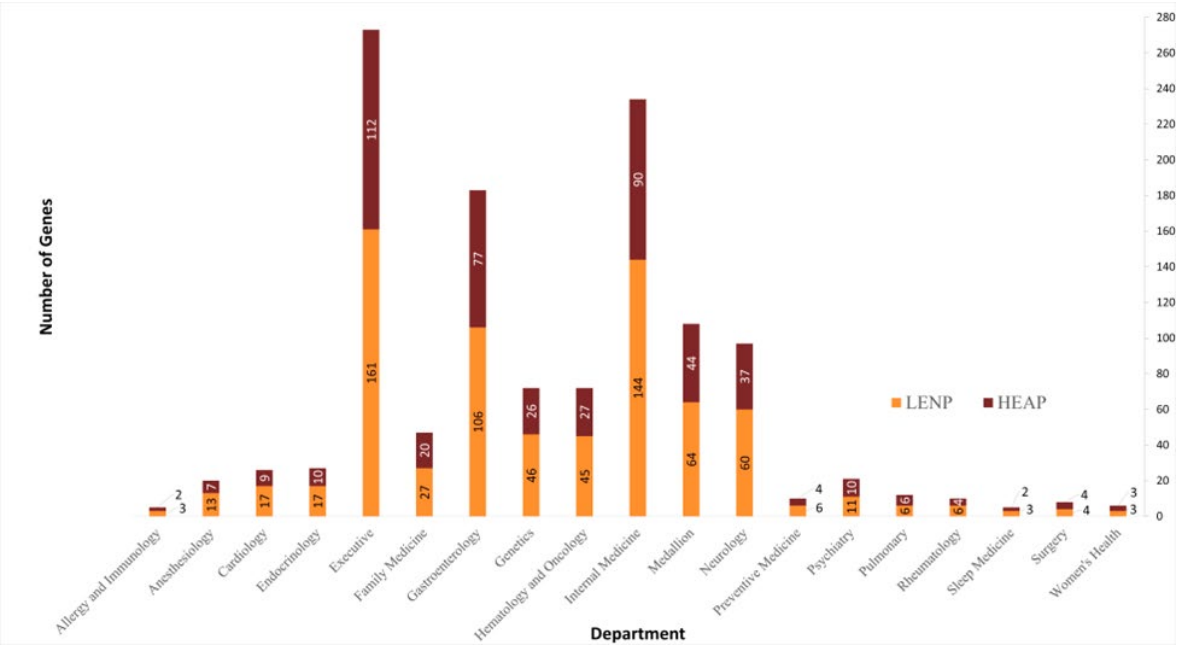


Figure 2: Low-Evidence Nonactionable Phenotypes and High-Evidence Actionable Phenotypes by Department



Supplement Table 1: Genes Tested by Lab

COMT, CYP1A2, CYP2B6, CYP2C Cluster, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, DPYD, DRD2, F2, F5, GRIK4, HLA-A, HLA-B, HTR2A, HTR2C, IFNL4, NUDT15, NUDT15, OPRM1, SLC6A4, SLCO1B1, TPMT, UGT1A1, and VKORC1

Supplement Table 2: Exclusion and Inclusion Criteria

Gene	LENP / Excluded	HEAP / Included
COMT	All Phenotypes	-
CYP1A2	All Phenotypes	-
CYP2B6	All Phenotypes	-
CYP2C Cluster	All Phenotypes	-
CYP2C9	NM, RM, UM	**PM, PM-IM, IM, IM-NM**
CYP2C19	NM, RM, UM	**PM, PM-IM, IM**
CYP2D6†	NM	**PM, PM-IM, IM, IM-NM RM, UM**
CYP3A4	All Phenotypes	-
CYP3A5	All Phenotypes	-
CYP4F2	All Phenotypes	-
DPYD	Normal Phenotype	**Atypical Phenotype**
DRD2	All Phenotypes	-
F2	Negative	**Positive**
F5	Negative	**Positive**
GRIK4	All Phenotypes	-
HLA-A	Negative	**Positive**
HLA-B	Negative	**Positive**
HTR2A	All Phenotypes	-
HTR2C	All Phenotypes	-
IFNL4*	-	All Phenotypes
NUDT15	Normal Phenotype	**Atypical Phenotype**
OPRM1	All Phenotypes	-
SLC6A4	All Phenotypes	-
SLCO1B1	Normal Activity	**Decreased or Poor Activity**
TPMT	NM	**PM, IM**
UGT1A1	NM	***28 Carrier**
VKORC1	Normal Activity	**Intermediate or Poor Activity**

†CYP2D6 Genotype-Activity Score-Phenotype Translation is based on the CPIC/DPWG Consensus
*IFNL4 was excluded because the HCV Guidance no longer recommends the use of peginterferon-containing regiments to treat HCV infection.[12]

PM = Poor Metabolizer
IM = Intermediate Metabolizer
RM = Rapid Metabolizer
PM-IM = Poor-Intermediate Metabolizer
IM-NM = Intermediate-Normal Metabolizer
UM = Ultrarapid Metabolizer

Supplement Table 3: Number of Patients with Actionable Phenotypes

Gene	Patients Number (%)
CYP2C9	**52 (33.8%)**
PM	1
PM-IM	1
IM	20
IM-NM	30
CYP2C19	**56 (36.4%)**
PM	5
PM-IM	0
IM	30
IM-NM	21
CYP2D6	**101 (65.6%)**
PM	5
PM-IM	15
IM	45
IM-NM	28
RM	1
UM	7
DPYD	**8 (5.2%)**
Atypical Phenotype	8
F2	**5 (3.2%)**
Positive	6
F5	**9 (5.8%)**
Positive	9
HLA-A	**6 (3.9%)**
*31:01	4
*31:03	2
HLA-B	**20 (13.0%)**
*15:02	0
*57:01	14
*58:01	6
NUDT15	**0 (0.0%)**
Atypical Phenotype	0
SLCO1B1	**48 (31.2%)**
Decreased Function	45
Poor Function	3
TPMT	**15 (9.7%)**
IM	15
PM	0
UGT1A1	**76 (49%)**
*28 Carrier	62
*28/*28	14
VKORC1	**98 (63.6%)**
Intermediate Activity	85
Low Activity	13