Abstracts

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Warfarin pharmacogenetics in a black Zimbabwean cohort: an observational prospective study

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Background: Warfarin is the most commonly used anticoagulant in Sub-Saharan Africa. Genetic variants are associated with inter-variability in patient response and frequently result in adverse events (AEs) such as hemorrhage. Clinical guidelines for warfarin dose based on CYP2C9, VKORC1, and CYP4F2 polymorphism have been demonstrated to minimize AEs differently between races.

Objective: This study assesses, for the first time, the feasibility of implementing known pharmacogenetics clinical guidelines for warfarin dose in Zimbabwean patients.

Methods: Whole-blood DNA was extracted and used to genotype CYP2C9 and VKORC1. Patients' INR values, clinical data, and warfarin starting dose were all documented.

Results: CYP2C9*1/*8, *1/*11, *1/*6, *1/*5, VKORC1 AG, AA were found at a frequency of 11.29%, 11.29%, 3.22%, 3.22%, 40.32%, 4.83%, respectively. Non-African variations were not found. 25 of the 62 recruited patients were taking warfarin at the standard 5 mg starting dose. Furthermore, only 13 of the 62 patients were on the appropriate warfarin starting dose based on INR (an INR of less than or equal to 1.3 corresponds to a 5 mg warfarin starting dose). Furthermore, 24.19% had *1/*1 and AG, 4.84% had *1/*1 and AA, 1.61% had *1/*6 and GG, 1.61% had *1/*6 and AG, 11.29% had *1/*8 and AG, 3.23% had *1/*5 and GG, 6.45% had *1/*11 and GG, and 4.84% had *1/*11 and AG. This means that only a pharmacogenetic guideline including African-specific variations could be appropriate for this population.

Conclusion: The current study found African-specific CYP2C9 variants that are essential in warfarin metabolism. Only the CPIC recommendation considers these variables for warfarin starting dose. As a result, the CPIC recommendation may be the only one appropriate in this patient population when compared to FDA and DPWG guidelines.

Development of a Pharmacogenetic Recommendation Prediction System Based on XGBoost Gradient Boosting Algorithms: Machine Learning Approaches to Personalized Medicine

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Introduction: Creating new pharmacogenetic (PGx) guidelines and updating existing ones require significant effort from experts in clinical pharmacology, genetics, medicine, bioinformatics, and more. This process ensures comprehensive and effective guidelines.

Objective: The study aimed to train and evaluate a model using XGBoost gradient boosting algorithms to predict pharmacogenetic recommendations for new molecules and updates, utilizing Morgan Fingerprints, genetic and protein profiles of drugs, and allele combinations

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in gene polymorphisms encoding pharmacokinetic and pharmacodynamic proteins.

Materials and Methods: Data from PharmGKB and proprietary datasets underwent preprocessing to handle missing values and generalize pharmacogenetic recommendations for analytical efficiency. An 80:20 training-test set division was used. The model's quality was assessed by ROC and Precision-Recall curves.

Results: The XGBoost model achieved a classification accuracy of 89.15%, with sensitivity and specificity ranges of 80.13%-89.43% and 88.32%-90.93%, respectively. Precision and negative predictive values were between 84.36%-92.95% and 94.02%-95.38%, indicating high prediction accuracy. The F1 score ranged from 80.54% to 86.82%, showing balanced performance. Additionally, a random forest model identified key features for classification, offering insights for future PGx research.

Conclusion: The XGBoost-based model demonstrates substantial capability in classifying PGx data, evidenced by high accuracy and AUC metrics. These findings lay the groundwork for further research and early-stage recommendations formation, potentially enhancing personalized treatment approaches in clinical practice based on genetic data.

Design of Clinical Decision Support to Promote DPYD-Guided Prescribing of Initial Fluoropyrimidine Doses

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Reduced function DPYD variants increase the risk for potentially life-threatening toxicities, even after just one fluoropyrimidine dose. Our health system has implemented DPYD testing and electronic health record (EHR) embedded therapeutic recommendations for patients with DPYD variants. The objectives of this study were to (1) evaluate whether prescribers were utilizing DPYD testing to guide the first fluoropyrimidine dose and (2), if needed, to implement an EHR-based intervention to facilitate preemptive DPYD testing.

All study data were obtained from the EHR. Of the 1134 patients who received DPYD testing at our institution, 276 (24%) received 1+ fluoropyrimidine dose. For 197 of these patients (71%), prescribers did not have DPYD results at the time of first fluoropyrimidine prescription. The average DPYD genotyping turnaround time at our institution was 7 ± 3 days [median ± IQR]. The first entry of relevant cancer diagnosis codes (as is required for reimbursement of medical oncologist clinical evaluations) occurred 25 ± 28 days [median ± IQR] prior to the first fluoropyrimidine prescription.

Thus, we designed an EHR alert to provide one-click access to the DPYD testing order entry screen. The alert is designed to trigger upon physician entry of colorectal cancer-related diagnosis codes for patients without DPYD test results in the EHR. The alert is currently undergoing institutional approval, after which usability testing will be performed by gastrointestinal oncologists over a period of 6 months to determine provider acceptability and if the alert facilitates return of DPYD results before first fluoropyrimidine prescriptions.

In conclusion, we determined that DPYD test results were typically not available to inform first fluoropyrimidine prescriptions at our institution. We are implementing an EHR alert with the goal of enabling return of DPYD results prior to fluoropyrimidine prescribing. We will perform usability testing of the alert before revising and expanding to other oncology disciplines.

Implementation of Pharmacogenomic Consultations at a Rheumatology Clinic

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Introduction: Patients with rheumatologic conditions take an average of five medications for rheumatology indications and are often treated by multiple providers to manage conditions affecting various organ systems. A high degree of polypharmacy has been observed in this patient population. Previous studies have demonstrated that 81% of rheumatology patients are prescribed medications with actionable pharmacogenomic recommendations. Pharmacogenomic data helps providers anticipate medication side effects, and avoid prescribing less-effective medications or medications that could be ineffective for a particular patient. Despite these benefits, pharmacogenomic testing of rheumatology patients is not routine. This study aims to assess both patient interest in and impact of a comprehensive pharmacogenomics consultation service for rheumatology patients. Primary outcomes of interest include rates of patient enrollment and number of pharmacogenomics-related actionable recommendations related to CPIC level A and B medications. Secondary outcomes include assessment of patient satisfaction, barriers to establishing the service,

and barriers to patient uptake of pharmacogenomic testing.

Methodology: This is a single arm, prospective, descriptive pilot study including patients aged 26 years or older who receive care from Stanford Rheumatology Clinic and are prescribed at least 2 CPIC level A or B medications. Medications of interest include immunosuppressive therapies (allopurinol, azathioprine, tacrolimus) and supportive care (ibuprofen, celecoxib, meloxicam, pantoprazole, omeprazole, ondansetron) and medications for concomitant conditions (e.g statins). Patients are invited to participate in a comprehensive pharmacogenomics consultation service by providing a buccal swab sample for analysis by an external lab vendor. The results are reviewed by a clinical pharmacist certified in pharmacogenomics, who provides recommendations to the patient's rheumatologist. The provider reviews pharmacogenomic testing results with the patient and counsels the patient on any resulting medication changes. The patient is sent a post-consultation survey to assess their satisfaction with the service.

Results: Research is currently in-progress

Conclusion: Research is currently in-progress

Pre-emptive Pharmacogenomics - a Clinical Implementation Pilot within the Singapore Healthcare System

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Pre-emptive pharmacogenomics (PPGx) is gaining popularity as an implementation strategy to increase the uptake of pharmacogenomics into practice. Singapore has jumped on the bandwagon and initiated a clinical implementation pilot project in an attempt to incorporate PPGx testing as routine clinical care.

The program aimed to recruit 2000 patients across various institutions in Singapore to undergo a PPGx panel of 16 genes. Results were returned to the respective institutions. For EPIC-enabled institutions, prescribing encountered involving significant drug-gene interactions triggered firing of Best Practice Advisories (BPA) to guide dosing or drug selection for pre-selected 30 drug gene pairs. The objective of this study to review the pattern and prescriber response associated with BPA firing 8 months into the launch of the program.

Slicer-Dicer (an informatics tool in EPIC) was used to extract BPA firing data from 1/8/23 to 26/3/24 for all recruiting locations. Descriptive statistics were used to summarize the data.

From 1/8/23 to 26/3/24, 1808 patients were recruited. 871 BPA were prompted in the electronic prescribing system for which 822 were passive inline prompts and 49 were interruptive prompts. For the interruptive prompts, 12 prompts resulted in removal of the drug order and 37 were overridden or acknowledged. 21 of the interruptive prompts were fired for phenytoin (3 unique patients), 18 for clopidogrel (13 unique patients), 9 for carbamazepine (7 unique patients) and 1 for warfarin.

The analysis of BPA firing pattern demonstrated genotype-guided alteration of prescription in association with pre-emptive testing. Further analysis is needed to explore the impact on clinical outcomes and cost-effectiveness with genotype-guided prescribing.

Genetic Risk Factors for Concurrent Tobacco Use and Schizophrenia

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Tobacco use disorder and schizophrenia are highly heritable, comorbid conditions that demonstrate substantial resistance to current treatments. Genome-wide association studies (GWASs) have proven useful for identifying biological risk pathways and potential new targets for drug development. In large GWASs conducted separately for tobacco use and schizophrenia, numerous risk genes were identified, some of which are overlapping. We hypothesized that a multi-GWAS approach that leverages the genetic correlation between tobacco use and schizophrenia would identify new risk loci not

captured in the single-trait GWASs. We used summary statistics from the largest GWAS conducted to date for schizophrenia (SCZ, N=130,644; 53,386 cases; 77,258 controls; European ancestry) and for cigarette smoking behaviour, defined by the number of cigarettes smoked per day (CPD; N=337,334; European ancestry). Through advanced LD Score Regression (LDSC) and Multi-Trait Analysis of GWAS (MTAG) analytical techniques, we identified a genetic correlation of 0.12 (p=5×10^(-8)) between these behaviours and revealed specific heritability estimates of h^2= 0.08 (±0.01) for CPD and h^2= 0.37 (±0.012) for schizophrenia. Our current research efforts involve comparing the number and nature of genome-wide significant loci identified in MTAG versus the original single-trait GWAS, for both schizophrenia and tobacco use. As a future goal, we aim to incorporate the use of GWAS of biomarkers of tobacco use, including cotinine levels and cotinine+3hydroxycotinine, which offer a more precise and objective analysis of smoking behaviours than self-reported cigarettes smoked per day. We also plan, using causal inference approaches, to examine whether tobacco use is likely to lead to schizophrenia, and/or vice versa. This project may unveil new insights that could improve the current understanding and approach to treatment for these comorbid disorders, opening potential new avenues for drug development and personalized medicine.

PharmVar NAT2 Gene Expert Panel: NAT2 Allele Nomenclature Update and Transition to PharmVar

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NAT2 nomenclature has been transitioned to PharmVar. NAT2 alleles usually contain more than one single nucleotide variation (SNV), with specific variants defining different allelic groups. Given the complex haplotypic nature of NAT2 alleles, it is important to maintain up-to-date information regarding sequence variation and star allele definitions. Major changes have been made to NAT2 nomenclature during transition from the original (https://nat.mbg.duth.gr/) to the new (https://www.pharmvar.org/gene/NAT2) "star" allele definitions: i) The NAT2 reference allele changed from former sequence X14672.1 to reference genomic sequence NG_012246.1 RefSeq, causing "variant switching" at position c.803 (rs1208). ii) The sequence of NG_012246.1 RefSeq corresponds to former allele NAT2*12A. Its renaming as NAT2*1.001 enables the use of NAT2*1 to describe the reference allele, in line with the star allele nomenclature of other pharmacogenes. To avoid confusion, NAT2*12 is now retired. iii) The former NAT2*4 reference allele is now considered a variant and listed as NAT2*4.001. Other alleles carrying c.803G>A as their only non-synonymous SNV will be grouped together as NAT2*4 according to the new nomenclature. iv) Several NAT2 star alleles have been renamed to conform to PharmVar rules. v) Haplotypes where the available evidence from the literature was deemed insufficient to support confident allele definition were not transferred to PharmVar, but they will remain posted on the original website. vi) According to PharmVar rules, new NAT2 alleles must cover SNVs within defined coordinates that enclose the 5' untranslated region (including the untranslated first exon), the coding exon, the exon/intron junctions, and the entire 3' untranslated region relative to NG_012246.1. While updating NAT2 nomenclature, we confirmed several of the former haplotypes, while also identifying new ones. PharmVar encourages submissions of novel haplotypes for star allele definition, as well as for existing definitions to either raise their evidence level, or to solidify their definitive status.

CYP2D6 Allele-Specific Copy Number Determination by Digital PCR

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Digital PCR (dPCR) is increasingly used for detection of CYP2D6 copy number (CN), which is integral for predicting phenotype and guiding drug therapy. However, even if CN and genotype (GT) are assessed, ambiguous results still occur because of the inability to determine which star (*) allele is duplicated. To address this issue, we developed a dPCR allele-specific copy number variation (AS-CNV) method that can

characterize the number of specific *alleles. Eight Coriell DNA samples, with known CYP2D6 GT and CN, were optically multiplexed with targeted TaqMan™ GT assays, then run on the QuantStudio™ Absolute Q™ dPCR System as recommended. The GT assay targeting rs16947C/T (CYP2D6*2) detected 3-copies of rs16947T (variant) due to its presence on all three *alleles; the GT assay targeting rs28371706C/T (CYP2D6*17) detected 2-copies of rs28371706C (reference) and 2-copies of rs28371706T (variant). These results for NA19224 support a CYP2D6*2x2 duplication. Taken together, AS-CNV is a cost-effective way to discriminate which *allele is affected by CN variation. This is most relevant for patients having gene duplications with decreased or no function alleles as their metabolizer status may change based on which allele is affected by CN variation. For example, discriminating between CYP2D6*1x2/*4 (AS=2) and *1/*4x2 (AS=1) allows the patients to be classified as normal or intermediate metabolizer, respectively. While this method is limited by the availability of GT assays interrogating selected variants and the requirement for orthogonal GT and CN testing for clinical use, it can also be adapted to test other pharmacogenes. Furthermore, it is currently being optimized with the ultimate goal of producing commercially available assays for CYP2D6 to facilitate clinical-grade testing.

Impact of Phenoconversion on Risk for Major Adverse Cardiovascular Events in Clopidogrel-Treated Post-PCI Patients

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The association between CYP2C19 genotype and clopidogrel effectiveness has been well documented. However, there are limited data on the effect of moderate-strong CYP2C19 inhibitors on clopidogrel-related outcomes. The objective of this study was to assess the impact of concomitant use of moderate-strong CYP2C19 inhibitors on risk for major adverse cardiovascular events (MACE) in clopidogrel-treated patients following percutaneous coronary intervention (PCI). Post-PCI clopidogrel-treated patients who underwent clinical CYP2C19 genotyping and did not have a CYP2C19 no-function allele were included. Patients were classified as inhibitor-exposed or non-exposed based on concomitant use of a CYP2C19 inhibitor at event or last follow up. Seven moderate-strong FDA clinical inhibitors, predominantly antidepressants and antifungals, were considered. Multivariable Cox regression was used to assess risk of the primary outcome of MACE (all-cause mortality, myocardial infarction, stroke, or stent thrombosis) between groups. A total of 955 patients (mean age 64±12, 36% women, 17% Black) were included; 27 (25 on fluoxetine and 2 fluconazole) were classified as inhibitor-exposed and 928 as non-exposed. There was a trend toward increased risk for MACE in inhibitor-exposed compared to non-exposed patients [21.4 vs. 7.7 events per 100 patient-years, adjusted hazard ratio (HR) 2.58, 95% confidence interval (CI) [0.83-8.03]; p=0.103]. Similarly, when limiting our analysis to serotonin reuptake inhibitor (SSRI) users, those on fluoxetine tended to be at an increased risk for MACE compared to patients on other SSRIs (n=127) [26.9 vs. 10.2 events per 100 patient-years, adjusted HR 2.86, 95%CI [0.81-10.08], p=0.103]. These data support further examination of the effects of moderate-strong CYP2C19 inhibitors on the effectiveness of clopidogrel after PCI.

Increased Odds of Opioid Overdose With CYP3A5 or DRD2 and Decreased With NK1R

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In 2023, 3,651 Ohioans died as a result of an opioid overdose. Of those opioid overdoses, 3,579 (98%) were attributed to fentanyl. This study evaluated the influence of genetic variants related to opioid overdose using multiple logistic regression analysis of self-reported non-fatal opioid overdoses from a sample of 1,301 adult patients (>18 years of age) seen in emergency departments of three medical centers in Ohio. Of the 821 patients who reported having been exposed to opioids in their lifetime, 95 also reported having experienced a lifetime non-fatal opioid-related overdose. A total of 180 candidate single nucleotide polymorphisms (SNPs) were tested for their potential association with non-fatal opioid overdose. These candidate SNPs included 120 related to the dopamine reward pathway and 60 related to pharmacokinetics. Logistic regression (adjusting for age, biologic sex, and opioid use disorder) was used to

characterize the association between each SNP and non-fatal opioid overdose. Three SNPs found in three genes were associated with non-fatal opioid overdose after Bonferroni correction: increased odds with CYP3A5 (rs776746) or DRD2 (rs4436578), and decreased odds with NK1R (rs6715729). Homozygotic CYP3A5 (rs776746) had the highest adjusted odds ratio (aOR) of 6.96 (95% CI [2.45, 29.23]) and homozygotic NK1R (rs6715729) had the lowest aOR of 0.28 (95% CI [0.14, 0.54], which represents the most extreme negative, or protective, association). Given that CYP3A5 (rs776746) has been associated with increased plasma concentrations of fentanyl, rs776746 could be potentially utilized as a prognostic risk indicator for the potential of an opioid overdose. NK1R regulates the expression of the neurokinin-1 receptor, a regulator of respiration. Therefore, NK1R (rs6715729) represents a novel genetic marker for opioid overdose risk.

Evaluation of tagged SNPs for HLA markers, HLA-B*15:02 and HLA-A*31:01, that are used to predict carbamazepine induced adverse effects.

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Objective: The tagged SNPs for specific HLA markers (HLA-B*15:02 and HLA-A*31:01) are known to predict the risk of carbamazepine induced adverse effects. Our objective is to study the presence of SNPs associated with the two HLA markers in Indian patient population.

Methods: The subjects included in the study were part of a multicentric study. The subjects included were cases who developed rash on any anti-epileptic drugs (AED) because of which the AED was discontinued and controls who never had any history of rash on AED. Blood and saliva samples were collected and extracted DNA was used for Taqman Genotyping SNP Assays using dbSNP ID rs number context sequences. The SNPs selected were rs10484555 (studied in Asian population), rs17179220 and rs144012689 (studied in US population of multiple ethnicities). In case of rs144012689 two assays were designed to prevent allelic dropout due to adjacent SNP. To confirm the findings of SNP assays for the presence of specific HLA type, we processed some samples with high resolution HLA typing.

Results: 1) Of 163 samples, minor allele frequencies (MAF) in our population for the three SNPs rs10484555, rs17179220 and rs144012689 were 0.03, 0.025 and 0.02 respectively. The corresponding MAFs for South Asian population in NCBI SNP database are 0.03, 0.01 and 0.01 respectively. 2) Based on SNP genotyping, in our samples, 5% were detected for HLA-B*15:02 and 5% for HLA-A*31:01. 3) Comparison with high resolution HLA typing showed 100% concordance for HLA-A*31:01. This work is still ongoing.

Conclusion: 1) Our method is cost effective, convenient especially in pediatric neurology cases and has quick TAT to detect HLA-A*31:01 and HLA-B*15:02.

2) In Indians, being a combination of Eastern European, Eurasian and South Asian ancestries, we suggest using three assays for two SNPs for the detection of HLA-B*15:02 and one SNP for the detection of HLA-A*31:01.

Allele-Specific Targeting and Haplotyping of the NAT2 Gene

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Variation within the NAT2 locus may impact enzymatic activity and stability. As a result, carriers of NAT2 genetic variants exhibit variability in processing of xenobiotic substrates, like drugs. The overall aim of this study was to determine the haplotypes of samples from worldwide populations of the International Genome Sample Resource (IGSR), validating previously described alleles and characterizing new ones. Sequencing data including the NAT2 gene region from 3202 individuals available in public databases were downloaded from IGSR and analyzed to manually assign the haplotype of each sample. In some cases, when the individual is part of a family that is included in the database, additional trio information was exploited to deduce the haplotypes of the family. In some cases, the available information was not enough to perform haplotypic phasing of the observed genetic variations in the family, so diplotype assignment for each individual was not possible. Aiming to resolve many of those cases, a laboratory methodology was devised to amplify and sequence the entire NAT2 gene in an allele-specific manner using long-range PCR (XL-PCR) and Sanger sequencing. A total of 22 previously reported haplotypes have been validated so far, while an additional 10 new non-synonymous variants and 14 new haplotypes have been discovered in the IGSR dataset analyzed. This work contributes to the development of a comprehensive strategy allowing identification of single nucleotide variants within the NAT2 gene and their haplotypic phasing experimentally. All newly discovered or validated alleles are submitted to PharmVar, where the new star NAT2 nomenclature is hosted.

Investigation of Genetic Variation within NAT1, NAT2 and CYP2D6 in the Greek Population

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Arylamine N-acetyltransferases (NATs) and cytochromes P450 (CYPs) catalyze reactions of endogenous and xenobiotic metabolism. Carriers of genetic variants of those genes exhibit different drug metabolizing capacities. The bulk of pharmacogenetic studies to date have focused on genotyping patients for single nucleotide variations (SNVs). In contrast, gene copy number variation (CNV) has been investigated only for a few pharmacogenes, such as CYP2D6, but not for NAT genes. Therefore, the aim of this study was to characterize variants of NAT1, NAT2 and CYP2D6 genes in the Greek population. A total of 114 fully anonymized blood samples were collected from Greek healthy volunteers. The biological material was investigated for CNVs within NAT1, NAT2 and CYP2D6 genes. Two assays were designed targeting the NAT genes, based on fluorescent probes that can be applied either in quantitative PCR (qPCR) or digital PCR (dPCR) technologies. The same samples were also screened for CNVs at the CYP2D6 locus, using standard diagnostic assays. Additionally, a protocol for targeted long-read sequencing using the Oxford Nanopore technology is currently underway, to allow haplotypic phasing of SNVs found in all three pharmacogenes. No CNVs were found at the NAT locus, which is in agreement with our literature and database searches indicating that structural variability is very rare. In the CYP2D6 locus, approximately 20% of the samples had a CNV and were further investigated using long PCR (XL-PCR) assays to validate the results. Since the Greek population has not been fully screened for genetic variation within those genes before, particularly in relation with CNVs at the NAT locus, this cohort can be also used as healthy control in future pharmacological and epidemiological studies. Moreover, the development of state-of-the-art protocols for variant detection and haplotype determination will facilitate diagnostics.

Clopidogrel metabolism is not affected by the CYP2C:TG haplotype

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Clopidogrel is the most widely prescribed P2Y12 receptor blocker to prevent recurrent cardiovascular event. The hepatic CYP2C19 enzyme is key in the activation of clopidogrel. Recently, a haplotype (CYP2C:TG) in CYP2C18 was reported to be associated with increased CYP2C19 activity. For clopidogrel treatment, increased CYP2C19 activity would result in increased production of active metabolites, increased platelet inhibition and subsequently potentially a higher bleeding risk. In this study, we investigated the correlation of the CYP2C:TG haplotype with platelet function and bleeding risk in patients treated with clopidogrel.

The study was conducted in a prospective cohort of 304 patients receiving dual or triple antithrombotic therapy after percutaneous coronary intervention (PCI). Patients were genotyped for CYP2C19*2, *3, *17, and the CYP2:TG variants (rs2860840 and rs11188059). Based on these variants, patients were classified as ultrarapid (UM, 24.7%, (*17/*17, TG/TG, *17/TG), rapid (RM, 31.9%, *1/*17, *1/TG), normal (NM, 14.1%, *1/*1), intermediate (IM, 26.3%, heterozygous for *2 or *3) or poor (PM, 3.0%, homozygous *2 and/or *3) metabolizer. Platelet reactivity was measured with VerifyNow P2Y12. Bleeding was included as an endpoint, therefore, all ischaemic and bleeding events were collected during follow-up visits at 6 and 12 months.

On-treatment platelet reactivity was significantly associated with CYP2C19 metabolizer phenotype ($P<0.001$). However, this association was mainly driven by the intermediate and poor metabolizers; the ultra-rapid and rapid metabolizers did not differ significantly on platelet reactivity from normal metabolizers ($p=0.42$ and $p=0.48$, respectively). Patients with an ultrarapid or rapid CYP2C19 metabolizer status did not report more bleeding events than patients with normal CYP2C19 activity. Statistical analysis based on genotype showed similar results.

We demonstrated that CYP2C19 intermediate and poor metabolism phenotypes results in higher residual platelet reactivity but the CYP2C:TG haplotype does not influence the platelet reactivity.

Pharmacogenetics Education for Pharmacy and PharmD Students: Measuring Knowledge and Attitude Towards Pharmacogenetics in Jordan

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Clinical implementation of pharmacogenetics (PGx) depends largely on healthcare providers, including pharmacists. A survey was used to assess the knowledge, attitudes, and perceptions among the 4th and 5th-year students (pharmacy and PharmD undergraduate students) before starting an elective course of PGx during the academic year 2023-2024. Out of the 95 participants, 72.6% have never attended a course or a workshop on pharmacogenetics but have heard the term pharmacogenetics before registering for the course.

The majority of the students believe pharmacists are responsible for implementing PGx testing before prescribing drugs (55.8%). Nevertheless, their knowledge of the basic principles was limited, suggesting the importance of such an elective course in the curricula for pharmacy undergraduate students. The baseline results indicate a strong agreement among respondents regarding the influence of genetics on drug response (89%). A significant majority acknowledged that genetic inheritance plays a crucial role in determining individual responses to medications, with a high percentage agreeing that differences in drug response between individuals and across different ethnicities can be attributed to genetic variations.

The findings highlighted varying levels of awareness and comprehension about PGx. For instance, 81.1% of respondents stated the potential to predict patients' drug responses by knowing specific gene mutations. In comparison, only 18.9% stated that the information provided in PGx-related courses delivered before this study intervention was sufficient for clinical implementation.

Additionally, there are concerns about ethical implications, such as 33.7% agreeing and 21.1% strongly agreeing that insurance companies might use genotyping in an unethical way. However, there is a strong belief that PGx testing can improve patient outcomes and safety, with 36.8% agreeing and 56.8% strongly agreeing.

These findings underscore the need for comprehensive education initiatives to bridge knowledge gaps and facilitate the effective integration of PGx into clinical practice.

Identifying the Obstacles to Putting Pharmacogenetic-Guided Treatments into Practice in Clinical Settings

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Despite the benefits of pharmacogenetic (PGx)-guided treatments in helping patients get well sooner, minimizing adverse drug effects, and saving healthcare costs, not much progress has been made with its implementation in routine clinical practice. The overall goal of this study is to identify potential obstacles to the implementation of PGx-guided treatments in clinical practice, examining viewpoints from healthcare providers (HCPs) and patients. We performed two anonymous online surveys across the globe for both HCPs and patients, respectively using the Qualtrics platform for survey collection. The survey was distributed online through social media and email platforms from 27th October 2023 to 7th March 2024. The survey was designed to gather information on participants' level of awareness about PGx, any prior experiences with PGx testing, their views on potential challenges to implementing PGx, and their opinions regarding the use of point-of-care (PoC) PGx testing devices. Statistical analysis including descriptive statistics, cross-tabulation analysis, chi-square tests, and independent t-tests was performed using Excel and SPSS when necessary. A total of 75 and 92 responses were collected from HCPs and patients respectively. 64% of HCPs had some level of familiarity with PGx but only 7% have either ordered or recommended PGx testing to their patients. On the contrary, only 52% of patients were familiar with PGx testing with 4% having undergone the test. There was an association between prior patient PGx awareness and positive PGx opinion ($p < 0.001$). Limited access/availability to testing and lack of knowledge were identified by 55% and 48% of HCPs, respectively, as an implementation challenge. Interestingly, 98% of HCPs and 71% of patients indicated that PoC PGx testing device will improve their implementation of PGx testing. In conclusion, robust PGx awareness campaign and PoC PGx testing devices may help promote the implementation of PGx-guided treatments in clinical settings.

Metabolism and genotoxicity of 4,4'-oxydianiline is dependent on N-acetyltransferase 2 genetic polymorphism

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Hookah smoking is increasingly popular. Among the aromatic amines detected, 4,4'-oxydianiline (ODA) was reported as the highest concentration in hookah smoke yet non-detectable in cigarette smoke. The metabolism and the subsequent toxicity of ODA remains unknown. Given that ODA is an aromatic amine, its toxicity may be dependent on metabolism by arylamine N-acetyltransferase 2 (NAT2). We hypothesized that ODA is N-acetylated by NAT2 and its genetic polymorphism modifies ODA genotoxicity and oxidative stress. We investigated this hypothesis with repair deficient (UV5) Chinese hamster ovary cells (CHO) expressing human CYP1A2 with either rapid or slow

acetylator NAT2 allele variants and with cryopreserved human hepatocytes expressing rapid, intermediate, or slow NAT2 acetylator genotypes. The N-acetylation of ODA catalyzed by human NAT2 was both concentration- and time-dependent and significantly higher in CHO cells expressing the rapid versus the slow acetylator NAT2 variant. In CHO cells, expressing human CYP1A2 and either a rapid or slow acetylator NAT2 allele, the induction of DNA damage was higher in the CHO cells expressing the rapid acetylator compared to the slow acetylator NAT2 variant. Induction of oxidative stress as measured by ROS/RNS, intracellular reduced glutathione (GSH) and oxidized glutathione (GSSG) or mitochondrial integrity were all significantly higher in CHO cells expressing the rapid acetylator compared to the slow acetylator NAT2 variant. In the cryopreserved human hepatocytes, a dose-dependent and NAT2 genotype dependent response was observed for ODA N-acetylation, DNA damage, and oxidative stress. These results provide evidence that exposure to ODA results in NAT2 genotype dependent genotoxicity and oxidative damage.

Impact of CYP3A5 Genotype on Tacrolimus Dosing Requirements and Trough Concentrations in Cardiac Transplant Recipients

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Background: Tacrolimus is primarily metabolized by CYP3A4 and CYP3A5 enzymes. The Clinical Pharmacogenetics Implementation Consortium recommends increasing the initial dose 1.5-2x for CYP3A5 expressers to enhance transplant outcomes. Our objective was to investigate the impact of CYP3A5 expresser status on tacrolimus dosing requirements and attainment of target trough concentrations in cardiac transplant recipients at our institution, where CYP3A4 and CYP3A5 genotyping were routinely conducted.

Methods: Retrospective chart review was performed to collect demographic information, CYP3A4 and CYP3A5 genotype, tacrolimus doses and whole blood concentrations, concomitant medications, hematocrit, and albumin levels from December 2020 to August 2023. The primary outcome assessed was the time to first therapeutic trough concentration. Secondary outcomes included the initial tacrolimus dose and the dose required to reach the target concentration. Stepwise multiple regression analyses were performed to account for demographic and clinical covariates.

Results: Among 33 patients (mean age 51 ± 13 years (mean ± SD), 69.7% male, 69.7% African American), cardiomyopathy was the leading transplant cause (60.6%). CYP3A5 expressers took longer to achieve therapeutic trough concentrations (expressers: 13 (95% CI: 9.7, 16) days, nonexpressers: 8.3 (95% CI: 6.7, 10) days; p value: 0.012) and required 1.9 (95% CI: 1.4, 2.6; p value: 0.007) times dose to reach target concentrations. No statistically significant difference was observed in the initial daily dose between the two groups (p=0.62). Multiple regression identified an association of initial dose and route (sublingual vs. oral) with the time to target concentration, and initial dose, race, and age with target trough dose.

Conclusion: Our findings highlight the impact of CYP3A5 expresser status on tacrolimus dosing requirements and the attainment of therapeutic concentrations in cardiac transplant recipients. Additional investigations are needed to determine the appropriateness of CYP3A5-guided dosing strategies to rapidly obtain therapeutic tacrolimus concentrations in this population.

The Impact of NUDT15 p.R139H on Thiopurine Tolerance in Children With Acute Lymphoblastic Leukemia

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Nudix hydrolase 15 (NUDT15) is a highly polymorphic gene for which genetic variants have been strongly associated with thiopurine-induced myelosuppression. Currently, NUDT15 deficiency is characterized by three "no-function" alleles, i.e., *2, *3 and *9. Although additional coding variants have been identified, there is insufficient data to ascertain their clinical significance. In

particular, the Hispanic-specific variant p.R139H (i.e., *4 allele) has been experimentally verified as Loss-of-Function but currently labeled with "uncertain function" by the Clinical Pharmacogenetics Implementation Consortium (CPIC) due to limited clinical data. In this study, we investigated the association of NUDT15 *4 with 6-mercaptopurine (6-MP) tolerance and metabolism. We retrospectively assembled a cohort of 1399 children with acute lymphoblastic leukemia (ALL) of diverse ancestries, all of whom were normal metabolizers of thiopurine methyltransferase (TPMT *1/*1 genotype). Tolerated stable dose during maintenance therapy was used to assess 6-MP toxicity. Leukocyte DNA-TG were measured to investigate 6-MP metabolism. Patients with NUDT15 *1/*4 (N = 16, all of Hispanic ancestry) tolerated a lower dose of 6-MP compared to NUDT15 *1/*1 (median of 39.0 mg/m² and interquartile range, IQR, 21.2-52.8, versus 62.2 mg/m², IQR, 47.9-71.6, P value < 0.001). There was no difference in 6-MP tolerance between patients with NUDT15 *1/*4 and those with NUDT15 *1/*3 (41.6 mg/m², IQR, 29.7-48.4, P = 0.68), the most common no-function allele. NUDT15 *1/*4 patients also had higher dose-adjusted concentrations of DNA-TG compared to wildtype patients (P = 0.004, median of 16.5 fmol/ug/MP, IQR, 11.4-20.7, vs 6.1 fmol/ug/MP, IQR, 4.5-8.9), consistent with reduced NUDT15 enzymatic activity. These results were validated in an independent cohort of patients clinically identified with NUDT15 *1/*4. In conclusion, our results underscore the importance of including NUDT15 *4 in testing for NUDT15 deficiency. The CPIC guideline prescribing recommendations and relevant supporting data are being updated to include *4 into pharmacogenetics-guided thiopurine dosing algorithms.

PGx-it: Pharmacogenomics Illumina testing suite

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Pharmacogenomic (PGx) testing is crucial for tailoring drug therapies to enhance drug safety and efficacy. The biobank at the Colorado Center for Personalized Medicine (CCPM biobank) has a nation-leading PGx return of results program that leverages the Illumina Global Diversity Array (GDA) platform with enhanced PGx. The CCPM biobank currently returns clinical PGx results for 7 genes, with plans to return results for 5 additional genes, from the GDA platform. The GDA platform stores PGx data in machine-readable formats, i.e., GTC(Genotype Call File) and CNV.VCF(Copy Number Variation Variant Call Format) files. To perform comprehensive technical testing and software validation of all PGx scenarios before returning clinical results, it is imperative to have sophisticated tools that can analyze these specialized file formats. Here, we describe software we developed to streamline technical testing and validation processes for PGx results obtained via the GDA platform.

We developed the Pharmacogenomics Illumina testing suite (PGx-It), an open-source academic software framework, at the CCPM biobank. Built on Python 3.10, PGx-It is designed to navigate, modify, and extract comprehensive information from GTC files. PGx-It reads in user-specified haplotypes for specific PGx scenarios and modifies GTC files to mirror the user-specified haplotype. Using a specialized naming convention, PGx-It also renames the GTC IDs for deidentification, as well as the plate manifest. If a haplotype with CNV is specified, PGx-It detects and subsequently modifies the corresponding CNV.VCF files to mirror the user-specified haplotype with CNV. We have successfully used PGX-It to test edge-case permutations for 12 PGx genes for the CCPM biobank PGx return of results program.

PGx-It extends functionality for researchers and developers by ensuring integrity of the original data. PGX-It facilitates modification of sample metadata and haplotype calls, aiding in software validation and edge-case testing, thus facilitating a wider range of genomic studies and personalized medicine applications.

The frequency of CPIC level A/B drug prescribing in patients with cancer: a case for pharmacogenetic (PGx) panel testing

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Background: Patients who receive chemotherapeutic agents such as fluoropyrimidines and irinotecan are tested for potential gene-drug interactions using pharmacogenomic (PGx) single gene tests. However, these patients often have concomitant medical conditions or are prescribed medications for cancer supportive care; these may be impacted by PGx variants (CPIC Level A drugs). It is unclear if PGx testing using a panel rather than a single-gene test would provide additional benefits for these patients. Our goal was to analyze the prescribing pattern of CPIC level A drugs after cancer diagnosis and assess actionability based on PGx phenotypes.

Methods: We included 77,566 patients who were listed in the Penn Abramson Cancer Center Registry Cancer Registry (1952-2020). We extracted prescription data from the electronic health record (EHR) to determine the number of CPIC level A drugs that were prescribed to each patient prior to and after cancer diagnosis. We used the Penn Medicine Biobank (PMBB) to determine PGx phenotypes of cancer registry patients.

Results: Over 93% of patients had at least one CPIC level A/B drug prescribed after cancer diagnosis. The median time from diagnosis to first prescription was 0.4 years (IQR 2.6). For patients who received at least one CPIC level A/B drug, the most common cancer types were breast, gastrointestinal, and genitourinary (18.2%, 16.4%, and 14.4%, respectively). Ondansetron, omeprazole, and atorvastatin were the most prescribed CPIC level A/B medications after diagnosis. We analyzed 7,436 patients from the cancer registry that had genetic data in PMBB; in these patients, 9.9% of CPIC level A/B prescriptions were actionable.

Conclusion: If PGx testing is ordered for cancer therapy, clinicians should consider using a multi-gene panel as a majority patients in the cancer registry were prescribed at least one CPIC level A/B drug after diagnosis.

Integrating DPYD/UGT1A1 with hereditary cancer germline genetic education via a point-of-care digital education tool for patients with pancreatic cancer

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Background: For patients with pancreatic ducal adenocarcinoma (PDAC), fluoropyrimidines and irinotecan are part of frontline chemotherapy and carriers of DPYD or UGT1A1 variants, respectively, are at high risk for developing severe, potentially life-threatening toxicities. The Food and Drug Administration recently updated the labeling of fluoropyrimidines to advise providers to educate patients about DPD deficiency and DPYD testing. National guidelines recommend germline genetic testing for hereditary cancer syndromes in all PDAC. The Genetic Information for Treatment Decisions (GIFTD) initiative at Moffitt Cancer Center was created to streamline genetic education and testing.

Objectives: To describe the integration of pretest DPYD/UGT1A1 with hereditary cancer germline genetic education using a digital education tool.

Methods: The GIFTD initiative involved (1) the establishment of a Genetics Risk Education Coordinator (GREC) role responsible for identifying eligible patients and facilitating genetic testing on the same day patients had visits with providers and (2) the use of a point-of-care digital tool by Nest Genomics to provide education to patients. Content on germline testing and DPYD/UGT1A1 testing was created in partnership with Nest Genomics.

Results: The hereditary cancer germline story launched on 11/20/2023. The DPYD/UGT1A1 content was embedded into the germline story and launched on 2/12/2024. Patients received a link via text/email from Nest Genomics in advance of their scheduled appointment inviting them to view genetic educational material to make an informed decision about testing and indicate their interest in undergoing testing. The GREC (1) performed outreach reminder calls to complete assigned education module, (2) met with all patients directly after scheduled appointment with the provider to address questions/concerns related to genetic testing, and (3) ordered genetic testing if patient gave consent.

Conclusion: We plan to assess the impact of the GIFTD initiative on uptake of DPYD/UGT1A1 testing and the availability of results prior to treatment initiation among PDAC patients.

Breast cancer pharmacogenetics in Botswana

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Breast cancer is the most common cancer in women worldwide. Importantly, in sub-Saharan Africa it is associated with a high mortality, despite its relatively low

incidence. In fact, patients are more likely to present with advanced stage disease, coupled with limited availability/access to treatments. In Botswana, breast cancer represents almost 20% of all cancers and accounts for more than 10% of cancer-associated deaths among women, and it is also associated with a high risk of treatment failure. Besides intrinsic tumor factors and drug-drug interaction, one possible explanation is also pharmacogenetics. Here we want to explore the possible association between patients' pharmacogenetic profile and 5-year overall survival. To achieve this a University of Botswana team is carrying out a retrospective study on tamoxifen (tam) and paclitaxel (ptx) pharmacogenetics. A cohort of 248 FFPE breast cancer tissues are undergoing DNA extraction and genotyping for SNPs in genes encoding for enzymes that metabolize tam and ptx. Breast cancer subtype, survival data, treatment duration, toxicity and other clinical characteristics of the patients will be associated to the genetic makeup of the subjects. Cytochrome P450 2D6 (CYP2D6) (tam) and CYP2C8 (ptx) genes are being analyzed for SNPs associated to an aberrant metabolism of the two drugs. Preliminary data shows a prevalence of CYP2D6*4 and CYP2C8*2 alleles among patients in Botswana being 3.8% and 10.9%, respectively. From this, it is possible to estimate a 7.0% and a 19.7% of reduced enzyme activity for tamoxifen and paclitaxel, respectively. Current work on additional "African" SNPs, namely CYP2D6*2, *17 and *29, will refine the expected metabolic phenotypes for tamoxifen. In summary, this work shows a non-negligible rate of subjects showing defective drug metabolism for tamoxifen and paclitaxel. Future work will analyze association with outcomes that could help personalize treatment and improve outcomes in patients with cancer in sub-Saharan Africa.

Deciphering Sex Differences in Cancer Treatment Response and Survival Outcomes by Studying Intratumor Microbiome-Host Interactions

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Objectives: Cancer patients exhibit significant sex differences in disease trajectories. To better understand the observed differences, our study focuses on intratumor microbiome, a newly recognized microbial population with direct impacts on cancer outcomes. We aim to uncover sex differences in intratumor microbiome and their influence on host gene expression, prognosis, and drug response.

Method: We examined intratumor microbiome in 5 gastrointestinal cancers for differential abundance (DA) microbiome between men and women. These findings were subsequently validated using an independent dataset. To explore host genes associated with DA microbiome, we conducted differential expression analysis followed by gene set enrichment analysis. Furthermore, we investigated the influence of Epstein-Barr virus (EBV) infection on the response of standard-of-care (SOC) treatments using in vitro models.

Results: Our comprehensive analysis revealed 11 DA microbiome, consisting of 7 bacteria, 3 fungi, and 1 virus, each validated using a different dataset. EBV is one of the 11 reproducible DA microbiome to be significantly male-enriched in gastric cancer (GC). Further analysis unveiled the association between EBV infection and better overall survival in GC patients. The in vitro experiments showed that EBV infection increased the sensitivity to 3 out of 5 SOC treatments (paclitaxel, docetaxel, and 5-FU), while had no effects on the others (cisplatin, oxaliplatin). Further analysis uncovered cell cycle pathways enriched in EBV-infected GC. Additionally, in head and neck cancer (HNSC), we identified Capnocytophaga as a bacteria enriched in females. Capnocytophaga infection in HNSC was significantly associated with improved survival. Pathway enrichment analysis further highlighted enrichment of infection-related and metastasis-related pathways in Capnocytophaga-infected HNSC.

Conclusion: Our research identified intratumor microbiome whose abundance is different between men and women in gastrointestinal cancers. The DA microbiome identified in our analysis have significant associations with patients' transcriptome profile, drug response, and survival outcomes.

PharMe: A Patient-Friendly Mobile Application to Return Pharmacogenomic Test Results

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Pharmacogenomics (PGx) can optimize therapeutic outcomes while minimizing adverse events. However, many barriers impede its widespread adoption. One of such barriers is the lack of trained healthcare professionals to adopt PGx into routine practice. To alleviate this burden, we have developed PharMe, a mobile application to return PGx results to patients, powered by Anni, a novel annotation interface.

Using CPIC and FDA guidelines and publicly accessible medication information, we created patient-friendly annotation text blocks in Anni. We implemented the text block approach in Anni to facilitate re-usability, consistency, and multi-language support within the app.

The PharMe application creates personalized PGx reports by matching patients' genetic data with the annotated guideline and medication information. The app is designed to be easily adaptable to various health data sources, including laboratories and electronic health records. In PharMe, patients can view their genetic information (gene name, genotype, and phenotype), update their active medications, and receive PGx-guided information on the active and other actionable medications. The PGx-guided information is classified as "standard precautions", "use with caution", and "consider alternatives". Moreover, PharMe supports phenoconversion and PDF export of personalized reports to health care providers. Patients' health data is handled securely and stored in an encrypted form. PharMe currently includes information for 17 genes and 154 medications and is available for iOS and Android. There are plans to have Spanish, German, and Italian translations of PharMe in future versions.

An IRB-approved validation study is underway to assess patient comprehension, satisfaction, attitudes, and perceptions of PGx with PharMe, as compared to standard-of-care pharmacist-led telehealth counseling. In all, we have developed a tool that can potentially scale the clinical adoption of PGx globally to support the limited number of trained clinical PGx experts.

CYP2D6 haplotyping at scale: An analysis of All of Us research program participants

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CYP2D6 is highly polymorphic with complex structural variation. Contemporary genotyping approaches focus on common alleles and total copy number variation, but rarely characterize hybrid genes. Limited coverage of haplotypes and sparse inclusion of participants from underrepresented groups may lead to a lack of equitable translation of pharmacogenomics in all populations. Our goal was to comprehensively evaluate the frequency of CYP2D6 haplotypes in the large diverse All of Us Research Program (All of Us) using srWGS.

CYP2D6 haplotyping was completed using CRAM files from the All of Us v7 cohort (n=245,394). Haplotyping was completed with Aldy, Cyrius, PyPGx, and StellarPGx using a highly efficient and cost-effective approach. A consensus call was developed along with an open-source parsing engine to facilitate common nomenclature reporting based on recent recommendations by PharmVar.

A consensus genotype call was assigned to 97% (238,087/245,394) of participants. Of the participants with an assigned call, 21.5% (51,305/238,087) carried a structural variant and 8.10% (19,286/238,087) carried at least one copy of a hybrid gene. Importantly, 54.89% (129/235) and 50% (33/66) of haplotype and activity score frequencies by genetic ancestry were significantly different than reported by CPIC. Interestingly, 42.62% (104,594/245,394) had a predicted CYP2D6 phenotype which has recommendations from CPIC for a change in dosing or therapy. Lastly, 5.00% (12,251/245,394) of participants were found to carry a possible novel haplotype.

All of Us provides valuable data on CYP2D6 variation in one of the largest and most diverse cohorts. PGx variation was very common and significant deviations from known frequencies were identified. Future work will continue to build on the results as the All of Us dataset expands, and novel haplotypes are characterized. The code from the project along with the CYP2D6 haplotype calls from all tools will be made available within the All of Us Researcher Workbench.

Development of an Ancestrally Inclusive Preemptive Pharmacogenetic Testing Panel Designed to Inform Commonly Used Pharmacogenetic Drugs

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Many drug classes frequently prescribed for medically underserved patients include drugs with pharmacogenetic (PGx) guidelines available, but preemptive PGx testing remains a financial burden for this population. In addition, current clinical PGx implementation patterns have favored European and Asian ancestral groups since they have been the most extensively studied. However, patients of African or Native American descent have a higher frequency of genetic variants that may influence their drug response

compared to those of European descent. To overcome these barriers, we aimed to design a low cost, clinically validated PGx panel utilizable within diverse patient populations. Pharmacogenes included in the panel were prioritized based on the number of drug/drug classes the results would potentially influence as well as the clinical severity of the potential drug-gene interaction and the strength of available CPIC recommendations. The variants were included if they had allele frequencies of approximately 1% or greater in any major ancestral population. A customized panel using the MassARRAY System (Agena Bioscience, San Diego, CA) was developed to include variants meeting the criteria above. A total of fourteen genes/gene regions and sixty-two variants were included in the panel design, including a CYP2D6 copy number assay (Table 1). To reduce test cost, we minimized array hands-on time and automated the translation and reporting of results. The automation pipeline considers all haplotypes that could be defined by the panel variants and assigns the most likely genotype based on linkage disequilibrium data. Our goal is to continue streamlining procedures and batching strategies to reduce cost. We have developed a low per-test cost preemptive PGx testing panel that includes variants common across a diverse patient population. Studies are currently being conducted to determine the feasibility of clinically implementing this panel in a medically underserved population as well as the effect of implementation on patient medication satisfaction.

Table 1. List of genes and variants included in the preemptive genetic testing panel design

Gene	Variants
CYP2D6	*2, *3, *4, *6, *7, *9, *10, *12, *17, *29, *34, *39, *41, *64, *65, *69, *109, *119, copy number
CYP2C9	*2, *3, *5, *6, *8, *11, *27
CYP2C19	*2, *3, *4, *6, *8, *9, *10, *17
CYP3A5	*3, *6, *7
CYP2C Cluster	rs12777823
CYP2B6	*6, *18
CYP3A4	*22
VKORC1	rs9923231
SLCO1B1	*5, *15, *37
ABCG2	rs2231142
TPMT	*2, *3A, *3B, *3C, *24, *41
NUDT15	*2, *3, *4, *6, *9
NAT2	*5, *6, *7, *14
DPYD	c.1236G>A, c.557A>G

Influence of CYP2D6 and risperidone pharmacokinetics on side effects experienced by pediatric patients in Lagos, Nigeria

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Risperidone is an atypical antipsychotic drug used in the treatment of schizophrenia, bipolar disorder, and autism-related irritability in youth. Despite its efficacy for multiple psychiatric indications, risperidone use is limited by the various common side effects that occur. Most studies to date have involved patients of primarily European ancestry, with no studies involving pediatric patients in Africa. In this study, we assessed CYP2D6 genetic variation, plasma risperidone, and 9-hydroxyrisperidone concentration in a Nigerian pediatric population and assessed the impact on common side effects (weight gain, hyperprolactinemia, extrapyramidal symptoms [EPS], drooling, and drowsiness).

Patients ≤ 18 years old who were taking risperidone were recruited from the Child and Adolescent Mental Health Service Center of the Federal Neuro-Psychiatric Hospital, Lagos, Nigeria. Clinical characteristics, dosing information, and side effects were obtained from parents or abstracted from paper charts. CYP2D6 genotyping was performed on 211 samples by Agena MASSArray for >20 variants and copy number. Plasma concentrations of risperidone (n=133) and 9-OH-risperidone (n=198) were determined by LC/MS. Generalized linear models were used to test for associations between each side effect and CYP2D6 or risperidone pharmacokinetics while accounting for relevant clinical factors and time since the last dose.

Overall side effect burden was related to the patient's age, weight, and 9-hydroxyrisperidone concentration. Drooling and drowsiness were correlated with risperidone and total active moiety, both adjusted for time after dose, though in opposite directions ($p<0.05$). Weight gain and EPS were not associated with risperidone metabolism or CYP2D6 status. Hyperprolactinemia was observed most in female patients and associated with weight but was not associated with risperidone metabolism or CYP2D6 status.

These results indicate that CYP2D6 status would not be helpful in predicting risk of side effects from risperidone, but risperidone pharmacokinetics may be.

Administration of a Pharmacogenomic Dose of Methotrexate Reduces Arthritic Disease Burden in Mice Expressing hSLCO1B1*14

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Low-dose (15-25 mg/m2) methotrexate (MTX) is a front-line disease modifying anti-rheumatic drug used to treat autoimmune diseases such as juvenile idiopathic arthritis (JIA). Single nucleotide polymorphisms in the liver transporter SLCO1B1 result in either reduced clearance of MTX (*5), leading to increased drug exposure and toxicity, or increased clearance (*14) and reduced efficacy in the treatment of JIA.

Increased function alleles are expressed by 8-20% of patients and have been associated with reduced efficacy in retrospective studies of JIA patients. Prior mouse studies have demonstrated a dose-response relationship between methotrexate and collagen induced arthritis, where lower doses are effective in mice lacking the Slco1b2 ortholog of hSLCO1B1. The purpose of this study was to evaluate whether arthritic disease burden is reduced by transitioning from uniform (2 mg/kg subcutaneous) to pharmacogenomic (2.6 mg/kg subcutaneous in *14 only) dosing of MTX in arthritic hSLCO1B1*1 and *14 DBA1/J transgenic mice.

Comparisons of uniform and pharmacogenomic MTX dosing in *1 and *14 expressing mice were different in a Kruskal-Wallis test (p=0.018). Using a uniform dose, *14 expressing mice had 29% greater arthritic disease burden (arthritic index area under the curve; AI-AUC) than *1 mice (p = 0.098). When the increased pharmacogenomic dose was implemented for *14 mice, arthritic disease burden was reduced by 37% relative to the lower uniform dose in this genotype (p=0.023) and was comparable to *1 (p=0.77).

Our data demonstrates that mice expressing hSLCO1B1*14 have poor response to doses that are effective in *1 mice, which is consistent with our prior work demonstrating poorer response in JIA patients carrying this allele. Our finding that *14 mice respond better to increased doses supports the next step of a prospective clinical trial of pharmacogenomic driven MTX doses in patients with JIA to improve response in patients carrying the *14 allele.

The Prevalence of Abnormal CYP2D6 Phenotypes in those with Treatment Resistant Depression

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Objective: The role of abnormal CYP2D6 gene variants in treatment-resistant depression (TRD) remains unclear. This study aims to explore the association of abnormal CYP2D6 gene variants with TRD.

Methods: In this retrospective analysis of 356 patients from a large southwestern US hospital system, we investigated the difference in abnormal CYP2D6 variants between those with TRD and those with other depression. The TRD group was defined as patients who had undergone adequate trials of two different antidepressants and whose symptoms persisted beyond the treatment window, required augmentation, or resulted in a suicide attempt. Other Depression was defined as those who had been diagnosed with a depressive disorder, were treated with antidepressants, but did not meet the definition of TRD as reported in their psychiatric treatment record.

Results: Our analysis found a significantly greater prevalence of abnormal CYP2D6 variants in those with TRD (47.12%) compared to those with Other Depression (31.51%) (p=.04). These findings suggest that abnormal CYP2D6 variants play a role in anti-depressant failure, increasing the risk of TRD in affected patients.

Conclusions: Our study provides further evidence of the complex genetic factors that influence treatment response in depression. Prospective studies are needed to confirm these findings and to explore the clinical implications for patients with TRD. Such studies could include a specific definition of categories, using surveys to determine the extent of TRD and confirm depression remission. A better understanding of the genetic basis of TRD could lead to more personalized treatment approaches and improved outcomes for patients.

Unexpected Associations of CYP2C19*3 with Ocular Disease in the All of Us Research Program Cohort

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CYP2C19 is highly polymorphic, and its encoded enzyme metabolizes a number of drugs. Many previous studies have established that CYP2C19 loss of function alleles, such as CYP2C19*2 and CYP2C19*3, are associated with increased risk of cardiovascular events in the context of drug treatment. Our objective was to determine the associations between the CYP2C19 *2, *3, and *17 and a broad set of phenotypes in a large and diverse cohort using a phenome-wide association study (PheWAS) approach. We established a cohort from the All of Us Research Program that had both short-read whole genome sequencing and electronic health record (EHR) data. PhecodeX mapping was used to generate phenotypes in the form of phecodes (n=3,473). Using the PheWAS software PheTK, each genetic variant was tested independently (assuming an additive genetic model), using logistic regressions adjusted for age, sex,

PCs1-16, code occurrence count, condition count, and EHR length. We tested only phenotypes with at least 50 cases and used a Bonferroni correction to control for multiple testing. No statistically significant associations were found for rs4244285 (CYP2C19*2, minor allele frequency [MAF]=0.15) or rs12248560 (CYP2C19*17, MAF=0.20). In the complete diverse cohort of 140,985 individuals, rs4986893 (CYP2C19*3, MAF=0.0019) was associated with pigmentary iris degeneration (odds ratio [OR]=42.15, confidence interval [CI]=9.15-197.55, p-value=1.71x10-^{6}) and degeneration of iris and ciliary body (OR=33.3, CI=7.34-150.66, p-value=5.47x10-^{6}). In the complete cohort, the p-value for the Hardy-Winberg equilibrium (HWE) exact test for CYP2C19*3 was 1.60x10-^{32}, but within ancestry subsets HWE p-values were greater than 0.001. CYP2C19*3 has not previously been reported to be associated with ocular disease. These results should be viewed with caution and further studies need to be performed to replicate and validate this finding.

Lack of Association of HMGN3 Copy Number Variation with Warfarin Dose in a Hispanic and Latino Population

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Warfarin remains the most commonly prescribed oral anticoagulant for the treatment and management of thromboembolic disorders worldwide. To better predict an individual's warfarin dose requirements, numerous dose-prediction algorithms based on demographic, clinical, environment and genetic factors have been developed, including single nucleotide polymorphisms (SNPs) in CYP2C9, VKORC1, CYP4F2, and GGCX. Prior studies have associated copy number variants (CNVs) with stable weekly warfarin dose (PMID-36507737). This study addressed whether CNVs are associated with weekly warfarin dose in a Hispanic/Latino cohort. We investigated the association of CNV at 6q14.1 intersecting the High Mobility Group Nucleosomal Binding Domain 3 (HMGN3) gene among warfarin treated patients from a Hispanic/Latino cohort (n=113). DNA was amplified by Taq Mann® assay using primers for HMGN3 (target gene) and TERT (reference gene). Copy Caller® Software analyzed copy number experiment data for HMGN3 gene in relation to the known copy number of the target in the calibrator sample. Of the total samples screened, 57% had a predicted copy number of 2 similar to the positive control, 36% had 1 CNV, 4% had 0 CNV whereas only 1 (0.9%) sample had a predicted CNV of 4. HMGN3 CN did not show any association (β=-2.49 [SE 2.7]; p= 0.374) nor correlation with weekly warfarin dose (Kendall's tau=-0.056; p=0.404). A sample size of 113 was sufficient for 89% power to detect a beta of 4.94, based on the prior publication. Our results indicate that the HMGN3 gene CNV at 6q14.1 is not associated with warfarin weekly dose in Hispanic/Latino patients on a stable weekly dose of warfarin. Even though findings disagree with a previous study, associations with more modest effect sizes may be detected if further study is done with larger number of recruits representing different populations.

Population-Scale Variability in the Human Uridine Diphosphate (UDP)-Glycosyltransferase Gene Family

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Human UDP-glycosyltransferases (UGTs) are central regulators of the endogenous and exogenous metabolism. As highly polymorphic genes, broad clinical interest exists around UGT genetic variants explaining interindividual differences in drug response and cancer risk. However, the study of this gene superfamily genetic variation has not been equally done across all four human UGT subfamilies, in diverse human populations, and for all the existing variation in these genes, leaving the substantial majority of observed UGT variants functionally uninterrogated. Here we aimed to fully characterize human genetic variation in all 22 UGT genes at the population-scale. Using whole-exome and whole-genome sequencing data from the gnomAD data source we exome-wide explored the load of mutations in all human UGT genes across seven major populations and confirmed these genes are subjected to low selective constraints. Multiple computational methods for the prediction of missense variant effects were implemented, compared, and evaluated, and the prediction performances of all of them were exploited under a prediction framework optimized for UGT variants. We functionally characterized all exonic variants per gene, identifying novel candidate isoform-specific and intra-population variants with potential deleterious effects, some of which disrupt critical catalytic and substrate selectivity amino acids of UGTs, adding evidence to the molecular roles of the latter and supporting their putative deleteriousness when mutated. Lastly, we ascertained the variable deleterious mutational burden in UGTs per individual across populations, recognizing Africans, South Asians, Finnish and Ashkenazi Jews as high priority human groups to be studied. These findings

emphasize the need of conducting more precise and all-encompassing research when studying genetic variation in this gene superfamily, and represent a big initial step forward to recognize UGT variants with clear functional consequences required to serve in personalized clinical decision-making.

Atlas of Pharmacogenomic Variants Underpinning Adverse Drug Effects: Unveiling Critical Insights for Advancing Precision Medicine

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Increasing evidence supports preemptive pharmacogenetic testing for predicting and preventing adverse drug effects (ADEs). Despite PharmGKB's coverage, irregular updates and incomplete literature coverage can limit its utility. Previous systematic reviews have focused on individual drugs, genetic variations, or specific ADE types. This study compiled a comprehensive list of genomic variants associated with ADE risks, focusing on serious ADEs with significant mortality and morbidity implications. Identifying variant–drug pairs linked to serious ADEs is crucial for evaluating the scalability of implementing pharmacogenetic tests.

Two literature searches were performed to identify pharmacogenetic studies within randomized controlled trials (RCTs), post-hoc analyses of RCTs, and meta-analyses. MEDLINE, Embase, Cochrane Library and Google Scholar were systematically searched. Meta-analyses were conducted as appropriate. The list of variants associated with ADEs was further curated to create a set of variant–drug pairs significantly associated with serious ADEs with fully specified and interrogable genotypes.

The compilation included 254 RCTs, post-hoc of RCTs, and 207 meta-analyses investigating variants associated with ADEs. Chemotherapy-based regimens were the most common therapeutic modalities examined. Among the identified RCTs, we conducted 24 meta-analyses involving 39 studies. The only meta-analysis with a significant summary effect size was for the association between G6PD A– and severe anaemia in patients receiving CDA or artemisinin-based combination therapy for malaria OR[95% CIs]= 15 [10.27, 21.9], p<0.0001

This study produced a comprehensive list of variants associated with ADEs, without constraints on patient characteristics, pharmacological interventions, follow-up, toxicity outcomes, or variants investigated. It also curated a set of variant–drug pairs significantly associated with serious ADEs with readily interrogable genotypes. These lists serve as reliable resources for regulatory agencies, researchers and healthcare professionals. This study highlights the need for improved indexing and standardized definitions of ADE seriousness in the literature.

Genome-wide Association Study of Major Adverse Cardiovascular Events in Caribbean Hispanics on Clopidogrel.

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Clopidogrel is a P2Y12 receptor inhibitor with proven antiplatelet properties that requires hepatic activation by mainly the CYP2C19-mediated metabolic pathway. Genetic polymorphisms in clinically relevant pharmacogenes, such as CYP2C19*2, have been previously found to be associated with a significant reduction in clopidogrel's response, potentially leading to Major Adverse Cerebrovascular and Cardiovascular Events (MACCEs). Despite extensive research primarily centered on European populations, Hispanics and particularly Caribbean Hispanics (CH) remain significantly underrepresented. This paucity of data exacerbates health disparities among CH patients on clopidogrel, emphasizing the need to fill this knowledge gap. With a very diverse and highly admixed genetic background, undiscovered genetic variants linked to MACCEs are likely, stressing the need for expanding these studies to CH. This study aimed to identify genetic loci associated with on-clopidogrel MACCEs in the CH population. A conventional Genome-Wide Association Study (GWAS) was conducted on a cohort comprising 511 cardiovascular patients of CH descent from Puerto Rico. This cohort was stratified based on the presence or absence of MACCEs as a combined clinical endpoint of cardiovascular death, myocardial infarction, stent thrombosis or stroke, during a six-month post-percutaneous coronary intervention (PCI) follow-up period. While no signal reached traditional GWAS significance, four SNPs showed suggestive significance at chromosomes 2, 4, 7, and 12, p-values where 3.131×10-6, 1.839×10-6, 4.338×10-6, 1.415×10-7 respectively. These results represent novel preliminary findings not observed in other cohorts and highlighting the unique genetic landscape of CHs. This is the first GWAS of clopidogrel-related MACCEs outcomes in CHs, which identified potential novel markers in a diverse patient population. Further studies are warranted to replicate our findings in other diverse cohorts and meta-analyses.

Knowledge and Perception of Precision Medicine among Hospital Pharmacists in Nigeria: A Multi-Centre Study

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Background: Precision medicine focuses on tailoring treatments to individual patients based on their unique genetic, phenotypic, or psychological factors. Developed countries have gradually integrated PM into mainstream patient management. However, Nigeria still grapples with wide acceptance, key translational research, and implementation of PM. This study sought to explore the knowledge and attitude of PM among hospital pharmacists as key stakeholders in the healthcare team.

Methods: A cross-sectional study was conducted in six select tertiary hospitals across Nigeria. A 12-item semi-structured questionnaire was administered by hybrid (i.e. online and physical) methods and the results were analyzed with SPSS version 25. Descriptive statistics were used to summarize the data. A chi-square test was employed to determine the association between knowledge of PM and the sociodemographic characteristics of the study population.

Results: A total of 167 hospital pharmacists participated in the study. A high proportion of the participants were familiar with artificial intelligence (91.75%), pharmacogenomics (84.5%), and precision medicine (61%). Overall, 65 (38.9%) of the pharmacists had good knowledge, 80 (47.9%) had moderate knowledge, and 22 (13.2%) had poor knowledge of PM and associated terms. The level of knowledge did not correlate significantly with gender (X2 =3.21, p=0.201), age (X2= 5, p=0.27), marital status (X2 =3.21, p=0.201), and professional level (X2=6.85, p=0.144). The most important value of precision medicine to hospital pharmacists is the ability to minimize the impact of disease through preventive medicine (49%) while a large percentage of the participants are pursuing and or actively planning to pursue additional education in precision medicine.

Conclusion: There is moderate knowledge about PM, its related terms, and prospects among hospital pharmacists in Nigeria. Education modules in this field are highly recommended as most do not have a holistic knowledge of terms used in PM.

Herbal and Personalized Medicines in West Africa, Nigeria: Incorporating Omics Technologies

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The process of personalized medicines in West Africa is key due to varying genetic makeup and ethnic compositions as well as the use of herbal medicines in managing diseases. The aim of the article is to scrutinize recent technologies that could be used for assessments and conducting comprehensive examinations such as efficacy, toxicity using ex vivo, in vitro, and in vivo models, carcinogenic assays, toxicokinetic studies, and immunotoxicity assessments, contaminant checks for heavy metals and microorganisms.

"omics" refers to a collection of molecular investigations, such as proteomics, genomics, transcriptomics, and metabolomics, that utilize bioinformatics to gain a holistic understanding of biological entities and essential apt technologies for Personalized care of black race. High-throughput technologies, such as genomics, transcriptomics, proteomics, and metabolomics, enable the simultaneous identification of many genes and proteins. The advancements in exposomics, adductomics, and volatolomics have expanded the range of applications for omics in the diagnosis of diseases and therapeutic interventions.

Gene chip technology is one of the most powerful tools for elucidating the molecular mechanism and the network under laying the complex pharmacological function of herbal preparation.

One of the most remarkable applications of proteomics in herbal medi¬cine is the capability of this technique to identify different species

In conclusion, these scientific tools and methods jointly contribute to the standardization, quality control, stability testing, and safety assessment of herbal medical products, ensuring their dependability and efficacy.

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"Drug Metabolizing Enzymes Pharmacogenetic Variation-Informed Antidepressant Therapy Approach for Common Mental Disorders: A Systematic Review and Meta-Analysis"

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Introduction: Up to 30% of individuals with depressive disorders and 40% with anxiety disorders may exhibit inadequate responses to antidepressants. The present systematic review and metaanalysis was conducted to assess the clinical effectiveness and occurrence of adverse drug events (ADEs) related to pharmacogenetic variation-informed treatment(PGxIT) compared to usual treatment (UT) using antidepressants in patients diagnosed with CMDs

Methods: A systematic search was conducted in PubMed, Scopus, and the Cochrane Library from inception to December 30, 2023.Following PRISMA guidelines, data extraction was independently conducted by two authors, with cross-checking for accuracy. The risk of bias was assessed using the robvis tool, and publication bias was evaluated via Doi plots and the Luis Furuya–Kanamori (LFK) index. GRADE certainty assessment and sensitivity analyses were performed.

primary outcomes of the study includes, (1) Clinical efficacy outcomes: remission of anxiety and depressive symptoms; (2) Safety outcomes: reported ADEs in patients with CMDs. The meta-analysis estimated remission and ADE rates with corresponding 95% CIs using fixed effect models

Results: Eighteen studies (n = 7021 patients) were included. The findings of the systematic review of DMEs that included PGx IT were associated with superior efficacy in the remission of anxiety disorders and depressive symptoms compared to UT. A meta-analysis of 16 studies (n=5029 patients) on the remission of depressive symptoms revealed that PGxIT was superior to UT (RR 1.51 [95% CI: 1.33-1.70], I2 = 46%), with a lower risk of ADEs (RR=0.65; 95% CI=0.52-0.82; I2=0%). The certainty of evidence for both outcomes was moderate

Conclusions: This systematic review and meta-analysis revealed that compared with usual treatment, pharmacogenetic variation-informed antidepressant treatment is more effective at remission of depressive and anxiety symptoms with reduced incidence of ADEs in patients with CMDs.

Frequencies of Common and Uncommon CYP2C9 Polymorphisms in Syrian Population

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Background: CYP2C9, a key liver enzyme responsible for metabolizing a significant proportion (approximately 16-20%) of all drugs, exhibits extensive genetic variability that greatly influences drug metabolism. Several well-studied allelic variants of the CYP2C9 gene, such as *2, *3, *5, *6, *8, and *11, along with numerous unknown variants, have been identified. Understanding the frequency and functional impact of these variants is crucial in pharmacogenetics, particularly in populations such as Syrians where limited information is available.

Methods: In total, 138 individuals were enrolled in this cross-sectional study. Genomic DNA was extracted from peripheral blood of volunteers from the governorates of Damascus and Homs. Following optimization of PCR conditions, the specific amplification products were purified and sequenced. The prevalence of CYP2C9*2 Rs1799853 and CYP2C9*3 Rs1057910 was compared to other populations, and linkage disequilibrium LD between SNPs was reported.

Results: The genotype frequencies observed were as follows: 1/1 (56.5%), 1/2 (23.9%), 2/2 (0.7%), 3/1 (12.3%), 2/3 (4.3%), 3/3 (0%), 1/41 (0.7%), 2/41 (0%), 3/41 (0.7%), 1/46 (0.7%), 46/2 (0%), and 46/3 (0%). The frequencies of *2 and *3 alleles were 14.8% and 8.3%, respectively, with 43.5% of the study participants carrying at least one of these variants. Additionally, two intronic SNPs were detected; rs933120 and rs933119, with frequencies 12.3% and 6.1%, respectively, and high LD was found between rs933119 and rs1799853.

Conclusions: The prevalence rates observed in our study highlight the importance of genotyping prior to the initiation of narrow therapeutic index drug therapies, enabling the application of genotype-based personalized medicine.

Global Investigation of Clinical Implementation Strategies for DPYD and UGT1A1 Pharmacogenetic Testing to Guide Anticancer Therapy

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Background: The safety of several anticancer drugs is impacted by genetic variants in DPYD or UGT1A1. Dihydropyrimidine dehydrogenase, encoded by DPYD, is the rate-limiting step in the catabolism of fluoropyrimidines. Uridine diphosphate glucuronosyltransferase 1A1, encoded by UGT1A1, metabolizes irinotecan, belinostat, and sacituzumab govitecan-hziy. DPYD and UGT1A1 variants can encode for reduced function enzymes that result in elevated systemic drug exposures and increased risk of severe toxicities. Globally, the integration of DPYD and UGT1A1 testing into clinical practice varies greatly ranging from standard of care in some countries to limited clinical use in others. The objective of this study is to better understand successful strategies for integrating DPYD and UGT1A1 genotyping into patient care.

Methods: The PGRN – Implementation Working Group created a multinational writing group of 15 members from Africa, Asia, Europe, and the U.S. to develop a global survey investigating DPYD and UGT1A1 implementation strategies. Implementation was defined as DPYD and/or UGT1A1 testing that is performed for clinical use with a site having infrastructure in place to support test ordering, test interpretation, applying results to drug prescribing, and/or returning results to patients. The survey assessed different aspects of implementation including workflows, testing platforms, variants tested, clinical decision support, patient education, among others. The survey was refined over multiple virtual meetings and email communications.

Results: An 89-question survey was generated and built into REDCap for distribution to PGRN sites that have implemented, or are in the process of implementing, DPYD and/or UGT1A1 testing. The survey will be disseminated to sites in May 2024 with analysis of results in August 2024.

Conclusions: The PGRN – Implementation Working Group successfully developed a global survey investigating DPYD and UGT1A1 implementation strategies. The results of the survey will be presented at the PGRN Scientific Meeting 2024 poster session.

Potential value of preemptive early pharmacogenomic testing to guide psychiatric prescribing in primary care

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Objectives: Despite the documented improvement in clinical outcomes from preemptive pharmacogenomic (PGx) testing, its utilization remains limited. At St. Elizabeth Healthcare, primary care providers order PGx testing to guide psychiatric medications after multiple failures, often stating concerns with costs and reimbursement. This study aims to investigate the utility of early PGx testing by assessing the prevalence of actionable findings among patients prescribed psychiatric medications with Clinical Pharmacogenetic Implementation Consortium (CPIC) guidance.

Methods: A retrospective chart review was conducted for 134 patients who underwent testing in a primary care setting. Data collection included medications before PGx testing, reasons for testing, whenever available, and genotype-inferred phenotypes of three genes (CYP2C19, CYP2D6, CYP2B6). Medications assessed included psychiatric medications with CPIC guidelines (e.g. atomoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, venlafaxine, and vortioxetine). Tricyclic antidepressants were excluded. Actionability was defined as a phenotype with CPIC guidance for dose adjustment and/or titration speed. The prevalence of actionable phenotypes was calculated for the entire cohort (N=134), and specifically among those with prescribed psychiatric medication with CPIC guidance, prior to testing. (N=38)

Results: Among the 134 patients, 37% (N=50) received testing due to "treatment failure". Overall, 62% had actionable CYP2C19 phenotypes, followed by CYP2B6 (50%) and CYP2D6 (48.7%). Among patients previously prescribed sertraline (N=26), 42% had actionable phenotypes in either CYP2C19 or CYP2B6. Similarly,

among those previously prescribed (es)citalopram (N=21), 62% had actionable CYP2C19 phenotypes. Further, among patients previously on atomoxetine, fluvoxamine, paroxetine, venlafaxine, or vortioxetine (N=13), 46% had actionable CYP2D6 phenotypes.

Conclusion: In a limited sample of patients who experienced multiple failures with psychiatric medications and subsequently underwent PGx testing, we observed a high frequency of actionable phenotypes. Our findings suggest that earlier testing can provide additional value, potentially saving multiple treatment failures. Future research will investigate the association between these phenotypes, treatment failure, and economic implications.

Gene-based analysis identify four loci for Second Generation Antipsychotics (SGA)-induced Metabolic Syndrome (SGA-MetS)

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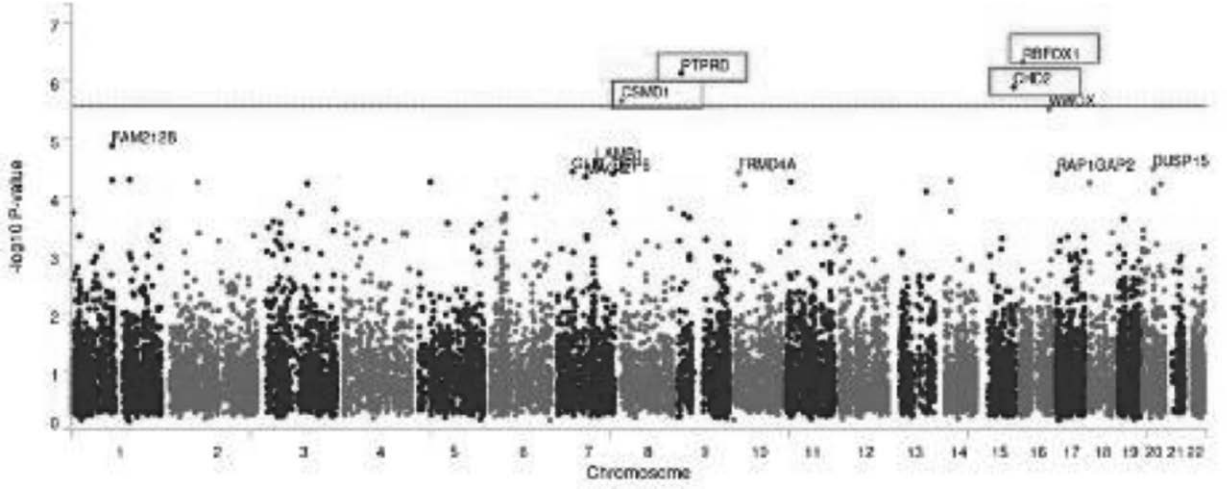
Background: Second Generation Antipsychotics (SGA) are the mainstay treatment of many mental disorders yet challenging because of their metabolic adverse events. Our study aimed to investigate genetic variation underlying SGA-induced metabolic syndrome (MetS) using a gene-based approach within the UK Biobank.

Methods: We created a case-control dataset (N=668 controls, 650 cases) for SGA-MetS using patient-reported medication data, lab values and ICD codes. A case was defined as a patient who reported taking an SGA and met three out of five of the National Cholesterol Education Program (NCEP) criteria of metabolic syndrome: 1) Blood pressure ≥130/85 mmHg, antihypertensive use or hypertension diagnosis; 2) fasting serum glucose ≥ 100 mg/dL, antidiabetic medication use or diabetes diagnosis; 3) serum triglycerides ≥150 mg/dL; 4) HDL-cholesterol < 40 mg/dL in men, and <50 mg/dL in women or antihyperlipidemic use; and 5) BMI ≥ 30 Kg/m2. A control was defined as an SGA user who met two or fewer criteria. We conducted a genome wide association analysis (GWAS) using SAIGE and adjusted for clinical covariates and ten principal components of ancestry. We used the GWAS summary statistics to conduct a gene-based analysis in Multi-marker Analysis of GenoMic Annotation (MAGMA), using the Functional Mapping and Annotation (FUMA) platform.

Results: Four loci RFBOX1 (ZSTAT=4.9, P= 4.9x10-7), PTPRD (ZSTAT=4.8, P= 7.6x10-7), CHD2 (ZSTAT=4.7, P= 1.3x10-6), and CSMD1 (ZSTAT=4.6, P= 2.2x10-6) were associated with SGA-MetS at the gene-level, significance threshold (P = 2.7x10-6 (Figure 1). RFBOX1 is an RNA-binding protein that regulates alternative splicing events. RFBOX1 is associated with weight and Insulin-like Growth Factor (IGF-1) levels. PTPRD has well documented associations with SGA-induced weight gain.

Summary: We confirmed the PTPRD association and identified other gene associations for SGA-induced MetS. These findings need to be validated in future studies, with additional experiments to understand the mechanistic underpinnings of these associations.

Fig. 1



Functional Characterization of a Rare CYP3A4 Variant in a Patient With Exceptional Cardiomyopathy During Sunitinib and Axitinib Therapy

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Sunitinib and axitinib can cause cardiomyopathy in up to 30% of patients. CYP3A4/5 are the primary enzymes responsible for metabolism of sunitinib and axitinib. A 58-year-old female with metastatic renal cell carcinoma experienced severe cardiomyopathy (maximum left ventricular ejection fraction drop of 34%) during sunitinib and later axitinib therapy that was reversed upon drug discontinuation. Whole genome sequencing data revealed that she was heterozygous for an extremely rare CYP3A4 variant (rs1483230173; p.P135L) that has not been functionally characterized or curated by PharmVar. The patient's CYP3A5 genotype was *3/*3. This study's objective was to characterize the function of this rare CYP3A4 variant.

CYP3A4 was expressed in 293FT cells via transfection of pENTR/D-TOPO vectors containing cDNAs of human CYP3A4, CYB5A, and POR. CYP3A4 activity was quantified using the Promega P450-Glo Luciferin-IPA assay in cells co-transfected with CYB5A and POR along with CYP3A4 plasmids, including the wild-type CYP3A4, CYP3A4*8 (rs72552799; p.R130Q), CYP3A4*30 (rs778013004; p.R130X), or the rare CYP3A4 variant (rs1483230173; p.P135L). Cells expressing the wild-type CYP3A4 were also treated with 1 μM itraconazole (CYP3A4 inhibitor) as an additional control. All luminescence values, as detected by a microplate reader, were normalized to viable cell count using the Promega CellTiter-Glo 2.0 Cell Viability Assay. All experimental groups were assessed using four biological replicates with 4-5 technical replicates performed for each biological replicate.

The average normalized luminescence, expressed as a percent of wild-type CYP3A4, was 2.3% ± 1.0% (mean ± SD) for CYP3A4*8, 0.4% ± 0.3% for CYP3A4*30, and 22.0% ± 7.1% for the p.P135L variant. Itraconazole reduced the luminescence in the wild-type CYP3A4 transfected cells by 94% ± 3.5%.

The p.P135L variant appears to be a reduced function CYP3A4 allele. This finding suggests that reduced metabolism of sunitinib and axitinib may have contributed to the patient's cardiomyopathy.

Functional Analysis of G6PD Variants Associated with Low G6PD Activity in the All of Us Research Program

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There is significant inter-institution variability in which G6PD variants are included in pharmacogenetic panels. Furthermore, there are over 800 G6PD variants which remain of uncertain significance, limiting clinical utility of G6PD genetic testing to reduce drug toxicity and other consequences of G6PD deficiency. We aimed to improve G6PD variant interpretations using data available in the v7.1 All of Us Research data and using a yeast functional assay.

G6PD coding variants were extracted from All of Us WGS data. G6PD activity was calculated as the measured activity value divided by the middle of the available or inferred reference range (details to be in poster). Each participant's lowest value was used. An exception was granted by All of Us to present findings of small sample sizes. Yeast assays tested human G6PD activity between strains transformed with plasmids containing the variants of interest.

We found that 13% of individuals with deficiency-causing variants would be missed by pharmacogenetic panels only testing the c.202G>A variant (alone or as the A- haplotype). We expand clinical interpretation for G6PD variants of uncertain significance; reporting that c.595A>G, known as G6PD Dagua or G6PD Açores, and the newly identified variant c.430C>G, reduce activity sufficiently to lead to G6PD deficiency. We also provide evidence that five missense variants of uncertain significance are unlikely to lead to G6PD deficiency, since they were seen in hemi- or homozygous individuals without a reduction in G6PD activity. We also applied the new WHO guidelines and were able to classify two synonymous variants as WHO class C.

In total, we have provided evidence to support new or updated classifications for nine variants according to both WHO and ACMG guidelines. We anticipate these results will improve the accuracy, and prompt increased use, of G6PD genetic tests through a more complete clinical interpretation of G6PD variants.

Genetic Variation in PTGS2 and Analgesic Response to Ibuprofen + Acetaminophen After Third Molar Extraction

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Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line analgesics for acute dental pain, but some patients require supplemental opioids for adequate pain relief. This study investigated the association between single nucleotide polymorphisms (SNPs) in PTGS2 and cyclooxygenase (COX)-2 activity and opioid use in patients following third molar extraction. Healthy adults (N=85, 18-37 years) underwent surgical extraction of partial or full bony impacted mandibular third molars. Prostaglandin (PG) E2 levels in lipopolysaccharide-stimulated whole blood plasma were measured to assess baseline COX-2 activity. At discharge, all patients received ibuprofen 400 mg plus acetaminophen 500 mg (IBU/APAP) as their primary analgesic regimen, with oxycodone 5 mg for breakthrough pain. Outpatient analgesic use was assessed on Day 7 after surgery. PTGS2 SNPs (rs20417, rs5275, rs2066826, rs4648276) were genotyped using Taqman Genotyping Assays. Patients with the rs5275 CC genotype had significantly lower baseline COX-2 activity ex vivo (median (interquartile range): 4.1 (2.3-6.6) ng/ml) compared to TT (10.5 (5.9-22.3) ng/ml; $p<0.05$)) and TC (10.4 (4.3-22.4) ng/ml; $p<0.05$). rs5275 genotype was associated with opioid use in addition to IBU/APAP ($p<0.05$ by chi-square test for trend), with a higher frequency of the C allele observed in patients who used opioids (56.3%) compared to non-users (35.0%; $p<0.05$). COX-2 activity was significantly lower in rs2066826 variant allele carriers (GA+AA: 6.4 (3.5-13.4) ng/ml vs. GG: 10.4 (5.5-22.5) ng/ml; $p<0.05$) and tended to be lower in rs20417 variant allele carriers (GC+CC: 5.8 (3.8-15.2) ng/ml vs. GG: 10.2 (5.2-22.3) ng/ml; $p=0.15$), but neither SNP was associated with opioid use. No associations with either COX-2 activity or opioid use were observed for rs4648276. rs5275 was associated with COX-2 activity and analgesic response to IBU/APAP after third molar extraction. Future studies are necessary to validate this association and determine whether rs5275 genotype can be used to guide analgesic therapy for post-surgical dental pain.

Activating Transcription Factor 3 Associated with Nausea in Gastroparesis Patients - a Whole Genome Sequencing Study

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Gastroparesis is a severe medical condition characterized by delayed gastric emptying and symptoms of nausea, vomiting, bloating, fullness after meals, and abdominal pain. Thus far, little is known about the genetic risk factors underlying gastroparesis nausea. We explored the association of genetic variants with nausea severity in a clinical gastroparesis study.

Whole genome sequencing data was obtained from adults with diabetic or idiopathic gastroparesis. Nausea score was assessed from a daily symptom dairy with a range from 0 mild to 5 severe. GWAS using linear model was conducted on variants with MAF ≥0.01 with adjustment of the subject's age, sex, BMI, etiology, and the first 3 PCs.

Variant clusters from multiple genes are significantly associated with baseline nausea score at p=1e-5 level. Top variants are within ATF3, PP2D1, CNTN4, BMP2, ABL1, CTNNA3 and KIF6. Interestingly, upon comparing our results with a transcriptomic analysis, we found that ATF3 and BMP2 were overlapping with genes differentially expressed in both diabetic and idiopathic gastroparesis when compared with controls. ABL1 was, however, differentially expressed in diabetic cases whereas CNTN4 was differentially expressed in idiopathic controls.

We expanded the analysis with single gene tests which shows that ATF3 is significant especially for MAF>0.05 variants (SKAT p=0.02). The top variant in ATF3 is rs79151334 (beta= 0.68, p=5.76e-6). Additionally, we report new associations of CTNNA3, PP2D1, and KIF6 as well as a cluster of variants between CDH2 and MIR302F, with baseline nausea score. Among those, ATF3 modulates the immune response, atherogenesis, cell cycle, apoptosis, and glucose homeostasis, and both CTNNA3 and CDH2 encode cadherin related proteins, suggesting this type of junction could play a role in the underlying mechanism.

Here we identified potential nausea related variants involved in immunological responses and metabolism that could provide further understanding of the pathophysiology to be tested in future investigations.

A Study on the Pharmacogenomics of New Oral Newer Oral anticoagulants (NOAC) in Patients of a Tertiary Care Hospital

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[4]*School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, India*,
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Background: Non-Vitamin K Antagonist Oral Anticoagulants have revolutionized the management of thromboembolic disorders. The inter-individual variability in treatment response and adverse outcomes necessitates a deeper understanding of the pharmacogenomic factors influencing NOAC efficacy and safety. Polymorphisms in CES1, P-glycoprotein ABCB1 have been implicated in altered NOAC metabolism and transport, affecting drug levels and efficacy.

Aim: The Primary Objective of the study is to determine the genetic factors behind the occurrence of NOAC failure. To determine the average time duration between anticoagulant use and occurrence of a thrombo-embolic event.

Methodology: A study was done on Stroke and AF patients who were on NOAC therapy. After collecting the data, the blood samples of the patients were taken and analyzed using HRM-PCR and sanger sequencing.

Result and Discussion: The following SNPs rs1128503, rs4148738, rs2231142, rs8192937 were found to have significant association with the occurrence of ischemic events in European and Asian populations. For rs2231142, 17 variations (4 cases) were found (p=0.432), for rs4148738, 10 variations (3 cases) were found (p=0.519), for rs8192937 4 variations (2 cases) were found (p=0.829) and no variations were found for rs1128503.

Conclusion: Genetic mutations in individuals can contribute to NOAC failure and an increased risk of repeated thrombotic events Alongside adherence, drug interactions, and interindividual genetic variation plays a significant role as a risk factor for NOAC failure. Certain SNPs, such as rs4148738, rs8192935, and rs2231142, have been associated with an increased likelihood of thromboembolic events in NOAC patients. However, not all genetic variants demonstrate meaningful relationships as observed with rs112850. The findings of this study can inform clinical decision-making and guide the usage of NOACs in patients having specific genetic profiles. By identifying genetic factors that may affect a patient's response to NOACs, healthcare providers can make more informed decisions about the appropriate use of these medications.

Genetics of G Protein Coupled Receptor (GPCR) Signaling: Relevance of Genetic factors in Ligand-free GPCR Signaling

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This overview addresses an underexplored area of GPCR genetics, namely ligand-free signaling. GPCRs signaling is thought to result from an active agonist-GPCR-G protein (or -arrestin) complex, with each GPCR existing in multiple distinct states. However, ligand-free GPCR basal signaling is pervasive, also involving distinct states and pathways (Sadee, Molecules 2022,27,5826). Many GPCRs signal spontaneously at levels often thought to be of little physiological relevance unless genetic mutation reveal pathophysiology. Less well appreciated is the process when the agonist dissociates from the activated receptor complex which then continues signaling, termed here 'acutely activated ligand-free signaling', potentially a prominent process for many GPCRs. In addition, continued receptor stimulation can further regulate and remodel the active ligand-free receptor complex and cause relocation to cellular sub-compartment, exerting various physiological functions. For example, we had proposed that repeated activation of the opioid receptor results in sustained basal signaling that drives opioid dependence (Sadee and McKew, Molecules 2022,27,5826. https://doi.org/. Genetic studies have revealed numerous examples of disturbed basal signaling with pathophysiological consequences. Novel methods are needed to measure acutely activated or sustained regulated ligand-free signaling, followed by genetic studies to reveal yet unknown factors in drug response, for example in opioid addiction and depression.

Impact of CYP3A5 genotype on tacrolimus management in adult heart transplant recipients

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Despite the established association between CYP3A5 genotype and tacrolimus exposure and dose requirements, clinical genotyping for CYP3A5 is not standard of care

at most transplant sites. In our adult heart transplant population patients are started on a fixed tacrolimus dose that's adjusted until therapeutic exposure is achieved and patients typically remain inpatient until the tacrolimus is therapeutic. A "booster" treatment may also be initiated if a therapeutic exposure is not achieved quickly. This study was performed to assess the impact of CYP3A5 genotype on tacrolimus dose requirements, time to achieve therapeutic steady-state (TSS), use of boosters, and length of stay (LOS) in adult heart transplant recipients. Clinical data was extracted from the electronic medical record. CYP3A5 genotypes were obtained from an internal research biorepository and categorized into phenotypes per CPIC definitions. The time to reach a TSS trough, tacrolimus dose (mg/kg) at TSS, and LOS were compared among CYP3A5 phenotypes via Mann-Whitney U or Kruskall-Wallis tests. Use of boosters was compared among CYP3A5 phenotypes via Chi-squared. 86 subjects achieved a TSS trough for inclusion in the analysis; 14 of these subjects had a CYP3A inhibitor. In CYP3A5 expressors, tacrolimus doses were ~40% higher at TSS ($p<0.01$) and time to achieve TSS was significantly longer (14 vs 10 days; $p=0.03$); these associations were similar when subjects with drug interactions were excluded. CYP3A5 expressors were more likely to receive a concomitant booster (37.5% vs 5.4%, $p<0.01$). LOS did not differ among CYP3A5 phenotypes. A post-hoc analysis of subjects discharged before or +1 day of TSS without drug interactions did find a numeric difference in LOS (17 vs. 13 days,$p=0.08$). Implementing CYP3A5 genotyping for adult heart transplant could help reduce the time to reach TSS and potentially post-transplant LOS in patients who are CYP3A5 expressors.

Using Bayesian Variable Selection to Develop a Minimal Genotype-Based CYP2A6 Activity Prediction Score

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CYP2A6 metabolically inactivates nicotine. Its activity is genetically variable, where higher activity is associated with increased smoking and risk of smoking-related health conditions. CYP2A6 activity is measured in vivo in regular smokers using the nicotine metabolite ratio (NMR: 3'-hydroxy-cotinine/cotinine). CYP2A6 has many common functionally impactful alleles. Genetic scores have been developed in order to predict CYP2A6 activity (particularly useful in studies without NMR data), using top hits from genome-wide association studies and known CYP2A6 alleles. In this study, we used an iterative Bayesian stepwise selection method to identify functionally important CYP2A6 variants in a European-ancestry (EUR) population, then used its output to construct a simplified NMR prediction score.

Genotypes for n=933 EUR individuals were obtained by merging data from: amplicon sequencing of CYP2A6 exons, an Illumina SNP array, and TaqMan structural variant (SV) genotyping assays (n=57036 variants). Genotypes were analyzed using the R package SuSiE with log-transformed NMR (logNMR) as the outcome. Variants identified by SuSiE as likely causal (>95% posterior inclusion probability) formed the inputs of a genetic score, generated using linear regression. The score will be evaluated in a validation dataset (n=196 EUR).

SuSiE analysis identified five credible sets of functional variants composed of: rs56113850, CYP2A6*2, CYP2A6*9 (in a set with two highly correlated SNPs), CYP2A6*12, and CYP2A6*53. Within the training dataset, a score composed of these five variants captured 39% of logNMR variation ($R2=0.39$).

This simplified CYP2A6 activity prediction score captures approximately the same portion (or more) of variation as recent genetic scores with more variants, allowing for more rapid genotyping and scoring. It can be used to predict logNMR in datasets without NMR data or including non-smokers. The functional relevance of rs56113850 as a causal variant itself, or a tag for causal variant(s), must be investigated further.

Retrospective study shows pharmacogenomic testing could reduce adverse events associated with clopidogrel use by 38%

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Objective: Existing efforts have developed recommendations to alter the use of several commonly prescribed drugs based on patient genotype. We demonstrate the real world implications of the use of pharmacogenomic testing through a retrospective study of adverse events in individuals with clopidogrel prescriptions given without testing.

Methods: We analyzed ~100K individuals from population health studies administered at multiple medical centers sequenced using the Helix Exome+® assay. We genotyped all individuals for CYP2C19 star alleles. We identified the formulation and inferred dosage of clopidogrel by processing the prescription with GPT-4. We checked concordance with the CPIC clopidogrel use guidelines based on individual CYP2C19 genotypes (Bousman et al. 2023). We define instances of thrombosis using a comprehensive codeset based on ICD9, ICD10, and SNOMED terms.

Results: We identified 27,688 clopidogrel prescriptions given to 2,444 participants. Of these,1,283 individuals had a calculable precise daily dose. 25% of these individuals have a mismatch between the recommended clopidogrel dosage guideline based on their CYP2C19 genotype and their prescribed dose. 12% of these mismatched individuals are poor metabolizers (PM), who should not use clopidogrel at all. The remaining 88% are intermediate metabolizers (IM). PMs and IMs receiving clopidogrel are much more likely to experience thrombosis than other metabolizers. 25% of PMs experienced thrombosis after the initiation of clopidogrel, with 40% of these occurring in the first two months (vs normal metabolizers, binomial p-value = 0.001).

Conclusions: As expected from a lack of testing and a high population frequency of pharmacogenomic variants, many patients are prescribed doses of clopidogrel that are too high given their subsequently derived pharmacogenomic information. There is at least a 38% excess of adverse events (as measured by thrombosis) in this group. At minimum, this testing could prevent 1 thrombosis event per every ~30 people prescribed clopidogrel, demonstrating tangible benefits of population-based pharmacogenomic testing.

Potential Impact of a Multigene Panel To Guide Oncology and Supportive Care Medication Prescribing Among Patients Receiving Single-Gene DPYD Genotyping

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Patients with cancer are often prescribed chemotherapy and supportive care medications with pharmacogenomic implications. The objective of this retrospective single-center study was to estimate the number of additional medication interventions per year that would be possible by using a multigene panel in patients currently receiving single-gene DPYD genotyping. We evaluated the frequency of orders for irinotecan or supportive care medication(s) with a CPIC guideline ("PGx medications") after the return of DPYD results among patients undergoing in-house DPYD genotyping in 2023. Phenotypes with non-indication/criteria specific recommendations to use an alternative agent or non-standard dose or titration schedule were considered actionable. Phenotype frequencies were estimated based on the cohort's self-reported race using CPIC frequency tables. To calculate the number of potential interventions per medication or medication class per year, the estimated frequency of each actionable phenotype was multiplied by the number of patients prescribed the medication and summed if multiple actionable phenotypes. In 2023, 655 patients underwent in-house DPYD genotyping; 334 (51%) male, 466 (71%) White, 147 (22%) Black. Most patients 518 (79%) had gastrointestinal cancer and 31 (4.7%) had an actionable DPYD result. There were 1,254 PGx medications prescribed for 586 (89%) unique patients after DPYD results were available. Most patients 556 (85%) received ondansetron, followed by proton pump inhibitors 219 (33%), codeine/tramadol 127 (19%), and irinotecan 102 (16%). An additional 151 medication interventions were expected if a multigene panel was used in 2023. Proton pump inhibitors yielded the most potential interventions per year 77 (51%), followed by sertraline 16 (11%), ondansetron 15 (9.9%), citalopram/escitalopram 13 (8.6%), and irinotecan 13 (8.6%). Use of a multigene panel can increase the number of interventions per year by nearly six-fold and should be considered in patients receiving DPYD genotyping. A pilot study to enroll patients receiving DPYD genotyping for multigene testing is in development.

Ancestry-Stratified Genome-Wide Association Meta-Analysis of 5-FU Induced Toxicity

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Colorectal cancer (CRC) patients are commonly treated with fluorouracil (5FU). 5-FU-containing regimens cause toxicity that is more frequent and severe in those with genetically reduced function dihydropyrimidine dehydrogenase (gene = DPYD). However, 5-FU toxicity also occurs in those without known DPYD variants; thus, the genetic underpinning for 5-FU toxicity could involve undiscovered variants in DPYD or other genes. We aimed to discover variants potentially contributing to higher risk for 5-FU toxicity.

We performed a meta-analysis across ancestries of a genome-wide association study of 5FU-induced grade

3-4 diarrhea in colorectal patients (n= 4617, dbGaP phs001290). Prior to the meta-analysis, individuals were stratified into European (EUR, n=3841), African (AFR, n =319), East Asian (EAS, n=185), American (AMR, n=149), South Asian (SAS, n=15), and admixed (mixed, n = 108) ancestry groups using 1000 Genomes Project Phase 3v5 reference panel. Admixed individuals were those with a superpopulation proportion <0.60 of their global ancestry. Genomes were imputed using TOPMED reference panel (r-squared >0.3). Variants were filtered for genotyping rates≥98%, MAF>1%, and LD <80%. Logistic regressions were performed in the stratified groups with sex, age of diagnosis, BSA, and study site as covariates. Inverse variance fixed-effects meta-analysis of results was performed and results visualized with the Bonferroni corrected significance threshold for 1,813,574 variants (p-value < 2.8x10-08).

An intronic variant in UHRF1BP1, rs556793499, reached genome-wide significant association with 5FU toxicity (p-value = 1.4 x10-08, OR = 7.2). Nine more common variants in DPYD had p-values < 0.001. Prevalence of diarrhea varied significantly by ancestry (SAS = 20.0%, EUR = 11.1%, AMR = 8.1%, EAS = 4.9%, AFR = 4.1 %, mixed = 2.8%, chi-squared p-value = 8.6x10-6).

We discovered several genes potentially contributing to 5-FU toxicity and that 5-FU toxicity differs by genetic ancestry. Further investigation is needed to determine the mechanism underlying these associations.

A pilot study to assess the frequency of CYP3A5*3 genotype in Nigeria

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The altered protein structure of cytochrome P450 (CYP) drug-metabolising enzyme is known to diminish or abolish its metabolic capacity. Among the CYP3A subfamily, CYP3A5 molecular diversity has been associated with altered pharmacokinetics of CYP3A5 substrates as well as defective therapeutic outcomes and disease risks, particularly CYP3A5*3 polymorphs. However, data to reflect the landscape of CYP3A5*3 polymorphisms in Nigeria is rarely available. This study investigated the existence of CPY3A5*3 polymorphism and its prevalence in Southwest Nigeria. Sixty-nine women were recruited from four health facilities in Nigeria, blood samples were collected as dried blood spots (DBS) and human genomic DNA was extracted from DBS samples using Omega E.Z.N.A DNA-isolation kits. Genotyping to detect single nucleotide polymorphism (SNP) in the gene coding for CYP3A5*3 g.6986A>G (rs776746) was performed by real-time PCR Taqman® assay. 68 participants were genotyped successfully. Genotype frequency for CYP3A5*3 g.6986A>G (rs776746) was distributed as AA 71% (n =48/68), AG 22% (n =15/68) and GG 7% (n =5/68). The frequency of CYP3A5*3 g.6986A was 82%, while CYP3A5*3 g.6986G was expressed as 18%. CYP3A5*3 polymorph, which occurs from alternative splicing and protein truncation was found in this study. The genetic variant which results in almost complete annulment of CYP3A5*3 activity had a prevalence of 18%. This conforms to the spectrum of CYP3A5*3 variants in other African populations. However, a widespread study of this polymorph's prevalence across Nigeria and its impact on therapeutic outcomes is highly desirable.

Integrating Pharmacogenetic Testing into Elective Coronary Catheterization: A Pilot Study

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Beginning January 2024 the pharmacogenomics (PGx) specialist for an academic medical center in Rhode Island began screening patients scheduled for elective coronary catheterization procedures to identify individuals for whom P2Y12 inhibitor therapy was likely so PGx testing could be ordered through a commercial laboratory ahead of their procedure. This study was a retrospective review to investigate the efficiency and impact of this service.

Between 1/12/24 and 4/3/24, a total of 415 patients were screened and 212 patients were deemed eligible and had PGx testing ordered. To date, 93 patients have had results returned: 14% before their procedure and 86% after. The post-operation rate of P2Y12 inhibitor prescribing for patients who had PGx testing ordered was 62% (113/181 patients). For patients whose results were not back at the point of post-op P2Y12 prescribing, 72% (38/53) were prescribed clopidogrel. It was revealed that 8 of these 38 patients had decreased CYP2C19 activity (6 intermediate metabolizers and 2 poor metabolizers). All 8 of these patients were subsequently switched to an alternative P2Y12 inhibitor at the recommendation of the PGx specialist (100% recommendation acceptance).

Testing was ordered an average of 11 days prior to the procedure, and the average turnaround time from order to results was 15 days. The PGx specialist spent an average of 130 minutes per day on the pre-catheterization workflow (21 minutes screening patients, 22 minutes placing the PGx lab order via the third-party laboratory's portal, and 87 minutes documenting and providing patient education).

These results show a considerable impact on improving P2Y12 inhibitor prescribing. Further work is needed to refine screening criteria, reduce time spent documenting and providing patient education, and reduce the turnaround time to improve efficiency of this process.

Implementing Pharmacogenomics at a Pediatric Hospital

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Pharmacogenomic (PGx) implementation faces multiple challenges and barriers. The objective is to describe implementation strategies, components, and initial results of a PGx program at a tertiary pediatric hospital. The Personalized Medicine Institute at Nicklaus Children's Hospital implemented a PGx program that went live in September 2023. The PGx program development included: securing funding, integrating third-party clinical decision support software (CDSS) in electronic health records (EHR), developing an in-house PGx laboratory, educating providers, initiating research and process improvement projects, and promoting pharmacist-led clinical services. Initial funding for the PGx program development and inpatient PGx testing was secured via hospital budget, charitable foundations, and appropriations funding from the State of Florida. PGx education was provided utilizing in-services, grand rounds, lunch-and-learns, pharmacy residents' rotations, and one-on-one physician education. Education targeted physicians, pharmacists, nurses, medical and pharmacy residents. A customized PGx panel was developed considering the unique South Florida population to accommodate rare alleles that are present in Caribbean and Central and South American populations. PGx test order for buccal sample collection was placed in EHR. Third-party PGx CDSS was built into the EHR platform to integrate PGx test results from the in-house lab for automated live alerts when drug-gene interactions are detected during a medication order placement. Research collaborations and initiatives were established to promote further PGx implementation and funding. Internal process improvement projects involving PGx data were initiated to monitor program success. PGx pharmacist-led services included pharmacist-to-pharmacist and pharmacist-to-physician consults and return of results to patients' families. From September of 2023 through March of 2024, we tested 137 patients at the in-house laboratory. At least six patients had immediate and significant interventions based on drug-gene interactions. Successful PGx implementation consists of a well-coordinated strategy involving multiple interdependent components for a lasting sustainability.

Characterization of drug-associated CYP3A4 regulatory variants for personalized drug dosage adjustment

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Drug metabolism, particularly via cytochrome P450 (CYP) enzymes, plays a crucial role in determining drug efficacy and toxicity. Among CYP enzymes, CYP3A4 is responsible for metabolizing over 50% of drugs and exhibits significant interindividual variability in expression levels due to genetic variations in its regulatory elements (REs). Despite their importance in pharmacogenomics, the functional effects of most CYP3A4 genetic variants remain poorly understood, hindering personalized drug dosing strategies.

We aimed to identify and quantify genetic variants in CYP3A4 regulatory elements across populations, cancer genomes and human evolution and functionally characterize these variants.

Traditional approaches to identifying genetic variants fail to annotate infrequent variants and accurately determine allele frequencies due to a small sample size. The accumulation of publicly available whole genome sequences and personal genomic databases opened the opportunity to overcome this obstacle. Here naturally occurring variants in CYP3A4 REs and their frequencies in the general population and nine different ethnic groups were mapped using genomic data from four sources: 1) The Genome Aggregation Database, with data of 76,156 genomes from nine different ethnic populations; 2) The Cancer Genome Atlas (TCGA) covering genomes across 2,577 patients and 21 tissues; 3) A collection of whole-genome sequences of 180 individuals from 12 indigenous African populations collected by the Tishkoff lab (UPenn); 4) The genome assemblies of two archaic humans: Denisovan and Neanderthal.

A Massively parallel reporter assay (MPRA) was used to characterize the functional effect of the identified variants. MPRA, a method where thousands of sequences are placed alongside a transcribed barcode, provides the ability to functionally test thousands of sequences in a high throughput manner in a proper cellular context.

This research addresses a knowledge gap in pharmacogenomics by characterizing CYP3A4 regulatory variants. The findings will contribute to optimizing drug therapy by enabling tailored drug dosing based on individual genetics.

Evaluation of Outpatient Pharmacogenomic Medication Prescribing Patterns in Relation to Community-Level Social Determinants of Health

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Understanding the relationship between social determinants of health (SODH) and PGx medication prescribing patterns may help facilitate equitable PGx implementation. We compared the prescribing frequencies of PGx medications among those experiencing different levels of social deprivation and social vulnerability in Colorado (CO). We conducted a retrospective analysis of adult patients prescribed at least one PGx medication in an outpatient setting at UCHealth in 2018. We evaluated the prescribing frequencies of 105 CPIC level A, A/B, and B medications. Social deprivation was determined using the Robert Graham Center's social deprivation index (SDI). Social vulnerability was determined using the CDC's social vulnerability index (SVI). SDI and SVI scores are percentile ranks indicating the extent of disadvantage in a community, with higher SDI and SVI scores indicating higher disadvantage. We used logistic regression to assess the relationship between SDI and SVI scores and the likelihood of being prescribed three or more PGx medications in an outpatient setting, while adjusting for demographics, geographic factors, and comorbidities. The analysis included 84,721 patients, with 6.4% residing in a CO rural area, 41.1% males, 84.3% white, 9.5% Hispanic, and mean age=55±17 years. The mean number of PGx medications prescribed was 1.47±0.81 and 10.1% of patients were prescribed three or more PGx medications. The median SDI and SVI scores in our cohort were 30 and 24, respectively, which are lower than the national median of 50. After adjusting for covariates, SVI score was significantly associated with being prescribed three or more PGx medications (OR 1.10; 95%CI:1.0-1.20; p=0.04), while SDI score was not associated with the outcome (OR 1.0; 95%CI:1.0-1.0; p=0.81). SVI, but not SDI, score was a modest predictor of yearly PGx medication burden in the outpatient setting. Additional studies evaluating SODH, including SVI, in relation to PGx medication prescribing and testing are needed in diverse patient populations.

Characterizing Hypertension in the United States: Insights from the All of Us Research Program

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Hypertension (HTN) remains a significant public health concern as the primary modifiable risk factor for cardiovascular disease. Apparent treatment-resistant HTN (aTRH), defined as requiring ≥4 antihypertensive classes to achieve blood pressure (BP) control, is a particularly high-risk HTN phenotype. We sought to evaluate prevalence, characteristics, predictors and genomic factors associated with HTN and aTRH in the All of Us (AoU), using 15-years of historical data. In AoU, we identified all adults with age data, ≥1 BP-measurement, prescribed ≥1 antihypertensive medication, and with ≥1 SNOMED "Essential hypertension" diagnosis code. Using this base cohort, we applied validated computable phenotypes of HTN and aTRH. We then added a criterion of having their Global Diversity Array data available in a separate cohort. We initially identified 99,461 HTN patients meeting eligibility criteria. Following the application of our validated computable phenotypes, an overall population of 81,462 were further categorized to aTRH (14.4%), Stable-Controlled HTN (SCH) (39.5%) or Other HTN; not meeting the criteria for aTRH nor SCH (46.1%). Patients with aTRH were older, more likely to self-report as Black or African American, had higher levels of social deprivation, and heightened prevalence of comorbidities such as hyperlipidemia and diabetes. Heart failure, Black or African American race and diabetes were the top predictors for aTRH. Beta-blockers were the most prescribed antihypertensives overall. The overall BP-control rate at index-date was 62%. We further identified 88,613 patients with available genetic data, 72,701 patients after applying our computable phenotypes, where 10,202 were classified as having aTRH (14.0%), 20,075 as having SCH (27.6%) and 42,424 as Other HTN (58.4%). The exceptional diversity in AoU provides a unique opportunity to characterize HTN in the US. Consistent findings with our prior research highlight the interoperability of our computable phenotypes. The study will continue to explore genomic factors associated with aTRH and adverse cardiovascular outcomes.

Enhancing Pharmacogenomic Predictions for Hospitalizations: Machine Learning Approach Using FDA's Adverse Event Reporting System and Virginia's All Payers Claim Database

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Recent studies show genetic testing can both identify individuals at risk, and those less likely to have opioid dependence. Despite this, pharmacogenomic testing has drastically dropped in Virginia in recent years. Machine learning can potentially identify those at high risk for opioid dependence through pharmacogenomic testing and even offer genetic counseling in individuals at risk. This study aims to show how drug data from available Virginia public datasets can be used for a predictive model to reduce hospitalizations.

Data is sourced from Virginia's All Payer Claims Database and FDA's Adverse Drug Event Reporting System (FAERS) database.

CPIC data queried via CPIC API. (https://api.cpicpgx.org/)

For our case study we filter APCD data to Richmond, VA area zip codes.

We use years 2016-2019 for training a CatBoost gradient boosted tree machine learning model with year 2020 as the final validation year. CatBooost was selected based on its design to specifically handle categorical data.

An initial model will be built with data from Virginia's APCD. A second model will include a 25% increase in data volume based on a data augment from the FAERS database for the same time period.

Models will use Recall as primary accuracy metric with CatBoost's loss function change feature importance value as the method for evaluating which CPIC drugs influence hospitalization outcomes.

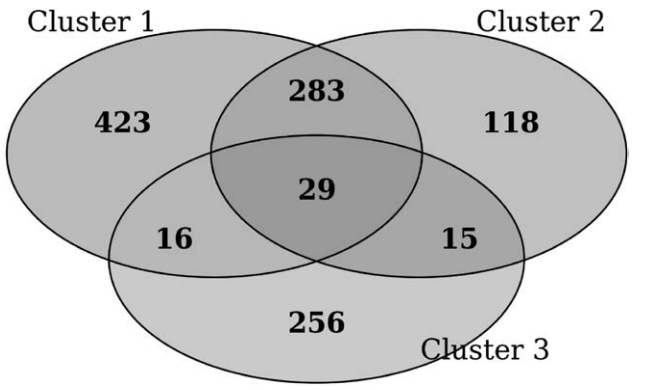
Model 1 performance with APCD. F1 Score: 0.75, Recall: 0.84, Precision: 0.68, ROC Score: 0.9139024

Model 2 performance with APCD and FAERS. F1 Score: 0.75, Recall: 0.80, Precision: 0.68, ROC Score: 0.89

Model 1 identified 751 drugs that influence hospitalizations. Model 2 (with the additional FAERS data) identified 445 drugs. 315 drugs with CPIC guidelines. Figure 1 is overlap between all three groups (APCD model, FAERS/APCD model, CPIC Guidelines)

Pharmacogenetic testing specific to these drugs may allow identification of those at most risk for hospitalization.

Fig. 1



Multi-Omic Drivers of Hepatic Drug Metabolism in African Americans

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Background: Variation in drug metabolizing enzymes (DMEs), their regulatory regions, or within regulatory proteins can contribute to interindividual variability of drug response and adverse drug reactions. Multi-omic data can give regulatory context to genomic regions of unknown function. Current multi-omic studies underrepresent minority populations, making results difficult to interpret and limiting their predictive clinical value. This study aims to identify genetic variation and epigenetic changes associated to pharmacogenomic genes using primary human hepatocytes in an African American (AA) cohort.

Method: Hepatocytes extracted from 75 AA cadaveric livers were genome-wide genotyped, mRNA sequenced, and DNA methylation profiled. Quantitative trait mapping (eQTL, eQTM, mQTL) was conducted with age, sex, and genomic principal components 1-2 as covariates. Probabilistic estimation of expression residuals (PEER) factors were calculated from the gene expression data to account for unmeasured confounding variables in transcriptome and methylation data. Significant results were prioritized based off overlap between quantitative trait mapping results and PharmGKB annotation.

Results: eQTLs, mQTLs, and eQTMs were identified, some with previous links to drug metabolism and differential allele frequency between AA and European populations. One variant, rs1332018, is a 5' UTR variant associated with increased GSTM3 expression (eQTL), decreased methylation at 5 different CpG sites (mQTL), and all five CpG sites are associated with GSTM3 expression (eQTM).

Conclusion: A significant portion of genetic variants that associate to gene expression (eQTL) associate to DNA methylation proportion (mQTL). CpG sites under genetic regulation (mQTL) largely do not overlap with CpG sites which regulate gene expression (eQTM). Rs1332018, (overlaps eQTL, mQTL, and eQTM) is associated with the known phase II DME GSTM3. These results will be integrated within statistical finemapping methods to prioritize results from a drug metabolism GWAS within the same cohort, resulting in a comprehensive surveillance of genomic, transcriptomic and DNA methylation landscapes for variation in drug metabolism.

CYP3A5 Genotype is Associated with Lower Tacrolimus Time in Therapeutic Range After Heart Transplantation

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The lack of association of CYP3A5 genotype with clinical outcomes like acute cellular rejection (ACR) has been a barrier to successful implementation of CYP3A5-guided tacrolimus dosing. The role of CYP3A5 genotype on tacrolimus time in therapeutic range (TTR) and the impact of TTR on the development of ACR in heart transplant has not been well-established. This was a retrospective, IRB-approved study with genotyping of biobanked samples using the Pharmacoscan array (ThermoFischer Scientific, Santa Clara, CA). TTR was calculated using the Rosendaal method. We assessed the impact of TTR on T cell-mediated ACR over the first year with a Cox proportional hazards model with cumulative TTR calculated through each endomyocardial biopsy and incorporated as a time-varying covariate. We compared the mean TTR in CYP3A5 expressers and CYP3A5 nonexpressers at hospital discharge and at 3 month and 6 months post-transplant using a t-test. 119 patients who received a transplant at UPMC from January 2017 through February 2021 were included for the analysis. There were 32 CYP3A5 expressers (27%). The incidence of ACR in the first year was 29%. After controlling for UNOS allocation period, HLA mismatch level, and use of induction agent, a 10 percentage-point decrease in TTR was associated with a 64% increase in the likelihood of ACR at any time point (p<0.0001). The mean TTR during the initial hospital stay was significantly lower in CYP3A5 expressers [36.6% (SD 20.6%)] than in CYP3A5 nonexpressers [48.6% (SD 19.8%)] (p=0.006). There was no difference in mean TTR at 3 months post-transplant (p=0.56), but CYP3A5 expressers had a lower mean TTR at 6 months [48.4% (SD 13.7%)] than CYP3A5 nonexpressers [57.4% (SD 13.9%)] (p=0.007). CYP3A5 expression was associated with a lower tacrolimus TTR after heart transplantation, especially in the early period after transplant. Lower TTR was associated with increased likelihood of acute cellular rejection.

Optimization and Validation of a Polygenic Risk Score Algorithm for Clopidogrel Response Predictions in Caribbean Hispanics using Machine Learning Methods

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Clopidogrel, a prodrug, is a prototype antiplatelet drug commonly used in dual antiplatelet therapy (DAPT) in cases of coronary disease or percutaneous intervention. Metabolism and activation of Clopidogrel is carried out primarily by CYP2C19, a member of the Cytochrome P450 family of enzymes, known for having an abundance of genetic variants with varying efficacies. High on-treatment platelet reactivity (HTPR) with clopidogrel is predictive of ischemic events in adults with coronary artery disease. Using results based on a prototype genome-wide association study (GWAS) of clopidogrel performed in Caribbean Hispanics, we set out to develop a predictive model for antiplatelet treatment paradigms.

We built our testing dataset based on a cohort of Puerto Rican individuals. 511 individuals that underwent platelet reactivity testing and genotyping in pursuit of genome-wide analyses were entered in our machine learning (ML) testing set. Several clinical factors, including polygenic risk score (PRS), as well as the relative genotype of each of several genomic variants found in a previous study were used to build the dataset with the intent of testing for prediction of HTPR.

we identified the Random Forest Classifier as the most accurate algorithm for our prediction model. Furthermore, we found that amongst all the features in our dataset, polygenic risk score had the highest importance value.

These results give us a clear picture for a predictive model for HTPR in Caribbean Hispanics. hopefully future works can put this foundation into more practical use for treatment predictions. The establishment of polygenic risk score as having high importance lends credibility to our usage of that statistic as an important qualifying feature for treatment prediction and further justifies the use of genomic data in precision medicine paradigms.

Unveiling Gene Expression Signatures for Alzheimer's Disease in the Dorsolateral Prefrontal Cortex: Insights from Comparative Analysis

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Alzheimer's Disease (AD) is a complex neurological disorder often first affecting the dorsolateral prefrontal cortex (DLPFC), crucial for cognition. Despite advancements in gene expression analysis shedding light on DLPFC involvement, we lack accurate AD gene expression biomarkers. In this analysis, we aim to explore the effect of AD observed on DLPFC from postmortem brains. Utilizing two methods, Differential Gene Expression (DGE) analysis and the Adaptive Signature Selection and Integration (ASSIGN) toolkit, AD-specific signatures were generated and compared for their predictive abilities.

Raw RNA sequencing gene count data of 632 postmortem brain tissue samples were sourced from ROSMAP. The acquired data was then filtered using criteria such as Braak staging, clinical diagnosis, and CERAD scores,

resulting in 205 samples. DGE analysis was performed using DESeq2 by comparing 77 controls to 128 AD training samples. Differentially expressed genes (DEGs) were selected based on log2 fold change > 0.6 or <-0.6 and p-adjusted <0.05. ASSIGN signatures were generated by comparing five healthy to 5 AD training samples. The optimal signature was determined based on the signature's ability to predict AD status in 196 samples using Braak staging, clinical diagnosis, CERAD, and MMSE scores.

DGE analysis identified 36 DEGs (27 upregulated, 9 downregulated). A 75-gene (56 upregulated, 19 downregulated) signature was generated using ASSIGN to predict AD activity on a scale of 0-1. Overall, both signatures were able to predict AD statuses in patients. Specifically, the 36-DEG signature performed slightly better than the ASSIGN 75-gene signature in predicting AD activity across CERAD and clinical diagnosis scores. The ASSIGN 75-gene signature performed slightly better for Braak scores. Additionally, a stronger negative correlation with MMSE scores was seen with the 36-DEG signature predictions (-0.503 vs. -0.433).

Although the 36-DEG signature exhibited marginally better predictive capabilities, both signatures effectively discerned AD activity, underscoring their potential utility.

TAPHing into Safety: Leveraging CYP2D6*4 and CYP2C19*17 Insights for Medication Safety in Older Adults

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Objective: Older adults are overrepresented among individuals experiencing adverse drug reactions (ADRs). Specifically, older adults are most likely to visit emergency departments, and experience hospitalizations because of ADRs. The American Geriatrics Society's (AGS) Beer's criteria advises clinicians on the appropriate use of medications for older adults to limit ADRs. Interestingly, 31 drugs from the AGS Beer's Criteria have CPIC guidelines for pharmacogenomics (PGx) implementation. However, PGx implementation efforts are lagging within community-dwelling older adults. Therefore, we aimed to evaluate the benefits of CYP2D6 and CYP2C19, PGx implementation on ADR susceptibility in community-dwelling older adults.

Method: We conducted a pharmacogenomic (PGx) implementation study within a cohort of community-dwelling older adults, utilizing data from the Translational Approaches to Personalized Health (TAPH) study. Statistical analyses were performed via SPSS, using one-way ANOVA, to investigate the relationship between genotypes and the risk of cognitive decline, as measured by MMSE scores.

Result: In our analysis, carriers of CYP2D6*4 variant loss of function alleles exhibited improved MMSE scores compared to wild-type carriers (WT=25, *4=26.47, and *4/*4=29, p=0.032). Additionally, CYP2C19*17 variant carriers also demonstrated altered MMSE scores relative to wild-type carriers (WT=25.73, *17=24.26, *17/*17=26.44, p=0.038). Finally, gene-drug mismatches occurred in 37% of CYP2D6*4 allele carriers and 31% of CYP2C19*17 allele carriers respectively.

Conclusion: Overall, our study highlights the importance of integrating pharmacogenomic principles into clinical practice to optimize medication safety and effectiveness in older adults. Further characterization of PGx implementation of 31 drugs from AGS Beer's criteria/CPIC is warranted.

The Impact of Gene-Drug Interactions on Diabetes Outcomes

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Introduction: Diabetes mellitus is one of the top 10 causes of morbidity and mortality among older adults. Glucose lowering agents such as sulfonylureas, have proven to be effective in decreasing blood glucose levels. However, interindividual variability in pharmacodynamic and pharmacokinetic genes may influence the safety and efficacy of sulfonylureas. Thus, the application of pharmacogenomics to optimize antidiabetic medications may help to improve the pharmacotherapeutic management of diabetes. Unfortunately, sulfonylureas cause recurrent episodes of severe hypoglycemia which are associated with depression and cognitive deficits. Therefore, the goal of this study is to evaluate if Single Nucleotide Polymorphisms (SNPs) in CYP2C9 influence the safety and efficacy of sulfonylureas.

Methods: 130 older adults were recruited via community clinics into the TAPH (Translational Approaches to Personalized Health) study. The Mini-Mental State Examination (MMSE) and Patient Health Questionnaire-4 (PHQ-4) were obtained via the NIH-Toolbox Cognitive Batteries. CYP2C9 variants (*2, *3, *5, *11) were assessed via genotyping on the QuantStudio 12K Flex system. Statistical analyses were performed on SPSS 29.

Results: CYP2C9 *2, *3, and *5 alleles were not associated with MMSE or PHQ4 Scores. However, CYP2C9 *11 alleles were associated with MMSE scores (WT=25, *11=27.78, and *11/*11 =29). One participant with *11 genotype was taking a sulfonylurea. We lacked sample size to conduct the gene-drug interaction on MMSE or PHQ4 scores.

Conclusion: Understanding the impact of gene-drug interactions on diabetes outcomes holds the potential for limiting adverse drug events that are associated with pharmacotherapy.

Keywords: Diabetes mellitus, gene-drug interaction.

MyPGx: AI powered Cloud-Based Platform for Integrating Pharmacogenomics into Clinical Practice

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Background: Pharmacogenomics offers valuable insights for optimizing drug therapy, but its complex nature hinders real-world adoption. This limited use contributes to adverse drug reactions globally.

Objective: We present MyPGx, a novel cloud-based application designed to empower clinicians with actionable drug-gene interaction information at the point of care.

Methods: MyPGx integrates diverse data sources, including electronic health records, genomic data, drug databases, and clinical guidelines, into a structured knowledge graph. A no-code builder allows clinicians to create customized workflows based on evidence-based guidelines. MyPGx distinguishes itself from other solutions through its integration with a knowledge graph that enables clinicians using the platform to dig into multiple layers of evidence all the way to the primary source, as well as access supplementary materials. All of this can be done in natural language with the help of Large Language Models (LLMs) that query the knowledge base and present information back to the user in natural language.

Results: MyPGx currently provides recommendations for four therapeutic areas and offers a public version for healthcare professionals (www.mypgx.org). The platform facilitates knowledge sharing through a community forum. A no-code application builder allows clinicians to build customized workflows based on evidence-based guidelines, seamlessly integrating pharmacogenomics insights into their existing point-of-care software.The Flowbuilder permits creation of new decision tree flows or customization of existing ones based on regional and state guidelines and policies, formularies, or population characteristics and needs.

Conclusion: MyPGx bridges the gap between complex pharmacogenomics data and practical application. This innovative tool empowers clinicians to potentially improve medication safety and efficacy, promoting wider adoption of precision medicine. Further development will expand drug coverage and integrate additional functionalities