1. Protocol title:

The Texas A&M Interprofessional Pharmacogenomics PILOT Whole Genome Sequencing (WGS) Cohort

2. Study team

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Regents & Distinguished Professor

3. Objectives:

Our primary aim is to evaluate polypharmacy-associated adverse drug reactions (ADR) in a pilot study of at-risk patients using state-of-the-art pharmacogenomic technology and to use this information to make recommendations for optimization of pharmacotherapy regimens. The data from the pilot cohort will be used to optimize and integrate a customized electronic decision support (ActX) dashboard to identify medications that should be modified, replaced, or discontinued. A secondary objective of the pilot study is to evaluate the capacity/saturation of CYP P450 enzymatic pathways in polypharmacy patients. A third objective is to determine the feasibility of the planned informatics workflows between the CLIA lab, the Electronic Medical Record (EMR), and the Family Medicine Practice, including Whole Genome Sequencing (WGS). There is no prospective comparison group because this is a pilot study for a registry. WGS sequencing data will be for research use only, will not be used for clinical decision making, and will not be reported back to prescribing practitioners - these data will only be used to assess the feasibility of use for that type of genetic test data in the IPGx informatics workflow.

This protocol adds an extra research component to the PILOT protocol: WGS for research use only (RUO). This data will not be stored in the medical record or made available to physicians for clinical decision support. No additional office visits or samples will be required during scheduled healthcare visits to Family Medicine or IPGx.

Performing WGS is essential for the following reasons:

1) To obtain real data for optimizing the complex data pipelines and workflows involved in WGS.
2) To enable the identification of novel variants that genotyping cannot accomplish.
3) To initiate concurrence analysis of WGS against genotyping for known variants in our PGx genotyping test.
4) To demonstrate and validate the use of our digital data governance tools for stakeholders.

Collectively, these essential functions are critical capabilities needed to successfully compete for federal grant funding.

4. Background:

We are concerned with patient safety and ADRs as these areas of clinical practice represent significant causes of death, ahead of many of the better recognized acute and chronic causes of mortality (1). While prescribing medicines can have life-altering benefits, a more precise way of choosing among the options is needed. A person's drug response can vary by means of drug-drug or drug-food interactions, as well as by sex, age, and disease status. Large interpersonal variabilities of up to 1000-fold exist in response to the same dose of a given medication (2). Genetic polymorphisms help inform pharmacokinetic and pharmacodynamic profiles, but these insights have not yet been consistently incorporated into clinical practice and standards of care. Several medication management programs have appeared in recent years, but these are mainly geared toward adherence, with only limited incorporation of pharmacogenomics-based medication management. Precision medicine advocates that one size does not fit all medical care. How might the provision of care get closer to the bullseye in polychronic disease management, and the management of polypharmacy?

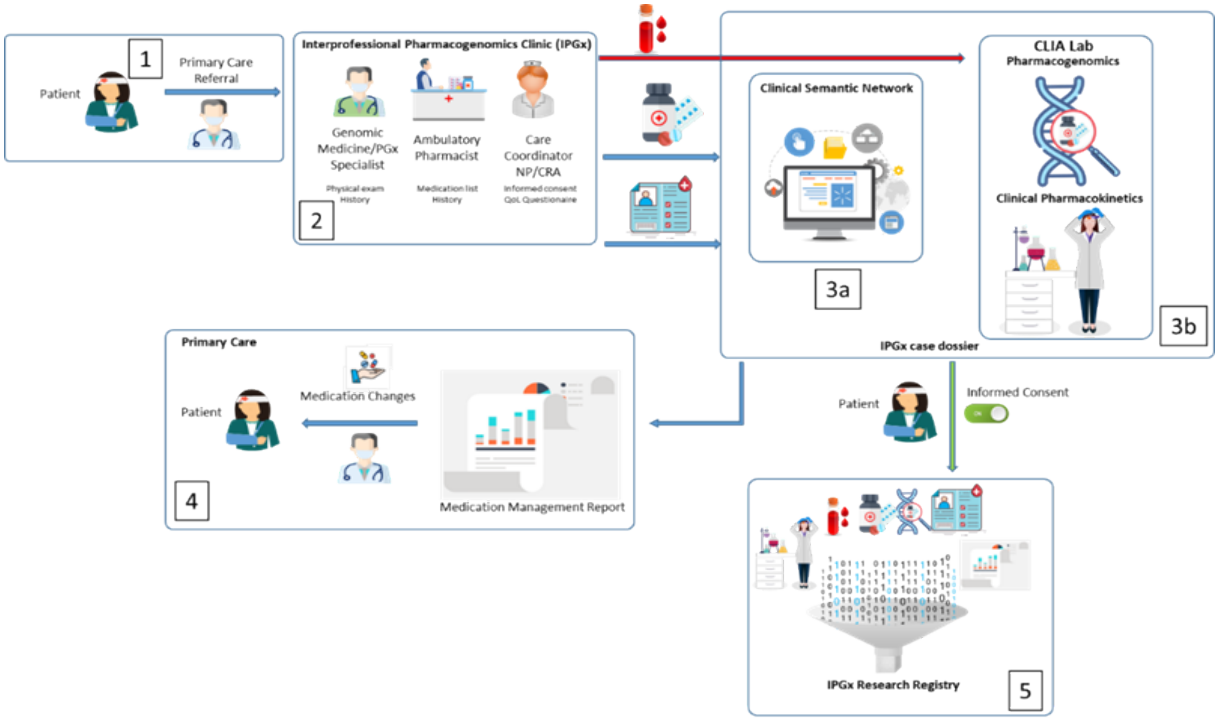
There exists a polypharmacy crisis in the United States that is large in scope, especially among the older populations who often have diminishing renal and hepatic functions. The prevalence of potential hepatic cytochrome enzyme-mediated drug-drug interactions was estimated to be as high as 80% in one study (3), with older adults considered to be more susceptible to problematic

drug interactions. Conventionally, polypharmacy refers to taking five or more medications concurrently. An estimated 15 million patients 65 or older have been identified as facing the challenge. Polypharmacy patients often have at least two comorbid chronic diseases, and nearly 50% of older adults are using at least one medication that is not necessary (4). Hospitalized patients average five to eight medications, and the number surpasses nine in 40% of nursing home residents. In a study of patients with cognitive decline or mild Alzheimer's disease, 88% of these patients met polypharmacy criteria, with anticholinergic cognitive burden, drug-drug interactions, and drug-gene interactions all prevalent issues in these populations (5). In an increasing number of extreme cases, polypharmacy can approximate 20 drugs posing risks for adverse drug outcomes that equal nearly 100% (6). The greater the number of medications in a regimen, the higher the risk to patient safety and compromised clinical outcomes. One in twenty polypharmacy outpatients seek medical care for ADRs (6). Polypharmacy has also been associated with hospitalizations among the elderly (Gutierrez-Valencia et al., 2017). Polypharmacy is associated with decreased medication adherence, nutrition, urinary incontinence, reduced activities of daily living, and loss of physical and cognitive functions. Increased falls occur along with accompanying morbidity and mortality (7). Financially, the impact of polypharmacy has been associated with a 30% increase in health care expenditures (8), and a major factor in ultrahigh healthcare utilizers (9). Analysis of the Observational Health Data Sciences and Informatics data set showed that 10% of diabetes patients, 24% of hypertension patients, and 11% of depression patients followed a treatment pathway that was unique among a population of 250 million cases (10), illustrating the need for electronic decision support (11) to flag drug interactions resulting from patient specific care plans and implement corrective measures.

Electronic Health Records (HER) continue to fall short regarding their level of interoperability, with significant deficiencies enabling a care plan and medication management that can draw data and decision support from across the provider continuum. This is a suboptimal situation in the provision and refinement of precision and personalized medical care. The clinical burden of polypharmacy and medication reconciliation often impacts primary care clinicians who may not have the necessary data at the point of service, a nidus for polypharmacy management problems. Innovative approaches to managing the polypharmacy challenge include the creation of medical management clinics with focused efforts on mitigating the cost and healthcare burden of polypharmacy and to systematically evaluate the incremental clinical changes that accompany medication alterations, modification or discontinuation where indicated.

Utilizing an interprofessional care team that includes physicians, pharmacists, nurses, case coordinators, along with telemedicine and digital tools, we can engage patients and garner information such as phenotypic, functional, and social determinants of disease profiles. These data are entered into the EMR(s) as computable and actionable data prior to a visit to facilitate better tracking of what happens in-between visits (adherence to the care plan, or lack thereof). We posit that this information is as important as what happens at an appointment, especially in clinical cases of polypharmacy. In the end, this information can become more readily available to both patients and providers.

Figure 1 Interprofessional Pharmacogenomics (IPGx) Model. 1. Referral of polypharmacy patient to the IPGx clinic. 2. Interprofessional team collects relevant medical history with an emphasis on information related to chief complaints, which also includes a transition of care history from primary care to the IPGx. This information is analyzed using the Clinical Semantic Network to identify complaints of possible pharmacological root cause. 3a. When warranted, pharmacogenomic profiling is performed. 3b. When warranted, pharmacokinetic profiling is performed. 4. A medication management report citing complaints of potential pharmacological root causes and suggested alternative medications or adjustments to drug regimen is provided to the referring physician. 5. If patient chooses to give informed consent, all clinical data, bioanalytic data and biological specimens are entered into a pharmacogenomic research registry (clinical-genomic database).



We are developing a care decision support protocol and pharmacogenomic/ pharmacokinetic dashboards that augment the capacity for primary care clinicians to manage medication more precisely for individual cases and that is minimally disruptive. Additionally, interoperability between electronic medical records, clinical decision support (CDS) and genomic test data formats remains a barrier for reuse of PGx tests and implementation of whole genome and whole exome sequencing across time and different healthcare providers. These efforts will inform the feasibility of using whole genome sequencing (research use only under this study protocol) across the informatics platforms used in the IPGx care model.

The dashboards, modeled on those CDS dashboards we have used to date (12), will be useful to providers and patients, helping to identify clinical cases where there might be benefit from proactive medication management to identify those who may not respond and those at heightened risk of ADRs. The dashboards would be informed by a growing library of clinical cases with a clinical data warehouse. The dashboard would generate and iteratively refine novel care decision trees (algorithms) centered on medication management. The data structure and care protocol are designed to enable concomitant and longitudinal observation (research) of the clinical activities toward validation of the ActX CDS and dashboards as a useful tool for patient-centric clinical research. The ideal databank will include drug blood levels (not relevant to this PILOT), drug list and other relevant modifier data that may impact medication use and effectiveness. This approach would also provide a means to learn more about drug adherence and help to systematically identify patients who may be candidates for a pharmacogenomic evaluation and longer-term participation in a medication management program.

Specific questions that this approach might inform:

- Does a drug level near zero mean non-adherence, or is the patient metabolizing a drug extensively such that blood or urine levels become undetectable after administration? Our phenotypic questionnaire coupled with drug blood or urine level measurements will inform that question.

- Is a protocol needed to determine when to order a pharmacogenomic test? Our data platform, powered by the ActX platform, can validate the clinical and cost-effectiveness of those decisions.
- What is the best use of pharmacogenomic data? If a patient has had a pharmacogenomic test, blood or urine drug levels might help refine knowledge about the metabolic activity for pertinent enzymatic pathways and help craft key questions to identify what constitutes an overloaded CYP P450 pathway in the setting of polypharmacy.

ADRs might be preventable in the psychotropic domain by applying the knowledge derived from a medication management consultation (18). For instance, in the case of antidepressants, weeks may go by before a clinical response can be evaluated after initiating medication based on standard dosing and trial and error. In a precision medication management scenario, the provider would know at the outset if the patient were an ultra-rapid metabolizer for a relevant CYP P450 enzymatic pathway and be better equipped to identify the drug of choice and to optimize dose titration. If the clinical dashboard reveals a patient that is receiving several medications competing for a common pathway, proper medication adjustments can also be made, as needed.

The ActX to be used here is a clinical decision support system containing millions of interrelated variant-drug concepts that arc with each other to create a knowledge network. As data is entered, weighted arcs are used to build clinical decision support and differential diagnoses. This provides a potentially strong environment for a pharmacogenomic profile to create a precision drug and dosing regimen tool while taking advantage of clinical workflows currently in practice. The pharmacogenomic dashboard is contained within the ActX platform.

Compare and contrast WGS and Genotyping

The ActX test is a genotyping test conducted in a CAP/CLIA-compliant laboratory for complex lab-developed tests (LDTs) to ensure that results can be used for clinical decision-making within the LDT regulatory framework. This type of test examines a limited number of features in the human genome, specifically just under 400 known genetic variants with clinical significance. The results from the ActX test will be returned to the provider and discussed with patients.

Whole Genome Sequencing (WGS) provides a complete comprehensive inventory of the entire human genome, which consists of approximately 4 billion base pairs. While WGS can be performed under CAP/CLIA regulations for clinical decision-making, the testing laboratory we will be using will conduct a Research Use Only (RUO) test and WILL NOT be an LDT. As a result, WGS results will not be provided to healthcare providers or patients.

5. Inclusion and Exclusion Criteria:

Inclusion

We will recruit up to 50 volunteers from the Texas A&M affiliated community health family medicine program.

- Individuals taking 5 or more medications, including over the counter drugs, supplements, natural products, cannabis produces, or other recreational drugs.

- Ability to give and comprehend the consent process.
- Consent to donate urine samples, genetic data through buccal swabs and blood samples, undergo a comprehensive history and physical examination.
- All genders.
- Age 18-100

Exclusion

- Subject has been diagnosed or is being treated for any cancer other than basal cell cancer in the last 5 years. Patients with metastatic melanoma in the last 5 years will be excluded.
- Admitted to hospice.
- Patient has ever been diagnosed with Hepatitis B or C.
- Patient has ever been diagnosed with active liver disease, hepatomegaly, grossly abnormal liver function. Meld score >10, ALT, or AST >100U/L or an AST/ALT ratio >2
- Patients taking imidazole antifungal medication.
- Declines to participate or interact with staff/share their medical status.
- A diagnosis of Alzheimer's disease or related dementias in a medical record indicates a progressive, debilitating condition that impairs memory, thought processes, and functioning.
- Pregnant patients will be excluded.
- Individuals who are unable or unwilling to provide consent will be excluded.
- Unable to verbally communicate and comprehend English language.

While ADRs are an important endpoint in the proposed study, ADRs are not an inclusion or exclusion criterion for enrollment. As such, under the polypharmacy inclusion criterion, severe side effects are expected in the enrolled population, but not a criterion for enrollment. Clinical efficacy of existing therapies will be indirectly informed by the disease specific quality of life questionnaires in the electronic health record of patients referred and enrolled.

Severe side effects are not uncommon in a polypharmacy population and severe side effects will not disqualify subjects from participation in the study.

6. Number of Participants:

Up to 50, with whole genome sequences from patients taking medications.

7. Multi-Site Research:

Texas A&M Health Family Care Clinic and the Texas A&M Interprofessional Pharmacogenomics Clinic (IPGx) (12) are co-located within facilities made available by the Department of Primary Care and Rural Medicine. Patients will be referred to the IPGx exclusively from the Texas A&M Family Medicine Clinic working closely with our laboratory collaborators, ActX and IC42 in Aurora Colorado. A research collaboration agreement has been promulgated among Texas A&M and ActX systems to ensure data sharing and reporting is compliant with all relevant regulations. ActX, and IC42 will receive specimens labeled with a

code that the TAMU research team will use to reidentify the reports when they come back to TAMU. ActX and IC42 will not have access to the codes.

Patient consent and research activities will occur only in the Texas A&M Health Family Care Clinic and the Texas A&M IPGx. All participating personnel, and organizations will have the most current version of the IPGx WGS Protocol, informed consent documentation, and HIPAA authorization. All required approvals will be obtained at each location including the site's IRB of record (or affirmation to recognize the TAMU IRB as the IRB of record, or documentation of exemption from IRB approval). All planned modifications to the Protocol will be communicated to the various primary care sites in addition to the site's IRB of record and implemented, upon IRB approval if required. All engaged participating sites will safeguard data as required by their local information security policies and in compliance with HIPPA. Regular dialogue and open communication will ensure that all investigators listed in this protocol conduct the study, manage specimens, and engage in research faithfully to the protocol.. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy and as specified in the Protocol.

8. Study Timelines:

Study participants can take part in the research during their visits to the IPGx clinic, and any follow-up medication management appointments referred back to IPGx by their primary care physician. The sharing of data will be limited to 180 days from the date of their enrollment in the study. Data analysis will continue indefinitely, but EMR data will not be collected or accessed after the 180-day period.

9. Variables and outcome measures:

- Frequency and nature of ADRs on the Naranjo Scale (19)
- Emergency department visits
- Hospital admissions
- Serum/plasma drug concentrations
- Pharmacogenomic genotype with corresponding ADR phenotype
- Drug-drug interactions, drug-gene interactions, drug-drug-gene interactions

10. Procedures Involved:

Patients will be referred to the Texas A&M Interprofessional Pharmacogenomics Clinic (IPGx) by their primary care physicians to evaluate polypharmacy status, genotyping, pharmacokinetic/ pharmacodynamic (PK/PD) assessment, and monitoring of potential for ADR.

An assessment at the IPGx will start with the pharmacist or physician doing a pharmacologic consultation to evaluate medications or other drugs currently being used by the patient and to identify any potential issues related to toxicity, drug interactions, or side effects that might be relevant to the clinical presentation. A physician or ambulatory pharmacist in the IPGx clinic or Family Care Clinic will obtain a complete medical history, physical examination, and validate the patient's current concomitant medication list at the IPGx during the office visit. Other clinical team members may include house staff or medical students, a clinical/research coordinator, and a nurse. Patients eligible for inclusion in the research study will be offered enrollment. Patients who choose not to participate in the study are still eligible to receive care, without prejudice. After providing detailed educational instruction and informed consent, including the risks and

benefits of the study, patient medical information would be input into the ActX CDS, which functions as a computable EHR. The **attached informed consent** obtains permission from every individual to use their clinical, genetic, and lab data.

The dashboards (12) will be useful to providers and patients, helping to identify clinical cases where there might be benefit from proactive medication management to identify those who may not respond and those at heightened risk of ADRs. The dashboards would be informed by a growing library of clinical cases with a clinical data warehouse. The dashboard would generate and iteratively refine novel care decision trees (algorithms) centered on medication management. The data structure and care protocol are designed to enable concomitant and longitudinal observation (research) of the clinical activities toward validation of the IPGx model and dashboard as a useful tool for patient-centric clinical research. The future, generalized databank will include drug blood or urine levels, drug list and other relevant modifier data that may impact medication use and effectiveness. This approach would also provide a means to learn more about drug adherence and help to systematically identify patients who may be candidates for a pharmacogenomic evaluation and longer-term participation in a medication management program.

Clinical or research staff will collect urine and a buccal swab to obtain DNA for a pharmacogenomic evaluation using sample collection kits from the CLIA lab. This process will take place at the beginning of the study simultaneously with the consenting process. Blood chemistry data will be extracted from the eClinical Works EMR. If the patient separately consents to WGS (research use only), additional blood samples will be collected subsequently.

For the measurement of drug levels, urine will be collected in biosafety kits provided by IC42 at room temperature and shipped to IC42 each day via FedEx using the provided biosafety shipping kits. Buccal swabs require no special preparation and will also be shipped to IC42 each day via FedEx in the provided biosafety shipping kits.

In certain cases, follow-up blood samples might be collected for medication management based on the judgment of the physician or pharmacist during scheduled visits to measure medication levels in the blood. The reasons for these follow-up measurements are numerous and depend on the medication, the disease constellation, and genetic determinants, making it impractical to list them all beforehand. These follow-up visits will not require a special visit, will not be billed to insurance, and will have no costs for participants as they will be paid for from research funds.

For whole genome sequencing, phlebotomy trained staff will draw blood into each DNA (2.5ml) and RNA (8.5ml) PAX vacutainer tube under gloved and alcohol clean conditions to minimize the risk of infection. Personal protective equipment will be used in accordance with established clinic safety protocols. WGS samples will be stored in the Family Medicine Clinic in a dedicated cold storage refrigerator under the supervision of Dr. Rogers or her pharmacy staff at 4^{o}C until transported to the Reynolds building by study staff with appropriate training per the study delegation rubric. Transport from the clinic to Reynolds will occur in compliance with TAMU Biosafety Manual Risk Group 2 specifications. Samples will then be batch shipped to a WGS provider that is to be determined at a future time.

A single pharmacogenomic test using DNA from the initial buccal swab will be conducted. An assay for pharmacogenomic variants of known clinical significance for the drug-gene pairs specified in the ActX knowledge base will be conducted and a report generated (per the CPIC guidelines (20, 21)). In certain instances, blood or urine levels of drugs or metabolites may need to be re-assessed periodically if warranted by standard clinical practice, on a case-by-case

basis. If the physician wishes to determine whether a change in dose or a change in medication has resolved undesirable steady state levels of medications or their metabolites, a follow-up urine or blood sample (depending on the drug being measured and the specifications for the corresponding CLIA test for that drug) may be ordered in accordance with drug labels where dose titration is warranted, or where an actionable pharmacogenomic variant (under FDA and CPIC guidelines) indicates a change in dose or medication should be considered. The sample will be obtained in a timeframe the physician determines as medically prudent. Patients will be seen in the clinic after the final report is submitted to the referring physician.

The Pilot Study will track and document any change in medication, but changes are not a condition of participation, and it is plausible some subjects will not have a change in medication recommended by the referring physician or may choose against a medication change recommended by the physician.

This protocol is observational in that it does not dictate a specific course of action in choosing which medications to prescribe. As is the case in medical practice, patients will be encouraged to contact the physician's office if they require medical advice and attention.

In the initial patient engagement (Figure 1), patients will present to the IPGx clinic with a detailed list of all their prescriptions and over the counter medications, supplements, or substance use. If available, the exact medication list will be acquired into the ActX CDS through Surescripts and validated in the initial IPGx encounter. (23). Any alternative medication prescribed would be medications that a licensed pharmacy would fill, such as medications described in First Databank (FDB). At the primary care physician or IPGx physician's discretion, they may choose to further inform their decision making, utilizing additional tools such as the ActX CDS, pharmacogenomic results at Actx , blood work, and questionnaires. These steps will also serve to mitigate risk. The care delivery model will generally be for the IPGx physician or pharmacist to assess the patient and analyze the case before and after genotyping and/or clinical pharmacokinetics and provide medication management recommendations for the primary care physician to consider. Should a primary care physician and a patient elect to go forward with therapy modifications as recommended, it would be based on the standard of care in medical practice and the clinical judgement of the referring physician. IPGx will actively participate in medication management at the request of the referring physician. **No intervention is mandated by the protocol.** Neither the physician nor the patient is required to change medication to participate in the study, but it should be clear that the purpose of participation is to enable the patient and physician to have a more informed discussion about the best standard-of-care medicines choices among the medications the patient is taking to treat chronic health problems. Overall, the clinical decision-making process will be conducted in accordance with standard of care and the statutory scope of practice for primary care physicians. It is possible that timing of ADRs may be gleaned from patterns captured in prior health records and the referral. The source of prior medical records would come from the referring physician as would be the practice in any specialized clinic such as recent, evaluation and management notes, allergies, hospital records, procedures, past medical-surgical, and family history. Patient protection would include HIPPA compliance.
Upon IRB approval of changes to the WGS Extension PILOT PROTOCOL, Drs. Neal and Rogers will be provided a copy of the revised protocol via email and updated on changes via Zoom. Study changes will also be summarized in the Quarterly IPGx investigators meeting. Investigators unable to attend will receive minutes as is standard practice.

Self-reported or documented ADRs. Documented ADRs will be classified in accordance with NCI USNCI Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse

Events (CTCAE) v3.0. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (accessed on 4 February 2020).

- Off-schedule, ED/Urgent care visit notes.
- Hospital visits
- Clinical Data Architecture documents, including but not limited to
    - OVS – Office visit summary document
    - VDT – View download transmit summary.
    - TOC—Transfer of Care ambulatory summary

11. Data and Specimen Management:

- Research and clinical workflows are delineated in Figure 2
- Data in the medical record (eCW) that are used for research, will be replicated and stored in the research data warehouse (using the BurstIQ platform)- completely separated from the eCW medical record.
- Whole genome sequencing is done in a research-use only (ROU regulatory framework, not in a CAP/CLIA lab Developed Test framework- WGS results will not be available in the EMR for clinical use.
- No incidental genetic finding will be returned to patients
-

Clinical Lab.

- CAP (College of American Pathologists)
- CLIA (Clinical Laboratory Improvement Amendments)
- ABFT (American Board of Forensic Toxicology)
- ANAB (ANSI National Accreditation Board) pending.
- ISO (international standards organization)

The building that houses the lab has video surveillance, a log of personnel. Authorized access to the building is designated to specific personnel. Keypad security access is used.

Specimens
Until use, clinical specimens will be kept at

Texas A&M Health Family Care
2900 East 29th St.
Bryan, TX 77802

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Research specimens will be kept at
Texas A&M
2121 W. Holcombe Blvd
Houston, TX 77030

Monitoring, refrigeration or freezing of samples as needed will be available.

Pharmacogenomic assays
Like most pharmacogenomic tests, the assays used in this IPGx are laboratory developed tests (**LDT**) conducted in **CLIA** certified, **CAP** accredited clinical laboratories. The tests will not be

submitted by the collaborating organizations for reimbursement by Medicare or private insurance, Buccal swabs for pharmacogenomics: Six samples will be obtained. The first four are discarded after DNA is extracted. The second two samples will be a back-up in case enough DNA cannot be extracted from the first sample and destroyed after 180 days.

Research Data Center
Texas A&M via Amazon Web Services
2121 W. Holcombe Blvd
Houston, TX 77030

Servers have software control. There are firewalls and encryption. In addition to software controls, there are physical controls/barriers to entry. There are procedures for offsite recovery. An authorized clinical user can sign in with a username and password and access patient's data, when warranted. The clinical annotation and phenotypic data (information obtained in examinations and physician consultations, genetic data) will be collected on site in Texas by the clinical team and entered into the AWS Research Data Warehouse through a cloud portal to the AWS data center. Geneial is during a Security Assessment Phase 1 by TAMU IT.

The frequency of data collection is estimated to be once or twice per month, in each clinical case, daily across the cohort.

Data Sharing
The IPGx will receive research data from the Family Care Clinic through import of Health Level Seven International (HL7) Clinical Document Architecture (CDA) documents under the patient authorization, HIPPA waiver, and informed consent specified in the Protocol. Clinical data generated by the IPGx, the ActX, and IC42 will be managed in the TAMU account in AWS Research Data Warehouse and on the BurstIQ platform.

The care team will receive a copy of a precision medication management dashboard report summarizing germane information about drug concentrations and relevant CYP variants.

The following data elements are expected to be collected and shared among the collaborators (and de-identified where appropriate):

Clinical EHR

- Demographics (age, race, zip code, sex)
- Medication history
- Diagnoses
- Hospitalizations
- Physician notes
- Pharmacy

Lab

- Variant calls and/or haplotypes (.VCF) and WGS sequence data (FASTQ or BAM), when available for NIH Genomic Data Commons submission
- Clinical chemistry
- Drug concentrations

Patients will be referred to the IPGx for evaluation and “consultation”. After the IPGx performs its evaluation, the digital dashboards rendered by in the ActX will be available to the referring physician in the eCW medical record.

There are several methods of accomplishing this.

- Initial phone call to discuss salient aspects of the evaluation.
- A Actx-generated PDF can be transmitted to referring physician via fax.
- Clinical Data Architecture (CDA)
- Create a screen sharing session so that referring clinics can see the IPGx Medication Management dashboards review what is being used to inform IPGx decisions.

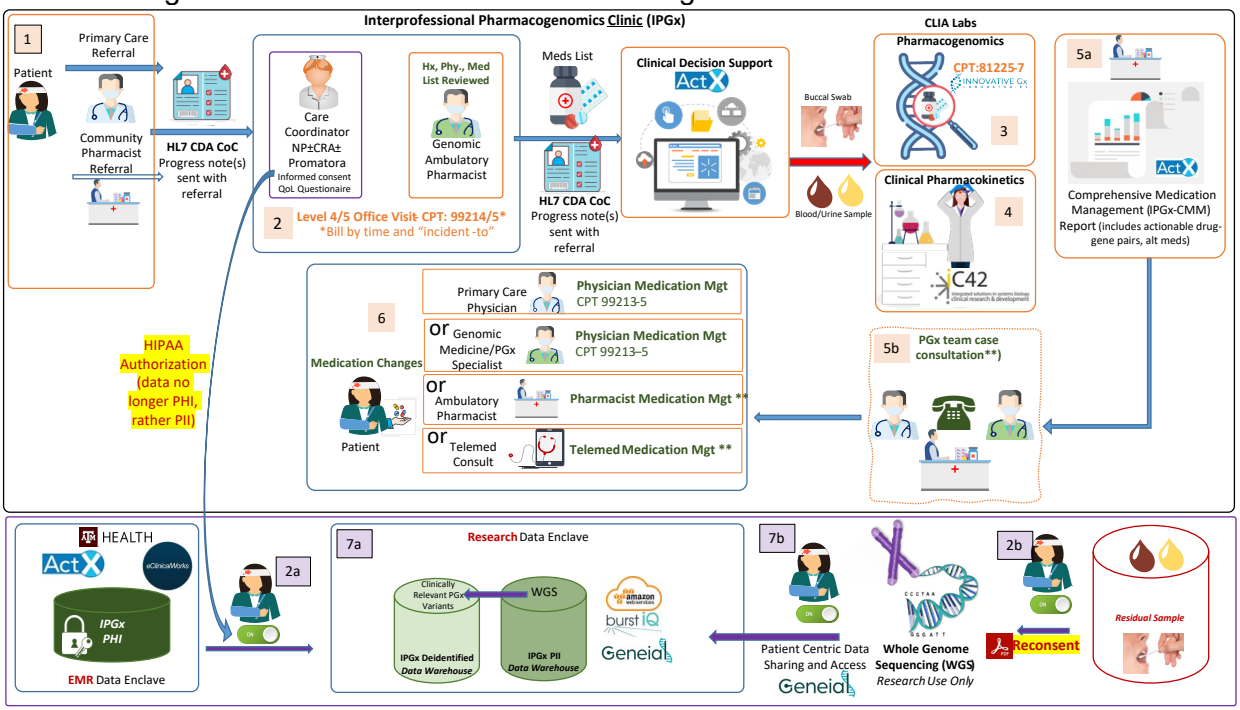

Figure 1*- Clinical and data care pathway of a case through the referring clinic (Texas A&M Family Medicine) care, the Texas A&M Health Interprofessional Pharmacogenomics Clinic, and the associated IPGx Data Repository schema for this study protocol.*

Clinical Decision Support

All clinically actionable variants (per CPIC guidelines) obtained from the pharmacogenomic and steady-state pharmacokinetic assays are rendered by the ActX CDS in eCW and available to the referring physician in the patient record. These genotyping reports are commonplace in the field of pharmacogenomics and the formatting of these reports whether in a paper form or electronic rendering, are not treated as experimental, rather fall under the Lab Developed Test regulatory framework for complex tests in CAP/CLIA medical laboratories. No experimental interventions will be utilized at any time in the IPGx clinic. Medication changes or dosing adjustments will be ordered by licensed physicians, in accordance with standards of care for a given drug or class of drugs and evidence-based recommendations, and within the applicable medical guidelines at the discretion of the physician. Specific medication or interventional protocols are NOT prospectively prescribed by this protocol. The IPGx test result, report, software rendering is not prescriptive and only provide analytic information from a lab test to a physician under CLIA regulations. This means that the menu choices of medications that a physician uses in the provision of standard of care remains the same. The IPGx report (whether in paper form or electronic rendering) is among all the other information (i.e., the patient’s chart)

that informs the choice of medication. The physician retains full control to consider or ignore the IPGx report when making medication choices, just like any other lab report order or any other piece of information in the EMR a physician normally considers when continuing, deprescribing, or prescribing a new medication.

At the point the patient signs an informed consent to participate in the IPGx PILOT WGS Extension Study, research activities (data collection only, there is no prescribed, randomized assignment to an intervention) will begin (Fig. 1). Any PHI and PII within the Pilot Study will be managed in accordance with the attached consent, and applicable contractual and statutory requirements restricting its use of sharing will be always applied.

Geneial
Geneial will be provided access to de-identified whole genome sequence data on a TAMU AWS enclave. Geneial uses privacy-preserving computing technology that precludes actual sequence data to be available in native form for their platform users. To be clear, in this IPGx PILOT WGS Extension, no third-party use of the data beyond the participants mentioned in this protocol are required or planned. As a site of multiple ongoing NIH-funded research studies, Geneial maintains an active Federalwide Assurance number (FWA00032475) with the OHRP. Within the Geneial platform, data will be stored on encrypted, HIPAA-compliant cloud servers within the USA, and data will be encrypted at rest and in transit. For individual participants or their guardians, their own data will also be temporarily stored in cache on their devices before being submitted to the central secure database. AWS Certificate Manager is utilized to create, store, and renew public and private SSL/TLS X.509 certificates and keys that are used to encrypt all data in transit between the browser and the application programming interface (API). The web app is served over AWS Cloudfront with an SSL certificate. Processed participant data at rest is stored in an encrypted AWS S3 data store and in AWS RDS (Aurora). AWS manages server-side encryption keys with Amazon S3 managed keys (SSE-S3). In Aurora, data is also encrypted at rest, including underlying storage for DB clusters, automated backups, read replicas, and snapshots. Industry standard AES-256 bit encryption is utilized. AWS Cloudwatch contains an audit trail of changes made to registry record, which is also encrypted at rest, managed by AWS. Digitally signed informed consent forms are collected and temporarily stored with Dropbox Sign, which includes participant name and email address. At Dropbox Sign, each document is stored behind a firewall and authenticated against the sender's session every time a request for that document is made. All communications use TLS (Transport Layer Security) encryption. Documents are stored and encrypted at rest using AES 256-bit encryption.

12. Data Analysis:

The data will be used by TAMU in implementation of informatics workflows for the IPGx. Lab results will be used in clinical management during clinical quality assessment and review and inform medication decisions by Dr. Neal and/or the PCP. Samples and clinical data will not be used for any analysis beyond the scope or timeframes specified in this protocol.

13. Participant Safety:

(*This section is required when research involves more than Minimal Risk to participants.)*

The study likely poses minimal-to moderate risk since it is not interventional: there is no prescriptive intervention and no requirement for patients or physicians to change medications The protocol will involve a standard of care medication management approach, albeit informed by drug metabolism and pharmacogenomics information. While polypharmacy patient

populations with co-morbidities are at elevated risk of ADRs, the proposed protocol involves similar or lower risk to participating patients compared to routine clinical practice. Study participants will benefit from standard of care medication management decisions made by clinicians who will be better informed about an individual's pharmacogenomic ability to metabolize the drugs they are taking, and any issues related to drug metabolism that could be affirmed by direct measurement of drug levels (and their metabolites) in blood (in clinical care, outside this study protocol, at the discretion of the provider). In short, the protocol is likely to enhance the safety of research subjects relative to patients receiving standard of care in a primary care setting without the information this study will provide. In this vein it should be noted that the FDA has a current posture of not regulating physician facing clinical decision support tools (24). However, the FDA has issued nonbinding guidance (25) for Software as a Medical Device (SaMD) that recommends design control and clinical evaluation standards, including the use of third-party certifications, for SaMD. While the ActX CDS and the pharmacogenomic dashboards being used in this protocol are not subject to FDA regulation under the SaMD framework (like most electronic medical record readouts), the ActX CDS platform has received certification from rigorous third party (ONC-Authorized Certification Bodies) evaluation. These established standards in the health informatics industry establish low tolerances for computational or design flaws in software that can render erroneous information for clinical decision making that poses risks to patients.

There are inherent risks of morbidity and mortality associated with taking, changing, or discontinuing medications in whatever standards-of-care are applicable to an individual's case. These risks are routinely weighted by the physician in the practice of medicine, and no actions beyond the exercise of physician judgments are prescribed under this protocol. IPGx will forward specific recommendations to the referring physician who in turn will make changes to the regimen, as desired. It is expected that changes made to mitigate a polypharmacy burden would reduce risk of ADRs. We do not expect these risks to differ from those inherent to the medication of choice and adjustments thereto during standard medical care.

It should be noted that standard of care for changing most medications is simply trial and error (22), with a few exceptions warranting pharmacogenomic testing though consensus medical guidelines for actions based on results of pharmacogenomic exist and are endorsed by Association for Molecular Pathology, American Society for Clinical Pharmacology and Therapeutics, and the American Society of Health-System Pharmacists. The working principle for this program is that the risks of being a polypharmacy patient without medication management care are greater than the risks of trying to ameliorate that burden with pharmacogenetic and drug level testing to inform medication management. In many respects that study can be viewed as a quality improvement project for participating clinics. For these reasons, the proposed study is one of minimal to no risk.

Any risk will be minimized by exercising the same level of clinical decision prudence that any active medical practice would take during clinical care delivery to monitor a patient's safety and condition. Licensed practitioners would be taking care for patients in compliance with standards of care, state licensure regulations and any rules of safety practices associated with the United States, the State of Texas, and Texas A&M University. Clinicians would make all final clinical decisions, in accordance with standard of care practices for the medical conditions in each clinical case.

It is expected that study participants remain engaged with the primary care clinic from where they were referred. Since the period of data collection is 180 days and the recommendation calls for periodic re-evaluation of the enrollee, if concerns arise the referring clinician would help

address the need to monitor safety. Lab data will be reviewed as it becomes available. We will establish a safety monitoring board constituted by team members to oversee and report any adverse events issues or episodes to the IRB. Because medication management is expected to align with standard of care and within normal parameters of physician judgment, the risk of adverse outcomes is minimal relative to a care plan that omits a medication management element and the polypharmacy and pharmacogenomics information that will be made available to the care team.

Data Safety Monitoring Plan.

Clinical study staff and investigators, under the supervision of the PI will review all data on an ongoing basis for data completeness and accuracy as well as protocol compliance. All data will be appended to the eCW medical record and reconciled by Dr. Rogers (or another ambulatory pharmacist in the clinic) when each subject first presents to the IPGx. Drs. Ramos, Neal, and Rogers will review the safety and progress of the study quarterly, after medication changes occur in at least 5 subjects. Study reports, including patient recruitment, retention/attrition, and AEs, will be produced following each of the quarterly reviews. Study reports will be compiled for each subject at the close-out of this pilot study, with a study report for each case appended to the ActX CDS for record keeping.

Items to be in the closeout report and reviewed by the PI include:

- Interim/cumulative data for evidence of any study-related adverse events and serious adverse events;
- Summary of data quality, completeness, and timeliness;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

AEs will be noted in the eCW categorized according to the likelihood that they are related to the study. Specifically, they will be labeled unrelated, related, probably related, or possibly related to the study intervention. AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience, and “severe” if it causes a substantial disruption to the patient’s well-being. In the final study report, the PI will attest that they have reviewed all AE reports.

A serious adverse event (SAE) is any adverse event that results in one or more of the following:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect

Any SAEs will be documented and reported to the TAMU IRB in accordance with HRP-029 (5 business days or less).

The PI or his designee will codify each review with their actionable recommendations to IPGx as to whether the study should continue without change, be modified, or be terminated.

Recommendations regarding modification of study could include:

- Changes of the study protocol raised by the review of the safety data;
- Suspension or early termination of the study because of serious concerns about subjects' safety, inadequate performance, or rate of enrollment;
- Corrective actions regarding a study center whose performance appears unsatisfactory or appears to raise questions regarding the conduct of the study.

Immediate Action Report: The clinical Investigators will notify the PI and TAMU HRPP/IRB of any observations of a serious and immediate nature or recommendations to discontinue all or part of the study. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to the PI and the TAMU HRPP/IRB in writing by e-mail, fax, or courier within 5 business days of occurrence.

The study period is limited (one visit and 12 months of chart analysis- 6 months before the index date and 6 months after the index date), the number of subjects is small (n=50), and the risks to subjects are of low likelihood and low magnitude of harm, so stopping for futility is not justified.

14. Withdrawal of Participants:

An individual can be suspended or removed from the research protocol due to non-compliance with visits. Issues such as pregnancy, admission to hospice, death, will be evaluated by clinical staff in consultation with the principal investigator. Adverse Drug Responses (ADRs) as defined by Aronson: *" arise when a compound (e.g. a drug or metabolite, a contaminant or adulterant) is distributed in the same place as a body tissue (e.g. a receptor, enzyme, or ion channel), and the encounter results in an adverse effect (a physiological or pathological change), which results in a clinically appreciable adverse reaction."* (26). For clarity, ADRs will not necessarily be a reason for removal of a subject from the study. An orderly termination procedure would include written notice and or documented phone call between the subject if appropriate, and a member of the care team. Enrollees will be given a two-week notice. The only safety reason for termination is the determination by the medical staff the patient's condition necessitates discontinuation of participation in the study. An example would be a determination by the physician that continued participation in the study would be deleterious to the enrollees' health. If a patient withdraws from the research, they will still be able to continue to be a patient at the IPGx.

15. Risks to Participants:

Risks involved:

- Other discomfort, hazards, or inconveniences, taking into consideration physical psychological, social legal, and economic risk of possible privacy breach of WGS data. ML

An erroneous test result could result in an unnecessary, or even harmful medication change PL, ML

- Phlebotomy along with its associated risks ranging from ecchymoses, hematoma, nerve injury, infection. PL

Key
Probability P | Magnitude M | Duration D | Short S | Low L | Moderate M Extensive E

The use of the PGx dashboard of the PGx test results does not alter the magnitude of risks to subjects whose medications are changed from one standard of care medication to another standard of care medication. These choices are made by physicians, within their professional discretion and statutory scope of practice, and regrettably, it is common for medications to be harmful because of the unknown genetics of the patient or unrevealed drug interactions. These choices are routinely made by primary care physicians (and specialists) without the benefit of understanding whether a patient may be experiencing adverse drug reactions and understanding whether those reactions may be a result of drug-drug interactions to drug-gene interactions. Put another way, the menu of choices of medications is not altered under the Protocol or by virtue of Pilot Study WGS Extension participation, only that the physician is more informed.

The likelihood of new risk is slightly increased in that test results could be erroneous or improperly rendered by the ActX CDS. In such a case, the physician may choose a new standard of care medication while ***mis****informed* about the genotype of a patient. This is no worse than choosing a new standard of care medication while ***un****informed* about the genotype of a patient. The likelihood of such errors is inherent in all CLIA tests that are used pervasively in the practice of medicine, and the probability and magnitude of risk to the patient is miniscule. One of the two principle of beneficence in the Belmont Report is to "maximize the possible benefit and minimize possible harms." In the present case, the benefits of informing medication management far outweigh the inherent risks of making suboptimally informed medication management decisions (or doing nothing) when the medications the patient is currently taking are suspected of currently inflicting harm. Subjectively, the likelihood and magnitude of harm to subjects are low while the potential benefits are highly probable.

Test results from CAP/CLIA laboratories for high complexity LDTs that have undergone proficiency testing have low probability of being erroneous. Additionally, the ActX platform classifies the predicted severity/magnitude of ADR for specific drug-gene variant pairs of known clinical significance and provides customizable alerts for such pairs. If patient experience with a medication is incongruent with predicted phenotypes (e.g. tolerance and response to a change in medication), medication levels can be measured under this protocol (with no cost to patient or insurance) to confirm the medication is within know therapeutic windows.

17. Potential Benefits to Participants:

The study is designed in alignment with the principles of *Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research – Report to PCORI* [11]. A description of the scope of the polypharmacy problem is described in more detail in Sections 3: Objectives, 4: Background, 9: Outcome measures, 13: Participant Safety.

Additionally, we seek to understand how and when polypharmacy begins the cascade of ADRs such as ED visits, falls, or expression of another comorbidity. Our expectation is that a patient will experience reduced polypharmacy burden, and that participation in a medication management program with pharmacogenomic and informed drug dose titration (when warranted), will reduce ADRs that are common and frequent in these populations. We also expect that participation will improve adherence.

The clinical burden of highly prevalent anticholinergic medications can be quantitatively monitored such that refined use of this class of drugs has substantial potential to inform and impact this major contributor to polypharmacy burden.

Benefits of the study for the healthcare and scientific communities

The potential benefit and reason for requesting this study is to develop a polypharmacy solution utilizing electronic clinical decision support, pharmacogenomic studies, and blood drug levels (derived from urine drug levels in this study). We might understand the impact of comorbidities such as depression or cognitive problems due to non-compliance. These phenomena are major drivers of high healthcare utilization, with genetic and social determinants. This care team strategy enables the collection of data underlying these factors. It can help inform clinical decision making (medication adjustments) in a manner that improves quality of life (reduced side effects), and clinical outcomes for patients (improved efficacy).

As the enrolled population and our database grow, we might identify novel genotypes for drug metabolism that inform precision dosing and improve risk management through medication management programs. Our informed consent form, collaborative structure, and contracts will thoughtfully account for the best way to allow for compliant and deidentified sharing of the data collected under this protocol with the clinical and scientific community, including but not limited to peer-reviewed publication.

18. Vulnerable Populations:

Not eligible.

19. Sharing of Results with Participants:

The results of the IPGx's evaluation and management, such as lab data, pharmacogenomics results, and drug blood levels (inferred from urine drug levels in this study), will be shared with the referring physician in Texas A&M Family Care Clinic and patients as soon as it is practical during care, referred back to the referring physician with a report to explain medication management recommendations. Results may be shared, utilizing all means of communication commonly available to physicians in the practice of medicine. For example, at the time of visit or by phone. The rationale for this is that clinical decisions will be made regarding medication management, and the patient will be an engaged participant in that process. Results in the form of a precision medication management dashboard report summarizing germane information about drug concentrations and relevant CYP variants, will be shared with the ordering physician and the referring physician/primary care physician in written form. Results of WGS are research use only and will not be clinically actionable and not shared with healthcare providers or research participants. Incidental findings will not be shared with participants under this protocol.

20. Setting:

Texas A&M University. Research participants will be recruited from the patients referred to the IPGX clinic from their primary care physician for polypharmacy problem consultation. The out-patient IPGx clinical site will be a clinic owned and managed by Texas A&M Health. Participants will be recruited from Texas A&M primary care clinics. Collaboration with the primary care

component would involve patients who meet inclusion criteria prescribed by this protocol. In some instances, as requested by the referring physician, IPGx clinicians will make medication change recommendations, and keep the referring clinic apprised of these recommendations. If a patient wishes to be seen at the IPGx but does not meet inclusion criteria, all recommendations will be directly reported to the referring primary care clinic for review and determination. The research will be performed at the clinic site designated by Texas A&M, but some bioanalytic sample analysis will occur offsite.

No community advisory review board other than what is customary for Texas A&M is considered currently. If the decision is made that a community advisory board is indicated, members might include those who represent the referring physicians, a community pharmacy, and a patient advocate.

21. Personnel and Resources Available:

Dr. Ramos MD, PhD, PharmB- Principal Investigator

Dr. Ramos is a licensed physician-scientist with training and certifications in clinical pharmacology, toxicology, forensic medicine, pulmonary and integrative medicine. He is an inductee in the National Academy of Medicine and a tenured professor at Texas A&M Health Science Center. Dr. Ramos also is Associate Vice President at the Texas A&M University Health Science Center and Assistant Vice Chancellor for Health Services for the Texas A&M University System. Previously, Dr. Ramos was founding director of the University of Arizona Health Sciences Center for Applied Genetics and Genomic Medicine and chief medical and scientific officer of the Arizona Precision Medicine Initiative and has been instrumental in developing precision health strategies, diagnostic technology, and clinical data strategies to improve health care delivery. Dr. Ramos will be the Principal Investigator and be the ultimate decision-maker and have supervisory authority for the conduct of the protocol and management of the Registry. Dr, Ramos will also participate in data analysis.

Dr. Gabriel Neal MD, Co-Investigator

Dr. Gabriel Neal is board certified in Family Medicine and received his MD from the University of Oklahoma in 2001. Dr. Neal first joined the Department of Family Medicine in 2008 and is faculty in the Texas A&M Family Medicine Residency. Over the past decade, he has taught in numerous pre-clinical and clinical courses for the College of Medicine. He is the Family Medicine Clerkship Director for the A&M Integrated Medicine Program at the Bryan-College Station College of Medicine Campus. His teaching illuminates applied evidence-based medical care and ethics. He was awarded Clinical Faculty Preceptor of the Year in 2011 and Outstanding Faculty in Family Medicine in 2019. Dr Neal holds several roles: Department Head, Primary Care and Rural Medicine; Clinical Professor; Faculty, Texas A&M Family Medicine Residency and is involved in several clinical research projects. Dr. Neal will assist in the recruitment and consenting of patients who might be eligible for, and benefit from participation. Dr. Neal will also participate in data analysis Dr. Neal will assist in the recruitment and consenting of patients who might be eligible for, and benefit from, participation in the IPGx pharmacogenomic program.

Sara Rogers, PharmD, BCPS
Sara Rogers is a Clinical Assistant Professor of Pharmacy Practice at Irma Lerma Rangel College of Pharmacy, Texas A&M University. Dr. Rogers has served as co-investigator for a

pilot study to identify ethical values and priorities related to pharmacogenomics. Her research focuses extensively on patient access to and reimbursement for pharmacogenetics testing. Rogers serves an organizational member of the NIH National Human Genomics Research Institute Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG), Pharmacogenomics Working Group and a member of the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dissemination Working Group. Rogers co-leads the Standardizing Laboratory Practices in Pharmacogenomics (STRIPE) Collaborative Community, a public-private multidisciplinary initiative to develop consensus-based industry standards for pharmacogenetics testing. She will be a healthcare provider in the IPGx clinic and assist in the recruitment and consenting of patients who might be eligible for, and benefit from, participation in the IPGx pharmacogenomic program.

Rick Silva, PhD, MBA Co-Investigator

Dr. Rick Silva is Executive Director Executive Director, Clinical | Translational | Industry Collaborations at Texas A&M Health Science Center and holds an academic appointment as Assistant Professor of Translational Medical Sciences in the Texas A&M Institute of Biosciences and Technology. He has scientific training in physiology and neuroendocrinology, with significant experience in implementation and management of clinical and translational research programs, including dimensions of regulatory science, diagnostic technology development, cohort strategy, and clinical data strategies in clinical translational collaborations among academic medical centers and industry. Dr. Silva will serve as coordinator of implementation of its data strategy with the IPGx and Family Medicine Clinics. Dr. Silva will also participate in data analysis.

George Udeani, PharmD, DSc, FCP, FCCP Co-Investigator

Dr. George Udeani is a Clinical Professor and Head of the Department of Pharmacy Practice at Irma Lerma Rangel College of Pharmacy, Texas A&M University. Dr. Udeani completed postdoctoral training in anticancer drug discovery and development with the National Cancer Institute-National Institutes of Health, Bethesda, MD. He is a Fellow of the American College of Clinical Pharmacology, and Fellow of the American College of Chest Physicians. Dr. Udeani has served as principal investigator for numerous pre-clinical, as well as Phase III and Phase IV clinical trials. Dr. Udeani has published extensively on the use of Clinical Decision Support Systems in Medicine and Pharmacy, as well as in the areas of pharmacokinetics, and pharmacodynamics. Dr. Udeani will consult on interpretation of pharmacogenomic and pharmacokinetic results and provide input on data collection and program strategies for the IPGx Registry. Dr, Udeani will also participate in data analysis.

Asim Abu-Baker, PharmD Co-Investigator

Dr. Abu Baker is Clinical Professor and Associate Dean of Clinical and Professional Affairs at Texas A&M University Irma Lerma Rangel College of Pharmacy. Dr. Abu-Baker previously held appointments at California Health Sciences University College of Pharmacy as Associate Professor of Clinical Sciences and Chair of the Department of Clinical and Administrative Sciences (2014-2017), St. John Fisher College Wegmans School of Pharmacy (2007-2014) as Tenured Associate Professor of Pharmacy Practice and Assistant Director of Experiential Education; and Assistant Professor of Pharmacy Practice at Lake Erie College of Osteopathic Medicine School of Pharmacy (2004-2007). He completed his PharmD and an Ambulatory Care Residency with a focus on Endocrinology and Internal Medicine at the Albany College of Pharmacy. Dr. Abu-Baker completed the American Association of Colleges of Pharmacy

(AACP) Academic Leadership Fellowship in 2014 and the Accreditation Council for Pharmacy Education (ACPE) Accreditation Reviewer training in 2012. His research experience is in clinical outcomes and practice research. Dr. Abu Baker will consult on interpretation of pharmacogenomic and pharmacokinetic results and provide input on program strategies for the IPGx Registry. Dr, Abu Baker will also participate in data analysis.

Fen Wang PhD, Co-Investigator
Dr. Wang earned his Bachelor of Science in Microbiology and Master of Science in Cell Biology degrees at Xiamen University, and his Ph.D. in Biochemistry and Cell Biology at Clarkson University at Potsdam, NY. He undertook postdoctoral studies for Cancer Research and Nutrition at Texas A&M University. Dr. Wang joined IBT as Assistant Professor where he was promoted to Associate Professor with tenure and Professor with tenure at the Texas A&M University System Health Science Center. Dr. Wang will serve as coordinator of the IBT Biobank. Dr. Wang will also participate in data analysis.

Marcia Ory PhD Co-Investigator
Is a Regents and Distinguished professor for the Department Environmental and Occupational Health at the Texas A&M School of Public Health. With a long-standing interest in aging and public health, Dr. Ory is the founding director of the university-wide Center for Population Health and Aging, chair of the SPH Health and Wellness Committee and academic partner for the Community Research Center for Senior Health with Baylor Scott and White Health. She chairs the HSC Opioid Task Force and is working with an interdisciplinary cross-campus group to foster innovative research, education and service projects emanating from the health Sciences Center. She co-leads Healthy Texas, a new system-wide effort to examine strategies for promoting health and wellness for all Texans. Dr. Ory was honored for her sustained commitment to her research, receiving The Association of Former Students' Distinguished Achievement Award in Research from Texas A&M University for 2021. Prior to coming to Texas, A&M University, Dr. Ory spent 20 years in federal service as chief of Social Science Research on Aging in the Behavioral and Social Research Program at the National Institutes of Health's National Institute on Aging. Dr. Ory received her Bachelor of Arts in sociology and psychology from the University of Texas, Master of Arts in sociology and human development from Indiana University, doctorate in family studies and human development from Purdue University and Master of Public Health in chronic disease epidemiology and behavioral sciences from John Hopkins University Bloomberg School of Public Health. Dr. Ory will participate in data analysis.

Institutional

A limited data and nondisclosure agreement for deidentified data has been promulgated with Actx, and IC42, In the event of termination of the collaboration the protocol and informed consent will be revised and submitted for approval of the amendments.

Collaborating organizations

Geneial. Geneial is a Houston, TX based genomics informatics company that has developed a platform for patient centric privacy-preserving data sharing of genomic test results and patient-generated health data. Geneial has service lines for rare disease patient registries to facilitate secure engagement with individual research participants and patients in the context of clinicogenomic registry programs.

Actx is a CAP/CLIA and ABFT certified clinical diagnostics laboratory. In terms of research related activity outside the institution, please see 12.0 Data and Specimen Banking. The Texas lab is CAP CLIA, and ABFT certified. Lab specimens for pharmacogenomics would be handled off-site in ActX Austin, TX clinical lab.

IC42 is a CAP/CLIA and ABFT certified clinical diagnostics laboratory. In terms of research related activity outside the institution, please see 12.0 Data and Specimen Banking. The Colorado lab is CAP CLIA, and ABFT certified. Lab specimens for drug blood levels (derived from urine levels in this study) would be handled off-site in IC42's Aurora, Colorado clinical lab.

22. Prior Approvals

IRB approval of this protocol, and amendments hereto, will be obtained from Texas A&M IRB, and any IRB of future collaborative health systems and research institutions.

23. Confidentiality

Please see above 7, 11, 12, 13 and 19

- *Where and how data or specimens will be stored locally?* Any samples will be collected at the Texas A&M Family Medicine Clinic using biosafety compliant collection kits provided by IC42, andActx, and shipped immediately by standard shipping. the samples will then be handled at IC42 and Actx, in accordance with a fully certified lab. Specimens for this pilot study will not be entered into a biorepository.

- *How long the data or specimens will be stored locally*? Specimens will be confidentially stored at IC42 and Actx, until analysis and destroyed within 60 days after usable results are generated.

- *Who will have access to the data or specimens locally*? Nobody will have access to the specimens locally other than the research staff at the TAMU clinic. Data within the eCW and ActX systems is available to authorized providers and personnel with a password.
- *Who is responsible for receipt or transmission of the data or specimens locally?* A clinic staff member at the TAMU clinic will ship specimens using the kits provided by IC42 and Actx. Clinical test results will be sent directly to TAMU Family Medicine and uploaded into the eCW by an investigator on this protocol or authorized staff under his/her supervision and accessed by TAMU staff and Investigators through secure access. Data from WGS will be uploaded to TAMUs AWS cloud enclave.
- *How data and specimens will be transported locally?* Local transport of specimens will be done by study staff or investigators. Data will be stored in the TAMUs AWS cloud enclave on the cloud.

24. Provisions to Protect the Privacy Interests of Participants:

We will obtain written informed consent for participation, interaction, and collection of medical data from a patient. No participant will be required to interact with anyone or share personal information with anybody other than their care team providers at their referring clinic and the

Texas A&M IPGx staff. See exclusion criteria about unwillingness to participate or consent. Participants will be made to feel at ease through open communication with Texas A&M IPGx staff and explanation of data use sharing and limitations thereof in the informed consent form. Participants should feel no more or less uncomfortable than when presenting to any general medicine clinic. There is nothing invasive to worry about other than giving urine and a buccal swab. Discomfort about sharing DNA information can be addressed in the informed consent form and consultation. Participants will be advised that their information will always be handled confidentially and on secure platforms with password protections and 2 factor authentication. Data will be protected by the lab, and within their medical record, in accordance with federal privacy laws. Authorized members of the research and care team will have a password so that they can access the secured electronic health record.

25. Compensation for Research-Related Injury

N/A

While outcome data will be collected, this protocol is not intended to evaluate or propose any experimental intervention outside standard of care (i.e., drugs for FDA approved indications, or off label use at the discretion and direction of the prescribing physician).

26. Economic Burden to Participants

Transportation to the clinic. The possible need to go to a pharmacy and pick up a new prescription. The costs of the tests will be supported by Texas A&M. Doctor visits will be billed to their health insurance carrier if healthcare services are provided outside the scope of this protocol.

27. Recruitment Methods

(*Describe when, where, and how potential participants will be recruited*.) Dr. Neal has identified many of his patients who might benefit from participation in this IPGx Pilot study. Research recruiting will be performed by Drs. Neal and Rogers and their staff using email, telephone calls, or in-clinic discussion as warranted for each patient. The collateral materials used will include a call/in person script, an email script, and a general brochure about clinical research participation.

Subject compensation not contemplated.

28. Consent Process

We will obtain consent in a basic informed consent form [**Appendix 1**]. Consent forms will be signed with a wet ink signature on a printed consent form or as a secure digital signature on the PDF file using the Adobe Sign function and attached to the WGS metadata.

An individual team member authorized by the principal investigator and IRB can obtain consent from patients. Regardless of who is obtaining consent, the Principal Investigator is responsible to ensure the correct procedures are carried out.)

- Where will the consent process take place? At the designated IPGx (Interprofessional Pharmacogenomics Clinic) or Family Care Clinic.
- Any waiting period available between informing the prospective participant and obtaining the consent? It would be at the discretion of the patient to consent when they decide they are comfortable participating.
- Any process to ensure ongoing consent? If any material changes to the research or significant findings that could affect their willingness to continue participation in the study, subjects will be notified. Participants may end their participation at any time.
- The role of the individuals listed in the application as being involved in the consent process. The role of the PI would include answering an enrollee's questions, discussing risk - benefit options and alternatives, and reporting back to the team. A patient consent to participate will be obtained in writing.
- The time that will be devoted to the consent discussion. As much as needed, 1 hour estimated, inclusive of medical history and prescription information collection.
- Steps that will be taken to minimize the possibility of coercion or undue influence. We can make it clear at the outset that this is completely voluntary, and the consent form will emphasize this. It will not in any way jeopardize the patient's relationship with their doctor or anyone else. No financial inducements will be used.
- Steps that will be taken to ensure the participants' understanding.) Patient will acknowledge in writing they understand. There can be a translator if needed for Spanish speaking subjects on select clinic days.

Waiver or Alteration of Consent Process:

NA.

Participants who are not yet adults (infants, children, teenagers)

N/A.

This study will focus on adults.

Cognitively Impaired Adults

Consent of such subjects will be done in accordance with Texas A&M policies, ethics, culture, and legal considerations.

Adults Unable to Consent

N/A, to be excluded. See inclusion/exclusion criteria.

30. Process to Document Consent in Writing:

See **Appendix 1- Informed Consent Form**

31. Drugs or Devices:

Clinical Decision Support

It should be noted that the FDA has a current posture of not regulating physician-facing clinical decision support tools (24). However, the FDA has issued nonbinding guidance (25) for Software as a Medical Device (SaMD) that recommends design control and clinical evaluation standards, including the use of third-party certifications, for SaMD. While the ActX CDS and the pharmacogenomic dashboards being used in this protocol are not subject to FDA regulation under the SaMD framework (as for electronic medical record readouts), the ActX CDS platform has received certification from rigorous third party (ONC-Authorized Certification Bodies) evaluation.

Pharmacogenomic Testing
These results will be used for clinical decision making and for research.
The pharmacogenomic tests being conducted by ActX are lab-developed tests (LDT) marketed under the Clinical Laboratory Improvement Amendments (CLIA) under the jurisdiction of the Centers for Medicare and Medicaid Services. Most medical decision-making is based on LDT tests marketed under the CLIA framework, which covers about 260,000 laboratories in the US, and is interpreted by physicians (and pharmacists) within the statutory scope of practice and accepted medical guidelines. Most clinical DNA sequencing and especially, pharmacogenomic are commonly made available under the LDT-CLIA regulatory framework and used in accordance with established consensus medical guidelines. Consensus medical guidelines for actions based on results of pharmacogenomic exist, are curated by the Clinical Pharmacogenetics Implementation Consortium (CPIC), and are endorsed by Association for Molecular Pathology, American Society for Clinical Pharmacology and Therapeutics, and the American Society of Health-System Pharmacists.

Clinical Pharmacokinetic Tests
These results will be used for clinical decision making and for research.
The pharmacogenomic tests being conducted by IC42 and Actx, are lab developed tests (LDT) marketed under the Clinical Laboratory Improvement Amendments (CLIA) under the jurisdiction of the Centers for Medicare and Medicaid Services. Most medical decision-making is based on LDT tests marketed under the CLIA framework, which covers about 260,000 laboratories in the US, and is interpreted by physicians (and pharmacists) within the statutory scope of practice and accepted medical guidelines. CLIA and CAP documentation is available upon request.

Whole Genome Sequencing
Whole genome sequencing results will be designated for research use only.

Whole genome sequencing will be conducted by Admera (South Plainfeild, NJ) at 30X depth. FASTQ/BAM and VCF will be uploaded to TAMU's AWS server instance.

32. Waiver of IND or IDE

Not relevant

33. Community-Based Participatory Research*

Describe involvement of the community in the design and conduct of the research. N/A

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