1. Protocol title:

The Texas Interprofessional Pharmacogenomics PILOT Cohort

2. Study team

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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 (clinical semantic network; CSN) dashboard to identify drug regimens 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 EMR, and the Family Medicine Practice. There is no prospective comparison group because this is a pilot study for a registry.

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 on a formulary continues to lag behind existing technologies. 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 define 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 elder 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 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.

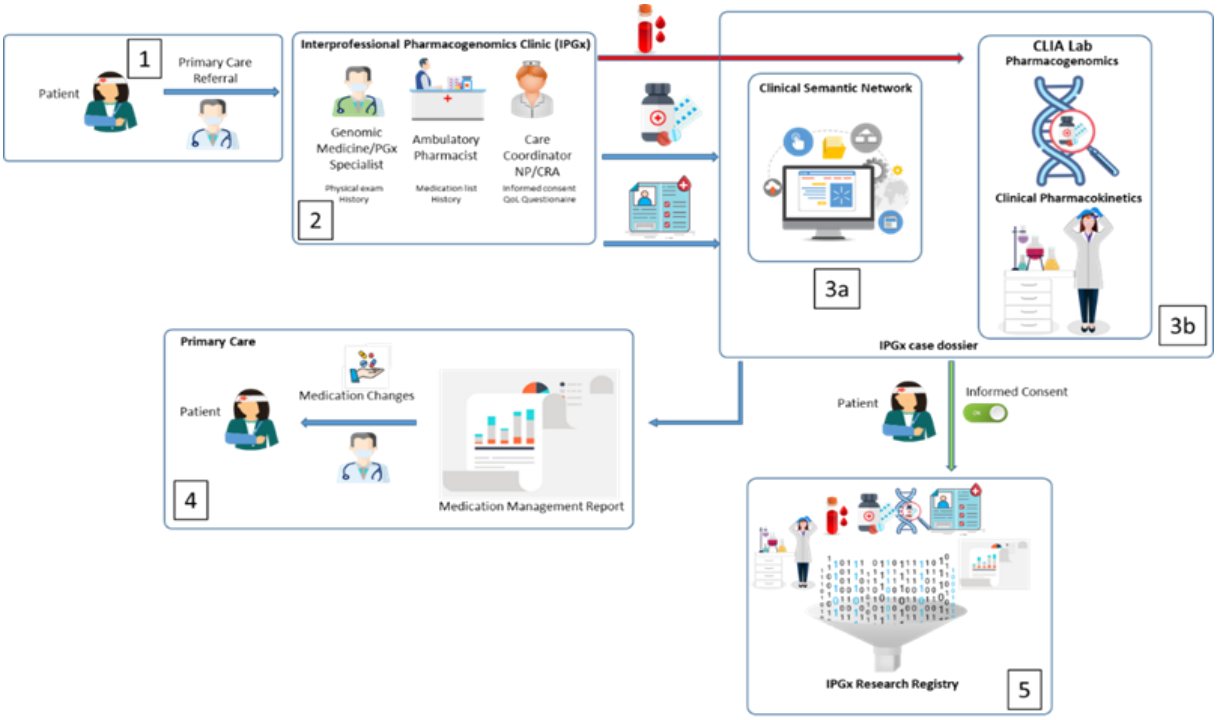


Figure 1 Interprofessional Pharmacogenomics (IPGx) Model. 1. Referral of polypharmacy patient to the IPGx clinic. 2. Interprofessional team collects relevant medical history with an emphasis on information related to chief complaints, which also includes a transition of care history from primary care 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).

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 can be entered as computable actionable data prior to a visit in order to better track 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, and this is especially true in clinical cases of polypharmacy. In the end, this information can become more readily available to both patient and provider utilizing the Interprofessional Pharmacogenomics (IPGx) care model.

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.

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 CSN 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 GENERALIZED 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 CSN, can validate the clinical and cost-effectiveness of those decisions.
- What is the best use 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 CSN to be used here is a proprietary computable health record system containing millions of interrelated medical findings 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 CSN.

5. Inclusion and Exclusion Criteria:

Inclusion
We plan to recruit at most 50 volunteers from the Texas A&M affiliated community health family medicine program.

- People 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, undergo a comprehensive history and physical examination.
- All genders.
- Age 45 and over.

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
- Pregnant patients will be excluded
- Unable/unwilling to consent.
- Unable to verbally communicate and comprehend English/Spanish 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

7. Multi-Site Research:

Texas A&M Health Family Care Clinic and the Texas A&M Interprofessional Pharmacogenomics Clinic (IPGx) (12) is co-located within facilities made available by the Department of Primary Care and Population Health. Patients will be referred to the IPGx exclusively from the Texas A&M Family Medicine Clinic. working closely with our laboratory collaborators, InnovativeGx, located in San Antonio, TX, IC42 in Aurora Colorado. A research collaboration agreement has been be promulgated among Texas A&M and Goldblatt systems to ensure data sharing and reporting is compliant with all relevant regulations. InnovativeGx, and IC42 will receive specimens labeleed with a code thathe TAMU research team will use ot reidentify the reports when they come back to TAMU. InnovativeGx, and IC42 will not have access to the codes .

Research activities will occur at all of the sites mentioned, but patient recruitment will be limited to Texas A&M Health Family Care Clinic and the Texas A&M Interprofessional Pharmacogenomics Clinic (IPGx).

All sites will have the most current version of this Pilot Study 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 and General Data Protection Regulation standards. Through regular dialogue and open communication will be made so that all local site investigators conduct the study appropriately. 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:

The duration of individual participation period in the study is limited to their medical encounter in the IPGx clinic, and any subsequent medication management visits their primary care physician refers back to the IPGx. No more than 180 days from the date of their enrollment in the study.

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 coordinator, and a nurse. Those patients who are eligible for inclusion in the research study would be offered enrollment. Patients who choose not to participate in the study are still eligle to receive care, without prejudice. After detailed educational instruction and informed consent, including risks and benefits of the study, patient medical information would be input into the CSN, which functions as a computable EHR. The **attached informed consent** obtains permission from every individual to use their clinical, genetic, and lab data.

Medical record analysis will be conducted as follows (Excerpt from Silva et al., 2021 (12)):

> Polypharmacy patients and patients demonstrating symptoms and complaints that might be indicative of possible medication interactions are referred to the IPGx clinic for evaluation by the attending clinician (Figure 1, step 1). Patients are not required to consent to the registry to receive the bioanalytic workup and medication management care; registry participation is optional and not a condition of care. The program entails a process of stepwise progression of electronic medical record analysis toward pharmacokinetic ground truth to inform primary care practitioners. The first step consists of a clinically aware computational analysis such that entry of complaints into the patient's record, updates the rendering of complaints that match the known side effects (from First Data Bank) of drugs taken by the patient. The second step strengthens these associations if a pharmacokinetic model of the medications renders potential instances of pathway overload (Epocrates). Next the CSN can further strengthen these associations by identification of pharmacogene variants of known clinical significance that are consistent with the list of candidate side-effects or pathway overload. Finally, pharmacokinetic data is incorporated to distinguish among and validate instances of drug-gene or drug-drug interactions.
>
> ***3.2 Medical Record Analysis and the Clinical Semantic Network***
>
> The first step is a computational and semantic comparison of case history to the medications the patient is taking. This is powered by DrugBank (13), Epocrates (14), and Lexicomp (15) to tally the subset of symptoms that are present *and* known to occur as side effects of the medications the patient is taking. At a clinical informatics level, cough with fever might be connected / mapped to curated ontologies such as SNOMED (**S**ystematized **No**menclature of **Med**icine (16)) about SARS COV2, or pneumonia in a weighted fashion, by subject matter experts who then have the capability to markedly enhance this highly navigable information. A net result is that a SNOMED identification can be established with multiple attributes built

into the CSN system. Other analogies in the CSN include instances when a chief complaint is entered such that the system knows which history of present illness questions should be used to interrogate. The technology works much in the same manner as Google can predict shopping preferences based on user actions.

For the purposes of this communication, we created a virtual patient with medication, pharmacogenomic and side effect profiles that were aggregated drawing from previous experiences with a number of real-life clinical cases. The clinical characteristics assessed included:

- Number of side effects / complaints / diagnoses identified in the patient and believed to be related to his/her current medication regimen,
- Number of medications possibly contributing to the identified / diagnosed side effects,
- Number of drug metabolic pathways identified as being potentially overloaded,
- Number of drug metabolic pathways identified as borderline overloaded,
- Number of medications with pharmacogenomic profiles,
- Number of medications putting the patient at risk for serotonin syndrome,
- Number of medications putting the patient at risk for QT prolongation,
- Number of anticholinergic medications.

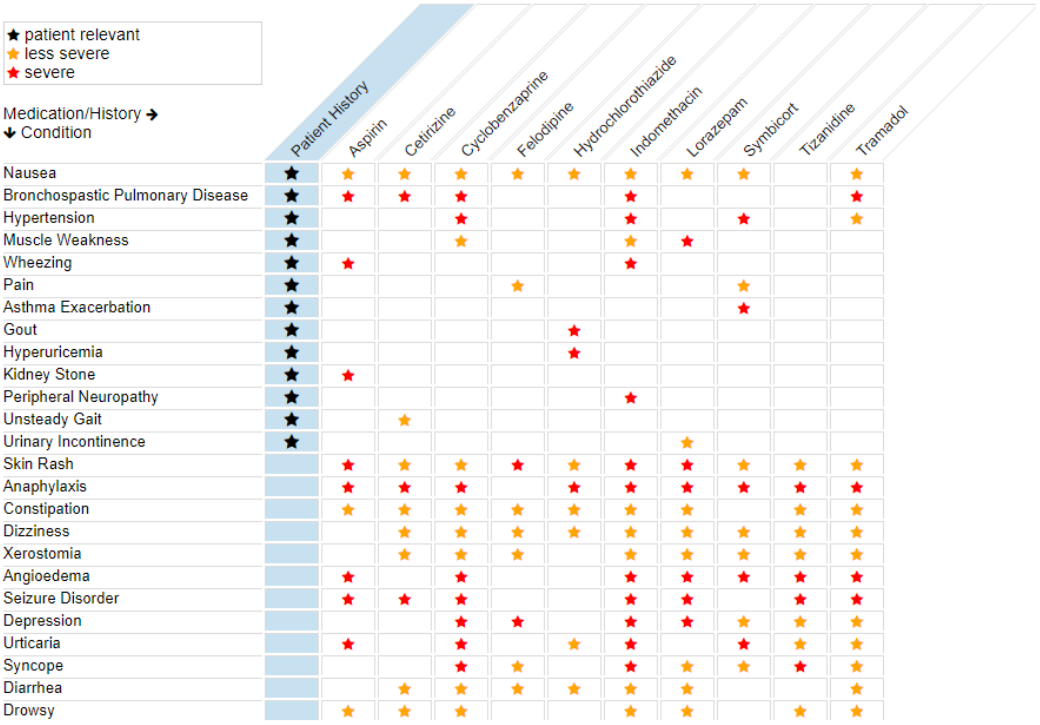
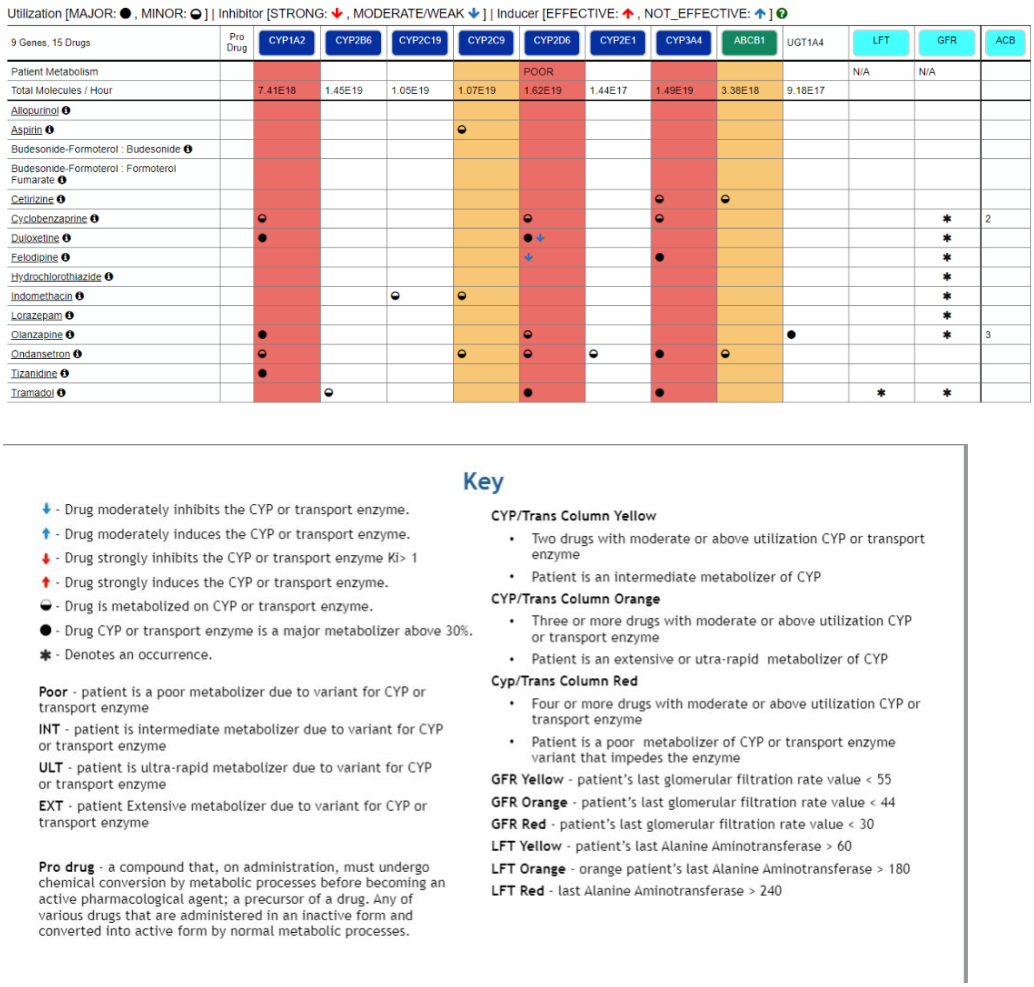


Figure 2: *Side Effects Dashboard*. List of symptoms indicating potential pharmacological origin.

At this step, a side-effects dashboard is created by the CSN utilizing any drug in the First Databank to distill complaints that could be of pharmacological origin. Figure 2 provides a summary of selected computational clinical findings for the virtual patient which are also a rendering of the complaints from Table 1, that correspond to the subset of complaints that are also known side effects of the medications the patient is taking. Those side effects, as initially rendered prior to pharmacogenomic profiling, may not inherently be of pharmacological origin, or may arise due to drug-drug interactions, or as a result of drug-gene interactions. Pharmacogenomic testing and pharmacokinetic testing can reveal whether these complaints are rooted in drug-gene or drug-drug interactions. . The CSN can be contrasted from step-and-fetch functionality of most electronic medical records by the interconnectivity of medical terms. Those medical terms are connected in a neural-like network of semantic associations that effectively represent knowledge and contextual awareness of potentially related data elements in a patient record. The network consists of nodes representing objects and arcs which describe the relationship between those objects. Semantic networks can categorize the objects in various forms and can link those objects making it particularly useful in an electronic health record which can utilize and act on computable data. Interconnecting a patient's clinical content (phenotypes) with this form of health care knowledge gives the data in these relationships actionable context. There is a pharmacokinetic modeling dimension in this analysis that examines the

repertoire of medications a patient has been prescribed and that models these data based on known pathways for those medications to assess drug-drug interactions that might result from pathways that are excessively taxed by virtue of the combination of medications (Figure 3).



Utilization [MAJOR: ●, MINOR: ◒] | Inhibitor [STRONG: ↓, MODERATE/WEAK ↓] | Inducer [EFFECTIVE: ↑, NOT_EFFECTIVE: ↑]

9 Genes, 15 Drugs	Pro Drug	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4	ABCB1	UGT1A4	LFT	GFR	ACB
Patient Metabolism						POOR					N/A	N/A	
Total Molecules / Hour		7.41E18	1.45E19	1.05E19	1.07E19	1.62E19	1.44E17	1.49E19	3.38E18	9.18E17			
Allopurinol													
Aspirin					◒								
Budesonide-Formoterol : Budesonide													
Budesonide-Formoterol : Formoterol Fumarate													
Cetirizine								◒	◒				
Cyclobenzaprine		◒				◒		◒				*	2
Duloxetine		●				● ↓						*	
Felodipine						↓		●				*	
Hydrochlorothiazide												*	
Indomethacin				◒	◒							*	
Lorazepam												*	
Olanzapine		●				◒				●		*	3
Ondansetron		◒			◒	◒	◒	●	◒				
Tizanidine		●											
Tramadol			◒			●		●			*	*	

Key

↓ - Drug moderately inhibits the CYP or transport enzyme.

↑ - Drug moderately induces the CYP or transport enzyme.

↓ - Drug strongly inhibits the CYP or transport enzyme Ki> 1

↑ - Drug strongly induces the CYP or transport enzyme.

◒ - Drug is metabolized on CYP or transport enzyme.

● - Drug CYP or transport enzyme is a major metabolizer above 30%.

* - Denotes an occurrence.

Poor - patient is a poor metabolizer due to variant for CYP or transport enzyme

INT - patient is intermediate metabolizer due to variant for CYP or transport enzyme

ULT - patient is ultra-rapid metabolizer due to variant for CYP or transport enzyme

EXT - patient Extensive metabolizer due to variant for CYP or transport enzyme

Pro drug - a compound that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; a precursor of a drug. Any of various drugs that are administered in an inactive form and converted into active form by normal metabolic processes.

CYP/Trans Column Yellow

- Two drugs with moderate or above utilization CYP or transport enzyme
- Patient is an intermediate metabolizer of CYP

CYP/Trans Column Orange

- Three or more drugs with moderate or above utilization CYP or transport enzyme
- Patient is an extensive or utra-rapid metabolizer of CYP

Cyp/Trans Column Red

- Four or more drugs with moderate or above utilization CYP or transport enzyme
- Patient is a poor metabolizer of CYP or transport enzyme variant that impedes the enzyme

GFR Yellow - patient's last glomerular filtration rate value < 55

GFR Orange - patient's last glomerular filtration rate value < 44

GFR Red - patient's last glomerular filtration rate value < 30

LFT Yellow - patient's last Alanine Aminotransferase > 60

LFT Orange - orange patient's last Alanine Aminotransferase > 180

LFT Red - last Alanine Aminotransferase > 240

Figure 3. *Medication and Pharmacokinetic Pathway Summary*. The green rectangles are a few salient transporters, and the light blue box represents anticholinergic burden. The left most vertical column denotes the patient's medications. Vertically the column beneath named alleles in red indicate that the respective pathway could be overloaded. Panel B Key

This dashboard can incorporate correlative associations (complaints-drug side effects) and bioanalytic associations (PGx genotypes and predicted or measured pharmacokinetic). As such, this computationally rendered dashboard provides useful insight on the potential root cause of complaints both before and after bioanalytic analysis is entered into the CSN case record.

3.1 Bioanalytics

Pharmacogenomics is used to assess the impact of individual pharmacogenomic variants on how subjects respond to their medication by evaluating specific medication receptor targets as well as transporter functionality (17). The informatics design incorporates all Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines and the knowledgebases contained in PharmGKB and PharmVar to provide a cogent front-end presentation of case-relevant and actionable pharmacologic considerations for use by the clinician at point-of-care. The point of care dashboard only renders CPIC Level 1 and Level 2, Pharm GKB Level 1 and 2, the FDA Table of PGx Biomarkers, and FDA Table of PGX Association In summary, the digital dashboard from the CSN reflects a comprehensive analysis of known pharmacogenomic knowledge through the filter of established consensus medical guidelines. For illustrative purposes Table 3 presents a list of CYP2D6 haplotypes that the CSN is configured to dynamically incorporate into the rendering of the pharmacogenomic analysis. The CSN is capable of incorporating all variants of known clinical significance per CPIC guidelines. The patient scope varies and is dynamically adjusted to the variants that are presented by the instrumentation. The CYP2D6 haplotype call is made from the core variants for each haplotype and all other variants are verified as constant relative to that haplotype so variants of unknown significance are not presented as normal.

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 CSN and dashboards 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 staff will obtain a buccal swab to collect DNA for a pharmacogenomic evaluation pursuant to the sample collection kits from the CLIA lab, which will occur at the start of the study period. Blood chemistry will be taken from the EMR. Any blood taken for clinical chemistry during this visit is purely for clinical care and as warranted by the provider and not mandated by the research protocol. For measurement of drug levels, urine will be collected in kits provided by IC42 at room temperature will be shipped to IC42 each day via FedEx in provided biosafety shipping kits. Buccal swabs need no special preparation, and will be shipped each day via FedEx in provided biosafety shipping kits.

A single pharmacogenomic test will be conducted using DNA from the initial buccal swab. An assay for pharmacogenomic variants of known clinical significance for the drug-gene pairs

specified in Exhibit A [insert table or online reference to genotypes interpreted] will be conducted and a report generated (per the CPIC guidelines (20, 21)). In certain instances, blood or urine levels of drug 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 followup 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.
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. However, consensus medical guidelines for actions based on results of pharmacogenomic tests for a number of drug gene pairs 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. Put another way, the status quo presents greater risk of adverse drug reactions to the patient than participation in the protocol. 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.

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.

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. 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 CSN 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 CSN, pharmacogenomic results at Innovative Gx, blood work, 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 are required to change medication in order 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 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:

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) pending

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
InnovativerGx
5410 Fredericksburg Road
Suite 304
San Antonio, TX 78229
(210) 352-5175
ruben.bonilla@innovativegx.com

_____
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.

Clinical Data Center
Goldblatt Systems Clinical Semantic Network (CSN).
5151 East Broadway Blvd
Tucson AZ 85711
Telephone 520 495-1009

Goldblatt Systems CSN, as an EHR the data “lives forever” in the EHR. It is a web-based system with security policies and procedures meeting the same standards of commercial EHRs regarding, security, encryption firewalls, access and authorization.

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, not including genetic data) will be collected on site in Texas by the clinical team and entered into the CSN (part of Goldblatt Systems) through a cloud portal to a data center housed in Tucson AZ. Goldblatt Systems CSN has completed 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 PHI 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 CSN, and IC42, and InnovativeGxwill be managed in the Goldblatt systems CSN electronic health record.

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):

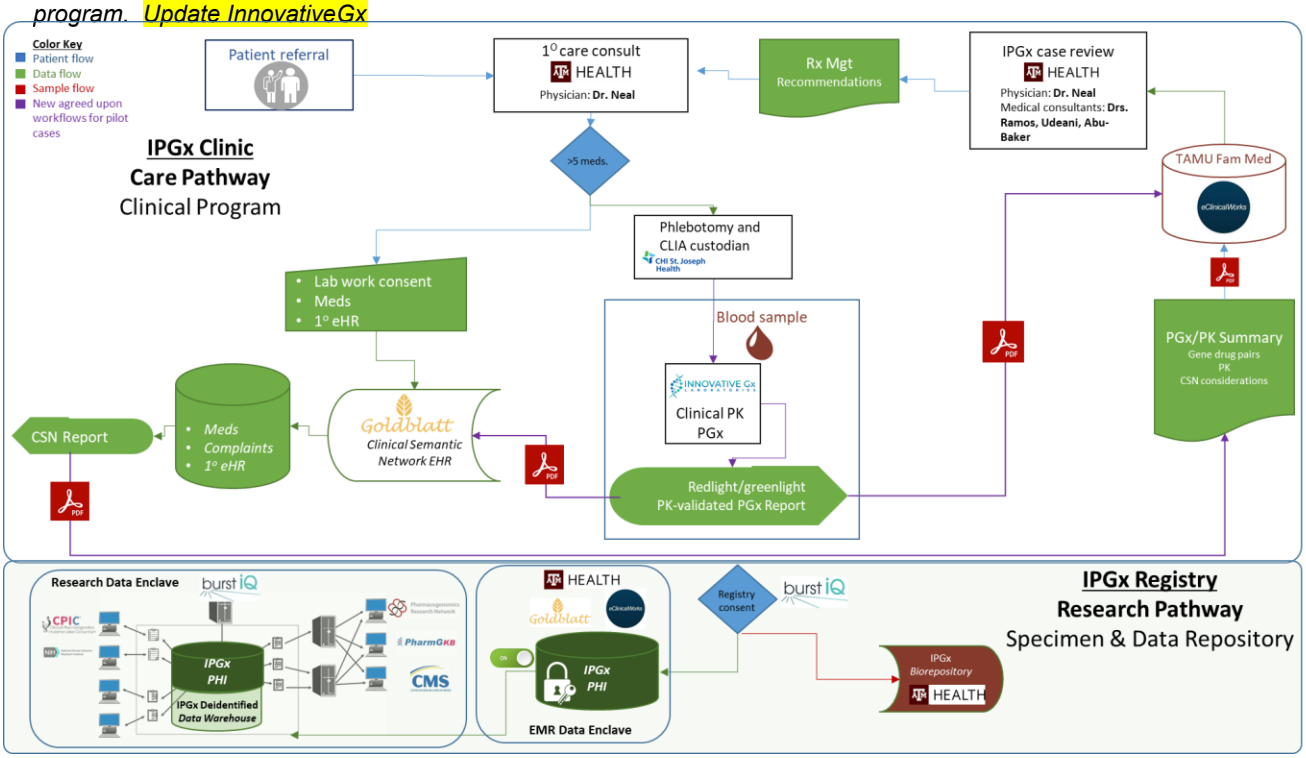
Clinical EHR

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

Lab

- Genotypes and raw sequence data, when available

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 program.* *Update InnovativeGx*



- Clinical chemistry
- Drug concentrations

Patients will be referred to the IPGx for evaluation and “consultation”. After the IPGx performs its evaluation, the document created in the CSN will be transmitted back to the referring physician.

There are several methods of accomplishing this.
- Initial phone call to discuss salient aspects of the evaluation
- A CSN-generated PDF will 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

All clinically actionable variants (per CPIC guidelines) obtained from the pharmacogenomic and steady-state pharmacokinetic assays will be compiled into the IPGx report and shared with the referring physician. 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. 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 are 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 Study, research activities (data collection only, there is no prescribed, randomized assignment to an intervention) will begin (Fig. 1). Any PHI 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 applied at all times.

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 CSN 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 CSN 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.

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.

It is expected that study participants remain engaged with the primary care clinic from where they were referred. Since the period of study 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 CSN Medical record and reconciled by Dr. Rogers, Abu-Baker, or Udeani,

under the supervision of Dr. Ramos and Dr. Neal 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 closeout of this pilot study, with a study report for each case appended to the CSN 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 CSN categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, definitely 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 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), the number of subjects is small (n=22), 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, their legal guardian, 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:

- ADRs consistent with standard of care for their disease burdens.
- Complications associated with a change in medication dose frequency or discontinuance of a medication. PL (probability low), see below
- Medication associated side effects such as nausea or vomiting, diarrhea, constipation, gastrointestinal, genitourinary, psychiatric, cardiac, or other medical system problems. PM MM DS (probability moderate, magnitude moderate, duration short) and so forth.
- Medication allergy such as rash, difficulty breathing, or as life-threatening as a Steven Johnson syndrome. PL, MM / L DS / M
- Other discomfort, hazards or inconveniences, taking into consideration physical psychological, social legal, and economic risk. ML
- Scheduling an appointment.
- Traveling to appointment.
- Transportation.
- Time spent in clinic.
- Phlebotomy along with its associated risks ranging from ecchymoses, hematoma, nerve injury, infection. PL

- Pharmacy and physician visit copay.
- Medication management in pregnant women, medication changes may carry significant inherent risk to the fetus. Pregnancy is both a reason for exclusion and being withdrawn from the protocol.

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 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 CSN. 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.

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, 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 the course of 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.

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. Please see section 7 above regarding multi-site. The CSN decision support will be handled either on-site in the Texas A&M clinic and or with assistance from CSN Tucson, AZ.

No community advisory review board other than what is customary for Texas A&M is considered at this time. 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, and pulmonary 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 for Research 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 Pilot Study. Dr, Ramos will also participate in data analysis.

Dr. David Jacobs MD, Co-Investigator
Dr. Jacobs is Chief Medical Information Officer for Goldblatt Systems, a health science company in Arizona that focuses on using a clinical semantic network with electronic health records and laboratory-based data focused on pharmacogenomics. He has been with the company since 2016 involved in the development and execution of a polypharmacy solution at the point of service for clinicians. Prior to that Jacobs practiced medicine in the areas of in-patient post-acute care and outpatient interventional pain management. During his tenure as medical director of an acute inpatient rehabilitation hospital, Jacobs became acutely aware and interested in the challenge of polypharmacy to the senior rehabilitation population and its impact on their functional outcomes, where he developed system-wide approaches to this issue prior to having tools and technology, such as electronic decision support or pharmacogenomic testing. Dr. Jacobs will consult with Family Medicine and IPGx on clinical workflows and clinical informatics implementation and coordinate the activities of Goldblatt systems to be optimally configured in support of the data collection and management strategies of the future IPGx Registry. Dr. Jacobs will mediate the decisions about which cases warrant additional pharmacokinetic assays (or no pharmacokinetic analysis) and will have access to identifiable data. He will not consent patients or provide care.

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. He is Director of the Texas A&M Family Care Clinic and 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 in the IPGx pharmacogenomic program. Dr. Neal will also participate in data analysis.

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 the Registry and 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.

John Kriak, Pharm.D, Co-Investigator
Dr. Kriak is a clinical pharmacist at MolecularDx and Goldblatt Systems with expertise in pharmacogenomics. He will consult on interpretation of pharmacogenomic and pharmacokinetic results and provide input on research analysis for clinical cases. Dr, Kriak will also participate in data analysis. Dr. Kriak completed his Doctor of Pharmacy degree in 1996 from Duquesne University in Pittsburgh PA. Since that time, he has become the president and CEO of CAMMCO, LLC, which is a clinical and strategic business consulting company. Dr. Kriak has over 25 years of experience providing clinical, medical education and business consulting services by authoring numerous educational programs, courses, and grants. Following graduation, he taught clinical pharmacology and biostatistics at Saint Francis University as well as worked as an author and subject matter expert for Kaplan educational centers in New York. Since 2007, Dr. Kriak has primarily been working with clinicians and technical engineers to help develop the clinical components of the Goldblatt Systems Clinical Semantic Network (CSN). He also currently works with MolecularDx scientists, clinicians, and technical architects on the development of genomic and therapeutic databases, business development for clinical testing services, writing of institutional review board (IRB) protocols, and clinical pilot program management.

Jim Garliepp, Co-Investigator
Jim Garliepp currently leads MolecularDx scientists, clinicians and Goldblatt systems technical architects on the development of genomic and therapeutic databases. He will supervise clinical informatics integration between Goldblatt Systems, and Texas A&M; develop steady state drug level modeling and dashboards; IPGx report formatting; and clinical data curation.

Reuben Guerrero, MD, DABMG, FACMG, MB(ASCP), CGMBS
Dr. Ruben Bonilla-Guerrero serves as Innovative Genomics (IGx) Laboratories' Chief Medical Officer. He is a laboratory professional, who is Mayo Clinic trained in Clinical Pharmacology, Clinical Biochemical Genetics, and Molecular Biology, a Fellow of the American College of Medical Genetics, the American Association of Clinical Chemistry, and is an active member of several distinguished professional organizations. Dr. Ruben Bonilla-Guerrero board certified in Clinical Biochemical Genetics by the American Board of Medical Genetics (ABMG) and in Molecular Biology by the American Society

for Clinical Pathology (ASCP), with expertise in clinical pharmacology, inborn errors of metabolism, genetics, vaccine development, and clinical pharmacogenomics. Having authored several peer-reviewed medical publications including book chapters, Dr. Bonilla-Guerrero is also the winner of the Henry Christian Award from the American Federation for Medical Research (2002) and the Mayo Clinic Department of Internal Medicine Outstanding Research Fellow Award (2003). Previously, Dr. Bonilla-Guerrero simultaneously served as Laboratory Director, Associate Medical Director, and Medical Director of Medical Affairs for the department of Genetics at Quest Diagnostics, as well as concurrently served as the Medical Director and Vice President of Medical Affairs at Admera Health. He is responsible for the clinical genomic-based testing at Innovative Gx Laboratories and leads the Medical Affairs team.

Institutional

The roles of Goldblatt Systems and Texas A&M Health for this limited scope pilot study is be codified in a Beta Testing Agreement, in which each party will have specified rights to terminate their involvement in the study. A limited data and nondisclosure agreement for deidentified data will be promulgated with Innovative Gx, 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

Goldblatt Systems LLC. The Goldblatt Systems LLC CSN Electronic Health Record will be used in the Precision Medication Management Practice and PHI/ePHI will be housed by Goldblatt in accordance with the BAA. The CSN in Tucson is HIPPA and ONC (Office of the National Coordinator for Health Information compliant). Goldblatt Systems LLC, as a small company, maintains no formal scientific/ethics policy. In the Tucson Office Goldblatt Systems has a staff of approximately 20 people, some of whom have worked with Dr. Goldblatt for many years prior, including Chief Technical Officer Jim Garliepp and the Director of Engineering. The team includes software engineers, content subject matter experts, implementation staff, and quality control and assurance staff. In Pennsylvania, Dr. Goldblatt employs approximately 20 people as well, which consist of world-class PhD's from places such as Johns Hopkins who have expertise in genomics, toxicology, mass spec, and includes operating various genetic arrays. At **InnovativeGx**in San Antonio, and IC42 in Aurora CO, there are several pathologists who have laboratory, toxicology, or forensic expertise. Goldblatt systems LLC has a clinical pharmacist (PharmD) on staff, in addition to business development legal and support personnel.

InnovativeGx 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 Innovative Gx's San Antonio, 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, and InnovativeGx, and shipped immediately standard shipping. Then the samples will be handled at IC42 and InnovativeGx, 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 InnovativeGx, until analysis and destroyed 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 phlebotomy staff at the TAMU phlebotomy lab. Data within the CSN is available to authorized providers and personnel with a password.
- *Who is responsible for receipt or transmission of the data or specimens locally?* A phlebotomy staff member at the TAMU phlebotomy lab will ship specimens using the kits provided by IC42 and InnovativeGx. . Test results will be sent directly to TAMU Family Medicine and uploaded into the CSN by an investigator on this protocol or authorized staff under his/her supervision and accessed by TAMU staff and Investigators through secure access to the CSN .
- *How data and specimens will be transported locally?* There will be no local transport of specimens. Data will be stored in the CSN on the cloud.
- This CSN Module is 2015 Edition compliant and has been certified by an ONC-ACB in accordance with the applicable certification criteria adopted by the Secretary of Health and Human Services.
- https://www.goldblattsystems.com/wp-content/uploads/2020/01/Goldblatt-2015-Edition-Certificate-1.pdf

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. Data will be protected by the lab, and within their medical record, in accordance with federal privacy laws. The genetic material obtained (see 12 above) will only be used to determine a patient's enzymatic handling of medications. The test to be administered will not delve into someone's heritage, or other sensitive information, beyond what they consent to. 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

Medication management decisions are up to the referring physician or the IPGx clinic physician (if appropriate).

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.

27. Recruitment Methods

(*Describe when, where, and how potential participants will be recruited*.) Dr. Neal has identified 22 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**].

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 older 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:

Electronic Medical record

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 CSN 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 CSN platform has received certification from rigorous third party (ONC-Authorized Certification Bodies) evaluation.

Pharmacogenomic Testing

The pharmacogenomic tests being conducted by I InnovativeGx, 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 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

The pharmacogenomic tests being conducted by IC42 and InnovativeGx, 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 interpreted by physicians (and pharmacists) within the statutory scope of practice and accepted medical guidelines. CLIA and CAP documentation is available upon request.

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

34. References

1. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009;4(2):e4439. Epub 2009/02/12. doi: 10.1371/journal.pone.0004439. PubMed PMID: 19209224; PMCID: PMC2635959 Chair of its Pharmacovigilance Expert Advisory Group. All the other authors have nothing to declare.
2. Ingelman-Sundberg M. Genetic variability in susceptibility and response to toxicants. Toxicology Letters. 2001;120(1-3):259-68. doi: 10.1016/s0378-4274(01)00278-8.
3. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. The Lancet. 2007;370(9582):185-91. doi: 10.1016/s0140-6736(07)61092-7.
4. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opinion on Drug Safety. 2013;13(1):57-65. doi: 10.1517/14740338.2013.827660.
5. Keine D, Zelek M, Walker JQ, Sabbagh MN. Polypharmacy in an Elderly Population: Enhancing Medication Management Through the Use of Clinical Decision Support Software Platforms. Neurology and Therapy. 2019;8(1):79-94. doi: 10.1007/s40120-019-0131-6.
6. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiology and Drug Safety. 2010;19(9):901-10. doi: 10.1002/pds.1984.
7. Tromp AM, Pluijm SMF, Smit JH, Deeg DJH, Bouter LM, Lips P. Fall-risk screening test. Journal of Clinical Epidemiology. 2001;54(8):837-44. doi: 10.1016/s0895-4356(01)00349-3.
8. Akazawa M, Imai H, Igarashi A, Tsutani K. Potentially inappropriate medication use in elderly Japanese patients. The American Journal of Geriatric Pharmacotherapy. 2010;8(2):146-60. doi: 10.1016/j.amjopharm.2010.03.005.

9. Lu WH, Wen YW, Chen LK, Hsiao FY. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. Cmaj. 2015;187(4):E130-e7. Epub 2015/02/04. doi: 10.1503/cmaj.141219. PubMed PMID: 25646290; PMCID: PMC4347788.
10. Quinn KJ, Shah NH. A dataset quantifying polypharmacy in the United States. Scientific Data. 2017;4(1):170167. doi: 10.1038/sdata.2017.167.
11. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, Delaney JT, Bowton E, Brothers K, Johnson K, Crawford DC, Schildcrout J, Masys DR, Dilks HH, Wilke RA, Clayton EW, Shultz E, Laposata M, McPherson J, Jirjis JN, Roden DM. Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project. Clinical Pharmacology & Therapeutics. 2012;92(1):87-95. doi: 10.1038/clpt.2011.371.
12. Silva P, Jacobs D, Kriak J, Abu-Baker A, Udeani G, Neal G, Ramos K. Implementation of Pharmacogenomics and Artificial Intelligence Tools for Chronic Disease Management in Primary Care Setting. Journal of Personalized Medicine. 2021;11(6):443. PubMed PMID: doi:10.3390/jpm11060443.
13. Chang HW, Chuang LY, Tsai MT, Yang CH. The importance of integrating SNP and cheminformatics resources to pharmacogenomics. Curr Drug Metab. 2012;13(7):991-9. Epub 2012/05/18. doi: 10.2174/138920012802138679. PubMed PMID: 22591347.
14. McConachie SM, Volgyi D, Moore H, Giuliano CA. Evaluation of adverse drug reaction formatting in drug information databases. J Med Libr Assoc. 2020;108(4):598-604. Epub 2020/10/06. doi: 10.5195/jmla.2020.983. PubMed PMID: 33013217; PMCID: PMC7524619.
15. Elovic A, Pourmand A. Lexicomp App Review. J Digit Imaging. 2020;33(1):17-20. Epub 2019/05/30. doi: 10.1007/s10278-019-00219-x. PubMed PMID: 31140006; PMCID: PMC7064701.
16. Wang Y, Halper M, Wei D, Gu H, Perl Y, Xu J, Elhanan G, Chen Y, Spackman KA, Case JT, Hripcsak G. Auditing complex concepts of SNOMED using a refined hierarchical abstraction network. J Biomed Inform. 2012;45(1):1-14. Epub 2011/09/13. doi: 10.1016/j.jbi.2011.08.016. PubMed PMID: 21907827; PMCID: PMC3313651.
17. National Institute of General Medical Sciences 2011 [updated 2-11-2021]. Available from: https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx.
18. Bousman CA, Forbes M, Jayaram M, Eyre H, Reynolds CF, Berk M, Hopwood M, Ng C. Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. BMC Psychiatry. 2017;17(1). doi: 10.1186/s12888-017-1230-5.
19. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics. 1981;30(2):239-45. doi: 10.1038/clpt.1981.154.
20. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011;89(3):464-7. Epub 2011/01/29. doi: 10.1038/clpt.2010.279. PubMed PMID: 21270786; PMCID: PMC3098762.
21. Caudle K, Klein T, Hoffman J, Muller D, Whirl-Carrillo M, Gong L, McDonagh E, Sangkuhl K, Thorn C, Schwab M, Agundez J, Freimuth R, Huser V, Michael Lee M, Iwuchukwu O, Crews K, Scott S, Wadelius M, Swen J, Tyndale R, Stein C, Roden D, Relling M, Williams M, Johnson S. Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. Current Drug Metabolism. 2014;15(2):209-17. doi: 10.2174/1389200215666140130124910.
22. Rollinson V, Turner R, Pirmohamed M. Pharmacogenomics for Primary Care: An Overview. Genes (Basel). 2020;11(11):1337. doi: 10.3390/genes11111337.

23. Kripalani S, Hart K, Schaninger C, Bracken S, Lindsell C, Boyington DR. Use of a tablet computer application to engage patients in updating their medication list. Am J Health Syst Pharm. 2019;76(5):293-300. doi: 10.1093/ajhp/zxy047. PubMed PMID: 30753287.
24. Sheon Amy R, Van Winkle B, Solad Y, Atreja A. An Algorithm for Digital Medicine Testing: A NODE.Health Perspective Intended to Help Emerging Technology Companies and Healthcare Systems Navigate the Trial and Testing Period prior to Full-Scale Adoption. Digital Biomarkers. 2018;2(3):139-54. doi: 10.1159/000494365.
25. Services USDoHaH, Administration FaD, Health CfDaR. Software as a Medical Device (SAMD): Clinical
Evaluation – Guidance for Industry and
Food and Drug Administration Staff. December 8, 2017.
26. Aronson JK. Distinguishing hazards and harms, adverse drug effects and adverse drug reactions : implications for drug development, clinical trials, pharmacovigilance, biomarkers, and monitoring. Drug Saf. 2013;36(3):147-53. Epub 2013/02/19. doi: 10.1007/s40264-013-0019-9. PubMed PMID: 23417506.