ORIGINAL RESEARCH

Implementation of a Standardized Medication Therapy Management Plus Approach within Primary Care

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Purpose: **The purpose of this study was to implement a clinical pharmacist-led medication therapy management (MTM) service within a primary-care setting that is enhanced by 1) a clinical decision support system (CDSS) that includes a unique combination of medication risk mitigation factors, which aids the pharmacist in interpreting the medication profile, and 2) pharmacogenomics (PGx) testing.**

Methods: **This was a service implementation study, whereby Medicare beneficiaries were eligible if they were patients of Elmwood Family Physicians, a private family, primary care practice with 2 locations in New Jersey, and were on at least 7 medications. Patients had a medication reconciliation completed by a pharmacist and performed a PGx buccal swab. Patient information was run through a CDSS to aid the pharmacist with screening for multidrug interactions and assessing patient's medication-related risks. The output of the CDSS was used to create recommendations and provide a consult to the physicians. Recommendations were followed up by return of the consult.**

Results: **Enrolled patients used a mean (± standard deviation) of 12.1 (± 4.6) medications. The turnaround time for the MTM Plus consults was 11.7 (± 6.2) days. During the consults, the pharmacist identified 138 medication-related problems (MRPs). The most common MRPs were drug-drug interactions (29.0%) and drug-gene interactions (DGIs; 24.6%).**

Conclusion: **Implementing a clinical pharmacist-led MTM Plus service in the primary care setting is feasible. This study highlights that DGIs are common in older adults in family practice and indicates that PGx testing identifies additional MRPs that may otherwise go unnoticed in these patients. The experiences we shared can aid other clinicians in establishing successful MTM Plus services. Future studies should also measure the impact of such personalized medicine services on economic, clinical, and humanistic outcomes. This study has been registered with ClinicalTrials.gov (study No. NCT02748148).**
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Primary care physicians (PCPs) are the most frequent prescribers of medications, with over 65% to 75% of medications being prescribed in the primary-care setting.[1,2] Although medications are a critical intervention for the prevention and treatment of medical conditions, they also can be associated with medication-related problems (MRPs). A MRP is

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Conflict of interest: EJS, JT, OVK, CHK, and KTB, as stakeholders in Tabula Rasa HealthCare, have financial interests in the proprietary, clinical decision support system the company has developed (Medication Risk Mitigation Matrix). JP, PP, HS, and AMI have nothing to declare.

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defined as any undesirable event experienced by a patient, involving or suspected to involve his or her medication, and potentially or actually interfering with a desired therapeutic outcome or leading to a deleterious outcome, such as an adverse drug event (ADE).[3] As might be expected, based on the frequency of medication prescribing alone, MRPs as well as the sequelae of ADEs are tremendously common in primary care settings.[4–6] A systematic review of 29 studies found an incidence of 15 ADEs per 100 outpatients per year, of which more than 20% were judged as being preventable.[7] According to the US Department of Health and Human Services, in these settings, ADEs account for over 3.5 million physician visits, an estimated 1 million emergency department visits, and approximately 125,000 hospital admissions per annum.[8]

One approach for reducing MRPs while optimizing medications for patients is medication therapy management (MTM) services. As medication experts, pharmacists have been providing MTM services throughout the United States since the enactment of the Medicare Prescription Drug, Improvement, and Modernization Act, which established a prescription drug benefit (ie, Part D) and required Prescription Drug Plans to offer MTM services to eligible patients commencing in 2006.[9] Part D enrollees who had multiple chronic medical conditions (eg, chronic obstructive pulmonary disease, heart failure), took multiple Part D drugs, and were likely to exceed a certain threshold in annual costs (eg, $3138 in 2015) were considered eligible for these MTM services. Since the enactment of the act, a plethora of studies have found that MTM services effectively reduce potentially inappropriate medication use, drug-drug interactions, and medication nonadherence.[10–20] However, a recently conducted systematic review of the cumulative evidence during the last decade showed that there is substantial variation in the performance of MTM services across Prescription Drug Plans.[21] Furthermore, according to Centers for Medicare & Medicaid Services, the current landscape is that Prescription Drug Plans are delivering MTM services only at a level necessary to meet the minimal government requirements (eg, eligibility criteria, completion rates), and these models are not well aligned with government quality improvement and financial interests, given that a significant proportion of Prescription Drug Plans have not definitively proven that their MTM services improve patient outcomes and/or reduce Medicare expenditures.[22] Notwithstanding these shortcomings, pharmacist-provided MTM services are commonplace in clinical practice. Still, enhanced MTM services provide opportunities to improve outcomes and/or reduce expenditures thereby overcoming these shortcomings. However, first and foremost, feasibility assessments for enhanced MTM services are needed.

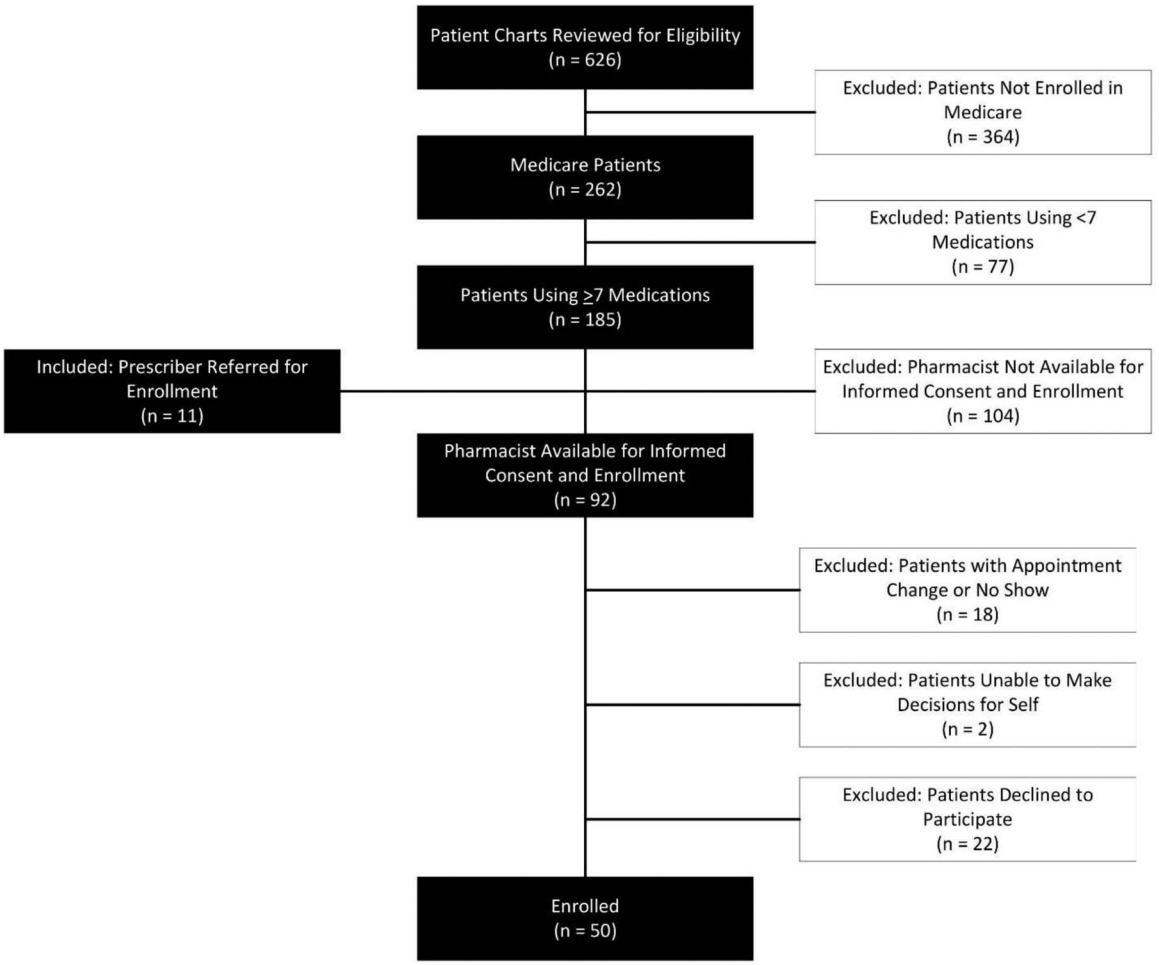
The purpose of this study was to implement a clinical pharmacist-led MTM service within a primary care setting that is enhanced by 1) a clinical decision support system (CDSS) that includes a unique combination of medication risk mitigation factors, which aids the pharmacist in interpreting the medication profile, and 2) pharmacogenomics (PGx) testing. The clinical-pharmacist-led MTM service was standardized by a systematic approach to evidence- and personalized-based medicine. In doing so, we intended to forego the traditional MTM requirements imposed by Centers for Medicare & Medicaid Services on Prescription Drug Plans. Although others before us have implemented MTM services within the primary care setting[23–26], with varying degrees of success, to the best of our knowledge, our MTM Plus approach is the first of its kind to align with both Centers for Medicare & Medicaid Services' most recent interest in enhanced MTM models[22] and with primary care's ever-growing focus on personalized medicine.[1]

Methods

Practice Setting

The practice setting was Elmwood Family Physicians, a private family, primary care practice with 2 locations in New Jersey (Marlton and Tabernacle). At each location, the practice is staffed with 3 PCPs, 1 nurse practitioner, 2 physician assistants, a nurse manager, and 3 medical assistants. The practice also is a training site for students of various disciplines (eg, medicine, pharmacy). Although there is not a staffed pharmacist at the practices, there is a pharmacist available to assist with training pharmacy students. In addition, for this study, a research pharmacist (postgraduate year 1 resident) was on site approximately 3 days per week for approximately 4 to 6 hours per day. The practice serves approximately 5000 patients and has approximately 1400 office visits per month.

Figure 1. Flowchart of patient eligibility and enrollment process. In March 2016, the onsite research pharmacist reviewed 626 patient charts to determine eligibility for enrollment in the study. Among patients screened, 185 met inclusion criteria. However, approximately 50% of the time, either the pharmacist or patient was not available for informed consent. Among the 92 remaining eligible patients, 42 were excluded from enrollment in the study for various reasons. A total of 50 patients were enrolled and received medication therapy management (MTM) Plus services led by the pharmacist.

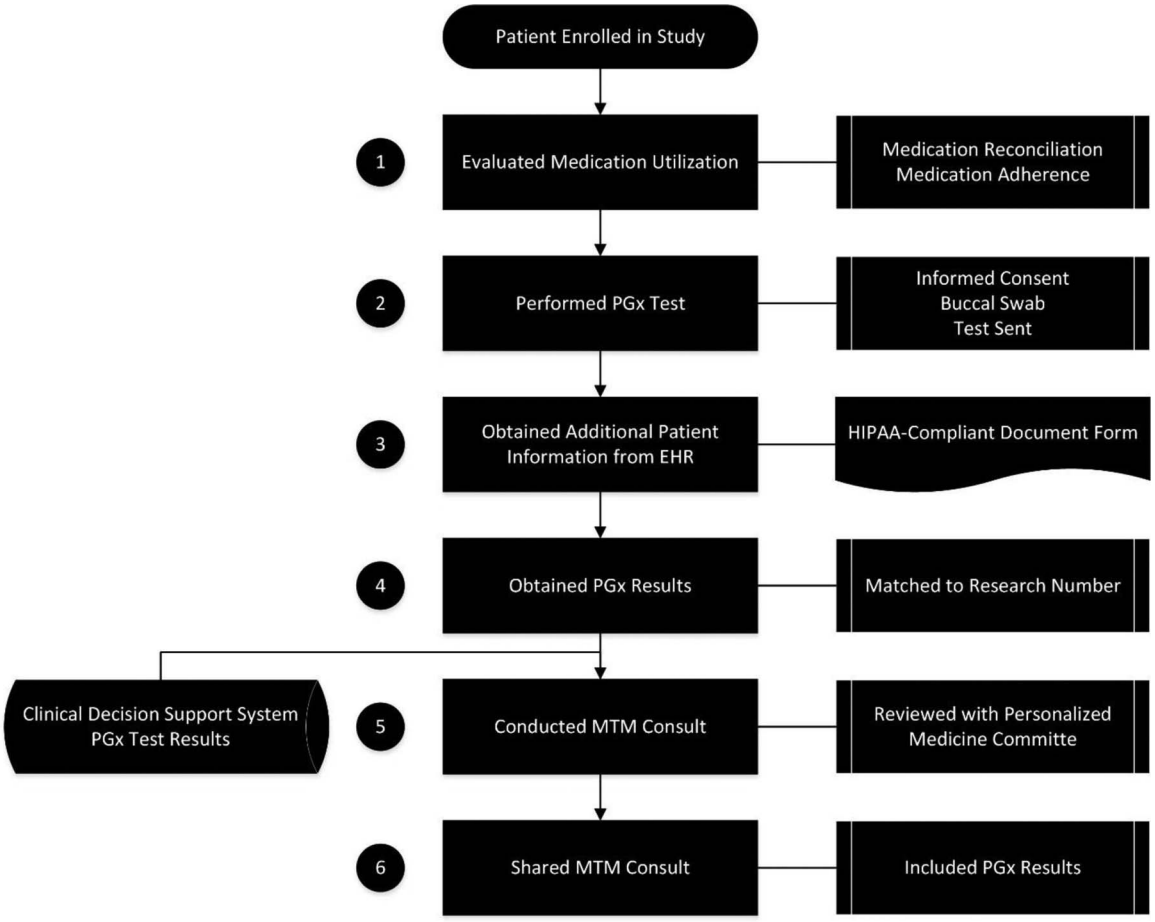


Patient Enrollment

Patient enrollment took place between April 1, 2016 and June 30, 2016, and informed consent was obtained by the research pharmacist. Patients were eligible for enrollment if they were a Medicare beneficiary prescribed 7 or more medications or if their PCP specifically referred them to the research pharmacist. Patients were excluded from enrollment if informed consent was not obtained (eg, patient declined to participate, or patient or research pharmacist was unavailable) or if the patient was non-English speaking with no language interpreter available. Figure 1 presents a flow diagram of patient eligibility and enrollment. Our goal was to enroll 50 patients from this primary care practice setting to receive MTM Plus services. This target sample size was estimated as sufficient to assess feasibility, as previous pharmacist-physician collaborative studies and pharmacist-led PGx studies have demonstrated implementation feasibility with similar sample sizes.[23,27–32]

In March 2016, the research pharmacist began reviewing charts of the practice sites' electronic health records to determine potentially eligible patients, and in April 2016, enrollment commenced. When the research pharmacist was on site, she collaborated with staff to introduce the consent process to potentially eligible patients and to ascertain whether these patients were experiencing any MRPs around the time of the scheduled

Figure 2. Medication Therapy Management (MTM) Plus process workflow. The MTM Plus process workflow employed the following steps: 1) evaluated medication utilization by performing medication reconciliation and assessing medication adherence; 2) performed PGx test by conducting informed consent specifically for the test, observing patient perform buccal swab for PGx test, and sending PGx test to laboratory with deidentified research number; 3) obtained additional patient-specific information from the EHR to inform the consult and documented this information into a secure, HIPAA-compliant form; 4) obtained PGx test results and matched them up to patient deidentified research number; 5) conducted consult, which was informed by clinical decision support data and PGx test results, and reviewed recommendations with a subgroup of a personalized medicine committee; and 6) shared consult, including PGx test results, with PCP. Abbreviations: EHR, electronic health record; MTM, medication therapy management; PCP, primary care physician; PGx, pharmacogenomics.



PCP appointment. Immediately following the PCP appointment, the research pharmacist visited with eligible patients in their examination rooms to obtain informed consent. Once consent was obtained, the patient was enrolled onto the study and assigned a random research number. The research pharmacist then started the MTM Plus process.

MTM Plus Process

The MTM Plus process is depicted in Figure 2. Medication reconciliation was performed by the research pharmacist by first obtaining the patient's prescription medication history from a third-party source (Cerner Medication History; Cerner Corporation, Kansas City, MO), then comparing that list to the medication list obtained from the patient's medical chart at the practice site, and finally reviewing the unreconciled lists of medications directly with the patient. The final medication list was based on the patient's self-reported medication use, whereby the research pharmacist reconciled medication discrepancies with the patient and subsequently, via the MTM Plus consult (Appendix 1),

brought to the PCP's attention. Medication adherence was assessed by the research pharmacist by using a validated, 4-item, self-reported medication adherence scale.[33] Patient responses are categorized as "yes/no" for each item and tallied for a total. A total score of "0" indicates high adherence, a score of "1 to 2" indicates medium adherence, and a score of "3 to 4" indicates low adherence.

The research pharmacist timed and observed patients perform a buccal swab for DNA collection using a PGx testing kit from Coriell Life Sciences (Camden, NJ). The kit cost approximately $300 and included a panel of genes associated with the metabolism, transport, and targets (eg, receptors) of numerous medications. Specifically, the genes included in the PGx testing kit were *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *VKORC1*, *SLCO1B1*, *TPMT*, *ATM*, *F2*, *F5*, *MTHFR* (*A1298C*), and *MTHFR* (*C677T*). Following DNA collection, buccal swab samples were sent directly to a Clinical Laboratory Improvement Amendments–certified laboratory (eg, Gene Trait Laboratories, Columbia, MO) for testing. Subsequently, Coriell Life Sciences received the test results from the laboratory, and interpreted the reference single nucleotide polymorphism (rs) numbers to genotypes and phenotypes. These results were sent to CareKinesis via a Secure File Transfer Protocol. Information about patients' medications was not shared with the laboratory or Coriell Life Science.

Following these steps, the research pharmacist entered each patient's final medication list and medication adherence category (eg, low, medium, high) into a secure, HIPAA-compliant form (Google Docs; Google Inc., Mountain View, CA). In addition, the research pharmacist collected other information about the patient from the medical chart, including demographics, pertinent biometrics (eg, height, weight) and clinical metrics (eg, blood pressure, heart rate), and laboratory data (eg, lipid panel, serum creatinine), as well as medication allergies and reported MRPs (if applicable). This information was also entered into the secure, HIPAA-compliant form. All information collected and entered into the form was deidentified to ensure protection of patient confidentiality. Finally, once the research pharmacist received the patient's PGx test results she matched the results back to the patient's research number for identification and interpretation.

MTM Plus Consult

Patient-specific information was entered into the CDSS proprietary to the study sponsor (Medication Risk Mitigation Matrix; Tabula Rasa HealthCare, Moorestown, NJ) to aid the research pharmacist with screening for multidrug interactions and to assessing the patient's medication-related risks. The CDSS is an evidence-based clinical decision support tool that identifies the likelihood and severity of drug-drug interactions and drug-gene interactions (DGIs) and assesses combinatorial factors to provide an overall risk score and individual medication risk values. Our CDSS has been described in more detail elsewhere.[34]

Using the output of the CDSS and guidance from clinical practice guidelines, such as those for diabetes[35] and heart failure[36,37] as well as specifically for PGx[38], the research pharmacist performed a consult. In performing the consult, the research pharmacist focused on identifying actual and potential MRPs for each patient and providing recommendations for the PCP to resolve MRPs and mitigate medication risks. The consult was reviewed by a subgroup of a personalized medicine committee before sharing with the patient's PCP. The subgroup was composed of 2 senior pharmacists with expertise in MTM, geriatric pharmacotherapy, and PGx. The purpose of the subgroup's review was to guide the research pharmacists' recommendations because she was in residency training at the time of this study.

After the subgroup reviewed and approved the consult, the research pharmacist sent it to the PCP's designated nurse by a secure (encrypted) electronic email message (Microsoft Outlook; Microsoft Corporation, Redmond, WA), along with an electronic copy of the patient's PGx results. In addition, the research pharmacist created a "gene card" (Appendix 2) that summarized the PGx results for the patient. Like the consult, the gene card was securely emailed to the PCP's designated nurse; and, subsequently, the nurse mailed the gene card to the patient's home. In cases where severe or life-threatening MRPs were identified, the research pharmacist spoke directly with the patient's PCP, in person, whereby changes were implemented as swiftly as possible. In other cases, the PCP reviewed the consult in written form, typically before the patient's next scheduled appointment, responded to the research pharmacist's recommendations by checking a box indicating a response (eg, "accept recommen-

dation"), and signed the consult. In turn, the research pharmacist either picked up the signed consult when she was back in the PCP office or an electronic copy was sent to her by office staff. Lastly, if the consult resulted in medication changes being implemented by the PCP, either office staff or the PCP communicated the intended changes directly to the patient.

MTM Plus Assessment

Although no formal assessment of the MTM Plus service implementation was conducted, to optimize integration of the process into the primary care practices' workflow, the research pharmacist actively engaged the PCPs and office staff for feedback. In doing so, the research pharmacist was prepared to make changes to the process to ensure successful implementation of the MTM Plus service; albeit, no suggestions were made and thus the MTM Plus service remained as described (Figure 2).

This study was approved by the Biomedical Research Alliance of New York Institutional Review Board (IRB), and is registered with ClinicalTrials.gov (study No. NCT02748148). Funding was provided by Tabula Rasa HealthCare. PGx testing was provided to patients at no charge.

Results

Patient Characteristics

Characteristics of the 50 patients enrolled onto this study are provided in Table 1. Their median (interquartile range) age was 69.5 (65.0 to 75.8) years, and 54% were male. According to the final medication list, patients used a mean (± standard deviation) of 12.1 (± 4.6) medications, and the most frequently used medications were aspirin (50%), vitamin D (48%), and atorvastatin (46%). Regarding medication risk mitigation factors, most patients had a relatively moderate risk for cognitive burden and falls.

Patient Enrollment

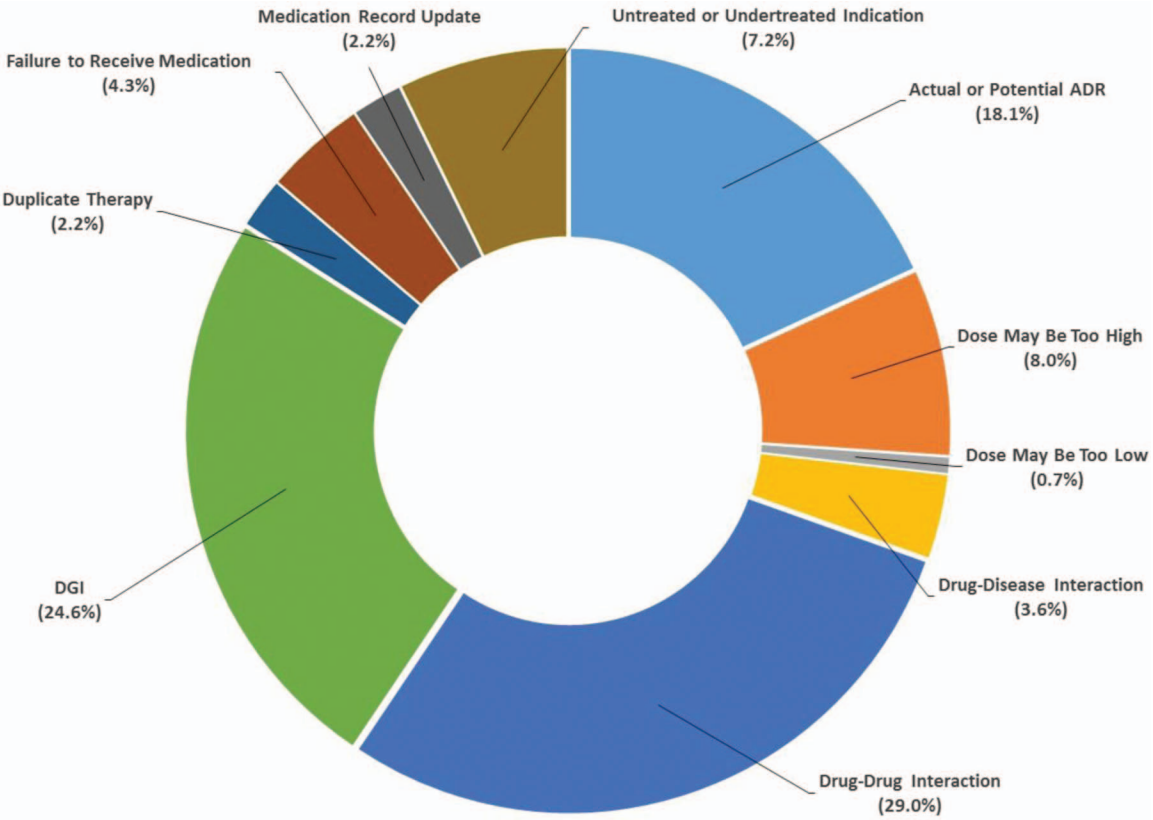
Among the eligible patients (n = 92), the majority (54%) consented to enroll onto the study (Figure 1). Of the 42 patients who did not enroll, 43% did not make their scheduled appointment, and 52% declined to participate. Most of the eligible patients who declined to participate indicated that they did not have sufficient time to complete the informed consent.

Table 1. Characteristics of Patients Participating in the Study (N = 50)

Characteristics	Value
Demographics	
Age, years, mean (range)	69.0 (42.0 to 94.0)
Sex, n (%)	
Male	27 (54.0)
Female	23 (46.0)
Ethnicity, n (%)	
White or Caucasian	42 (84.0)
Hispanic or Latino	2 (4.0)
Other or unspecified	6 (12.0)
Most frequent diagnoses, n (%)*	
Hyperlipidemia	38 (76.0)
Hypertension	38 (76.0)
Type 2 diabetes mellitus	23 (46.0)
Hypothyroidism	16 (32.0)
Vitamin D deficiency	16 (32.0)
Allergic rhinitis	11 (22.0)
Anxiety	10 (20.0)
Gastroesophageal reflux disorder	10 (20.0)
Major depressive disorder	8 (16.0)
Insomnia	7 (14.0)
Medications	
Number, mean (± SD)†	
Total medications	12.1 (± 4.6)
Chronic medications	10.4 (± 4.3)
Medication risk mitigation–associated factors	
Cognitive burden risk score	2.0 (± 1.7)
Falls risk score	5.5 (± 4.0)
Number of PIMs	1.4 (± 1.2)
Creatinine clearance (mL/min)	66.2 (± 20.8)
Heart rhythm risk score	3.6 (± 3.6)
Most frequently prescribed, n (%)‡	
Aspirin	25 (50.0)
Vitamin D	24 (48.0)
Atorvastatin	23 (46.0)
Levothyroxine	17 (34.0)
Omega-3 fatty acids	14 (28.0)
Amlodipine	13 (26.0)
Esomeprazole	11 (22.0)
Clopidogrel	8 (16.0)
Metoprolol succinate	8 (16.0)
Omeprazole	8 (16.0)

*As reported in the patient's chart. Percentage out of total patients included.
†As determined by the pharmacist's medication reconciliation process.
‡As determined by the pharmacist's medication reconciliation process. Percentage out of total patients included.
Abbreviations: PIM, potentially inappropriate medication; SD, standard deviation.

Figure 3. Types of medication-related problems identified by the pharmacist (N = 138). While performing consults, the pharmacist identified a total of 138 MRPs for the 50 patients enrolled onto the study. The most common types of MRPs identified were drug-drug interactions (29.0%), such as competitive inhibition involving 2 drugs (eg, metoprolol interfering with oxycodone activation) and multi-drug combination (eg, metoprolol and atorvastatin interfering with mirtazapine clearance), and DGIs (24.6%), such as inability to activate clopidogrel to its active metabolite and poor statin uptake into the liver. Abbreviations: ADR, adverse drug reaction; DGI, drug-gene interaction; MTM, medication therapy management; MRP, medication-related problem.

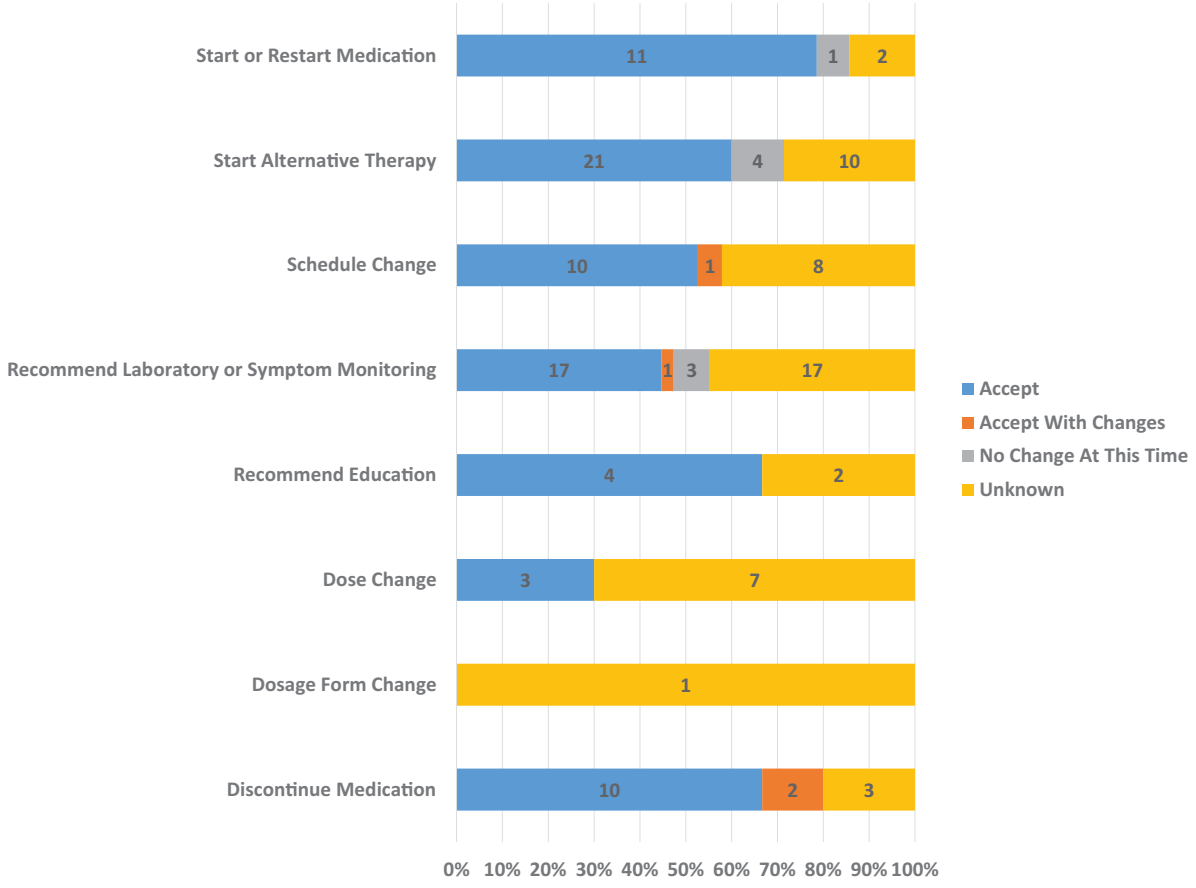


Implementation Results

The turnaround time for MTM Plus services was 11.7 (± 6.2) days. This included the time required for the research pharmacist to create the consult as well as the time required for the subgroup of the personalized medicine committee to meet, review, and agree on the consult recommendations. Early in the implementation phase, it took approximately 14 days (up to 19 days) to complete a consult. However, as implementation progressed, it took approximately 3 days (up to 5 days). On average, it took 23 (± 11.4) days for the research pharmacist to receive a response to the consult from a PCP.

The research pharmacist identified 2.8 (± 0.9) MRPs per patient (range, 1 to 4), for a total of 138 MRPs for the 50 patients enrolled in this study. The types of MRPs identified and recommendations made by the research pharmacist are depicted in Figure 3 and Figure 4, respectively. The most common types of MRPs identified were drug-drug interactions (29.0%), typically multi-drug potential interactions, and DGIs (24.6%). The majority of patients (n = 44, 88%) had at least 1 DGI, with 17 patients (34%) having ≥4 DGIs (range, 4 to 10). Statins were the most common class of drugs involved in a DGI (13.4%), followed by antidepressants (12.8%), proton pump inhibitors (12.8%), β-blockers (10.1%), anticoagulants (9.4%), opioids (7.4%), antidiabetics (6.0%), antiplatelets (4.0%), calcium channel blockers (3.4%), and sedative hypnotics (3.4%). The most frequent recommendations made were to monitor the patient (n = 38; 27.5%) and start alternative therapy (n = 35; 25.4%). Based on returned consults, the majority of the research pharmacist's recommendations (n = 80; 90.9%) were accepted by the PCPs (Figure 4).

Figure 4. Types of recommendations made by the pharmacist (N = 138) and physician acceptance rates. For each MRP identified (N = 138) as part of the consult, the pharmacist made a recommendation for the PCP to resolve the MRP. The most frequent types of recommendations made were to monitor the patient (n = 38; 27.5%) and start alternative therapy (n = 35; 25.4%). Examples of monitoring recommendations included monitor for ADRs from nebivolol due to decreased CYP2D6 isoenzyme activity and monitor for side effects from mirtazapine due to multi-drug competitive inhibition. Examples of recommendations to start alternative therapy included switch clopidogrel to an alternative antiplatelet with a different metabolic pathway (eg, prasugrel or ticagrelor) due to a DGI and decrease dose of simvastatin or switch to an alternative statin (eg, rosuvastatin or pravastatin) due to a DGI. The majority of the pharmacist's recommendations (90.9%) were accepted (ie, accepted or accepted with changes) by the PCPs. Abbreviations: ADRs, adverse drug reactions; DGI, drug-gene interaction; MTM, medication therapy management; MRP, medication-related problem; PCPs, primary care physicians.

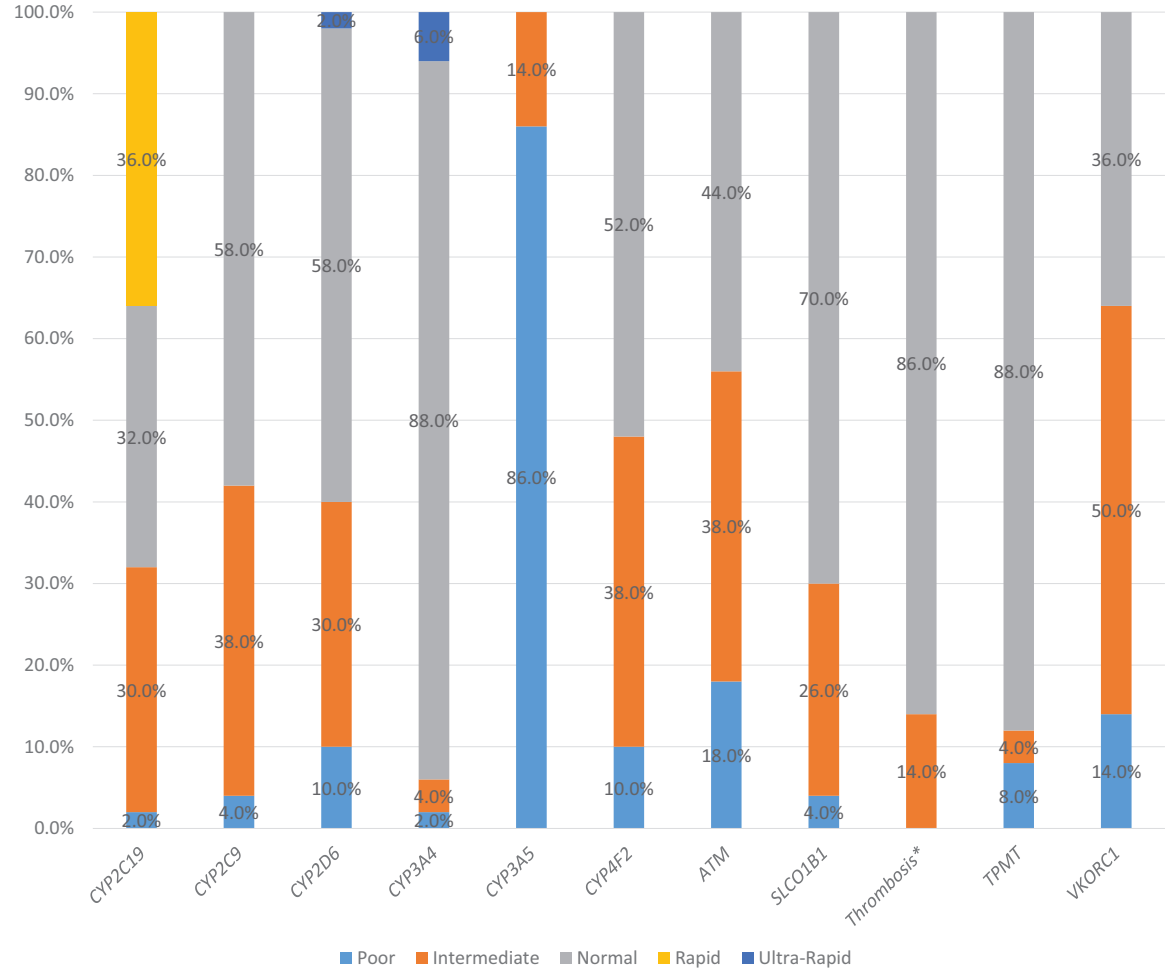


The turnaround time for the PGx test results to be completed by the laboratory and returned to the research pharmacist was 5.8 (± 2.2) days. The results of PGx testing, specifically the phenotype distribution of the genes tested for the 50 patients enrolled in this study, are depicted in Figure 5. All patients had at least 1 genetic variant, and the majority (66%) had at least 5. Notably, among the genes tested, 36% of patients were identified as rapid metabolizers for the CYP2C19 isoenzyme; 40% were considered intermediate or poor metabolizers for the CYP2D6 isoenzyme; 30% were determined to have reduced activity for the SLCO1B1 transporter; and 50% and 14%, respectively, were identified as having reduced and significantly reduced VKORC1 activity.

Discussion

We successfully implemented a clinical pharmacist-led MTM Plus service within a primary care setting. In leading the service, the research pharmacist used a sophisticated CDSS and took a standardized approach to complete consults for PCPs. The con-

Figure 5. Phenotype distribution of the genes tested in 50 patients. All 50 patients who underwent PGx testing had at least 1 genetic variant, and the majority (66.0%) had ≥5. Notably, among the genes tested, 36.0% of patients were identified as rapid metabolizers for the CYP2C19 isoenzyme; 40.0% were considered intermediate or poor metabolizers for the CYP2D6 isoenzyme; 30.0% were determined to have reduced activity for the SLCO1B1 transporter; and 50.0% and 14.0%, respectively, were identified as having reduced and significantly reduced VKORC1 activity. (Reduced and significantly reduced refer to intermediate and poor phenotypes respectively as shown in the figure.) *Thrombosis profile included testing the following genes: *F2*, *F5*, *MTHFR (A1298C)*, and *MTHFR (C677T)*. Abbreviations: PGx, pharmacogenomics; CYP, Cytochrome P450.



sults entailed identification of MRPs, interpretation of PGx results, and personalization of recommendations to mitigate medication risks. During consults, the research pharmacist identified 138 MRPs, including 34 (24.6%) DGIs, for 50 Medicare beneficiaries and provided recommendations to resolve the MRPs. Based on direct response to the research pharmacist's recommendations (ie, written response to consults), the overwhelming majority (90.9%) of recommendations were accepted by the PCPs. In sum, the results of our study provide encouraging support for the ever-emerging roles of pharmacists, collaborating with physicians, in both enhanced MTM and personalized medicine initiatives. The results also support the need for effective interprofessional practice in primary care.[39]

Professional pharmacy organizations and other experts in the field have proposed the integration of PGx testing into MTM to enable further refinement of medication management to identify ineffective and/or harmful drugs or drug combinations.[38,40–46] Few studies to date have assessed the feasibility and value of integrating PGx testing into MTM in clinical practice, and most have been pilot studies or surveys.[29–31,41,47–49] In our study, we found that enhancing MTM services by integrating

PGx testing and pharmacist interpretation is not only feasible in the primary care setting, but also allows the pharmacist to successfully identify additional MRPs that should be addressed with the patient's PCP.

Among the MRPs detected by the research pharmacist in our study, nearly 1 of 4 involved DGIs, such as patients with a CYP2C19 loss-of-function allele unable to activate clopidogrel to its active metabolite and patients with reduced statin uptake into the liver due to a genetic variant of the *SLCO1B1* gene. Further, almost two thirds (61.7%) of the drugs involved in DGIs, in our study, are listed in the Food and Drug Administration's (FDA) table of PGx biomarker list.[50] In a study published in 2014 that integrated PGx data into a *CDSS*, it was reported that while drug-drug interactions accounted for 66.1% of the total interactions in a sample of 501 patients, DGIs accounted for 14.7% of all potential major and substantial interactions identified.[51] Similarly, in a study published in 2016, researchers identified that 69.1% of 20,534 patients had at least 1 reported drug interaction and, of those interactions determined to be severe, 24.6% were DGIs.[52] Collectively, these data indicate that genetic variations can substantially contribute to MRPs among older adults. These results are clinically important because genetically determined interindividual differences in drug disposition and response can affect clinical outcomes in older adults, whom are more susceptible to therapeutic failures and adverse drug reactions.[53] In addition to the benefits of integrating PGx into the medication decision-making process, enhancements to MTM services, such as those implemented in this study, might also reduce patients' concerns about side effects and increase confidence that medications are effective. This would address 2 key factors that impact patients' medication adherence: concern and necessity.[41]

The implementation of this pharmacist-led service was not without its challenges. However, in this particular setting, we were able to overcome most of the challenges that early integrators of PGx into MTM encountered before us.[29–31,41,47–49] We share these experiences—challenges and solutions—so that others may consider them when initiating a similar service.

First, the primary care office has electronic health records, but was not capable of interacting with our clinical decision support software, thus data had to be manually entered into the system to assess patient's medication-related risks. This was an expected challenge because there was not an investment in technology development. We overcame the lack of system interoperability by handling the service similar to a consult service; the research pharmacist was on site for a significant portion of time, but completed the consults off site and used secure electronic communication to exchange consult information. This method reportedly worked well for the PCPs with whom the research pharmacists worked. If this type of MTM service is desired in a more prospective manner, it would be beneficial to implement interoperable technology to allow PCPs to use the CDSS and facilitate better communication and workflow.

Second, patients must be willing to undergo PGx testing in order for this type of service to be implemented. Although the majority of eligible patients elected to enroll in our study, most patients who opted not to enroll indicated that they did not have sufficient time to participate in the informed consent process. Although informed consent was a legitimate challenge, it may not be applicable to other primary care settings interested in implementing a similar service because we were involved in a formal research study while others may implement this service as a part of standard clinical care, thereby potentially bypassing the informed consent process. Further, as we expected going into the study, most patients seemed to have insufficient understanding of PGx and appreciation of its benefits. The research pharmacist spent an appreciable amount of time (30 to 40 minutes) educating patients about PGx and the benefits and risks associated with testing. The time seemed to be well spent, given that the majority of patients (54%) consented to PGx testing and agreed to participate in the study once they learned more about PGx. As demonstrated by other studies,[31,32] this finding suggests that patients empowered with knowledge about PGx are receptive to undergo PGx testing, which could improve their medication management. Further, this indicates that either prescribers need to have sufficient time to educate patients on PGx before testing, or will need to implement a consult-based service, such as ours, and allow a pharmacist to provide this education.

Last, with regard to PGx testing, we were somewhat challenged with the turnaround time. Specifically, it took approximately 3 to 7 days for the

research pharmacist to receive PGx test results back from the laboratory. Although this is a reasonable turnaround time to expect for integrating PGx test results into MTM services, as reported by others,[29,31,47,54] this delayed the time before the research pharmacist could start the consults. In the future, consults may be able to be started and then modified once genetic results are received, depending on prescribers' preferences.

In conclusion, implementing a clinical pharmacist-led MTM Plus service in the primary care setting is feasible. This study highlights that DGIs are common in older adults in family practice and indicates that PGx testing identifies additional MRPs that may otherwise go unnoticed in these patients. The experiences we shared can aid other clinicians in establishing successful MTM Plus services. Future studies should also measure the impact of such personalized medicine services on economic, clinical, and humanistic outcomes.

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Appendix 1: Example of MTM Plus Consult

PROTOCOL NUMBER: MTM-309 | NCT02748148

TABULARASA HEALTHCARE®

MEDICATION THERAPY MANAGEMENT (MTM) CONSULT

PATIENT INFORMATION

Appointment Date: 4/5/2016	**MTM Date:** 4/24/2016			**Research Number:** 80502016	
First Name: [redacted] **Last Name:** [redacted]			**DOB:** 10/21/1948 (68 years)	**Prescriber:**	
Gender: Female	**Race:** Hispanic or Latino		**MRPs:** Not sure if Oxycodone and Aripiprazole are working; patient is always in pain	**Location:** [redacted]	
Estimated CrCl: 43.8 mL/min	**Adherence Score:** 1 = Medium Adherence				

MRPs = medication-related problems

EXECUTIVE SUMMARY OF RECOMMENDATIONS: [PLEASE REFER TO PAGE 5-7 FOR FULL RATIONALE]

1. Change opioid pain medication due to (a) insufficient pain control, (b) drug-gene interaction, and (c) drug-drug interactions.	☐ ACCEPT RECOMMENDATION ☐ ACCEPT WITH CHANGES: [redacted] ☐ NO CHANGE - AWARE OF RECOMMENDATION
2. Consider multiple medication changes (hydrochlorothiazide, metoprolol, tizanidine) and therapeutic and laboratory monitoring to decrease risk for cardiovascular events (torsades de pointes), please see below for specifics.	☐ ACCEPT RECOMMENDATION ☐ ACCEPT WITH CHANGES: [redacted] ☐ NO CHANGE - AWARE OF RECOMMENDATION
3. Consolidate NSAID therapy to just Naproxen.	☐ ACCEPT RECOMMENDATION ☐ ACCEPT WITH CHANGES: [redacted] ☐ NO CHANGE - AWARE OF RECOMMENDATION
4. Consider switching Sitagliptin to an alternative drug (e.g., glipizide) or, at minimum, decreasing the dose of Sitagliptin to 50 mg daily.	☐ ACCEPT RECOMMENDATION ☐ ACCEPT WITH CHANGES: [redacted] ☐ NO CHANGE - AWARE OF RECOMMENDATION

GENETIC RESULTS SNAPSHOT			
ATM		CYP4F2	
CYP2C19		SLCO1B1	
CYP2C9		TPMT	
CYP2D6		VCORC1	
CYP3A4		CYP3A5	
		ApoE	
Thrombosis Profile:			
F2	F5	MTHFR (A>C)	MTHFR (C>T)

	PRE-INTERVENTION	IF ALL RECOMMENDATIONS ACCEPTED	POST-INTERVENTION
Total Meds:	15	13	
Chronic Meds:	14	13	
Cognitive Burden Risk Score:	3	2-3	
Falls Risk Score:	13	13	
Number of PIMs:	5	4	
Renal Function:			
Heart Rhythm Risk Score:	4.5	1.5	
Competitive Inhibition:			

No variant | 1 variant | ≥1 [decreased] variants | ≥1 [increased] variants

Low Risk | | | | High Risk

Prescriber Signature: _____

Appendix 2: Example of Gene Card

Gene	Genotype	Phenotype (Result)
ATM	N/A	N/A
CYP2C19	*1|*1	Extensive (Normal) Metabolizer
CYP2C9	*1|*1	Extensive (Normal) Metabolizer
CYP2D6	*1|*4 or *4J|*39 or *4M|*10	Intermediate Metabolizer
CYP3A4	*1A|*1B	Ultra-Rapid Metabolizer
CYP3A5	*3|*1D	Intermediate Metabolizer
CYP4F2	N/A	N/A
SLCO1B1	*1|*5	Intermediate Liver Uptake
TPMT	N/A	N/A
VKORC1	G|A	Normal Responder to Warfarin
ApoE	E3|E3	Typical Risk for Cardiovascular Disease
Thrombosis Profile*		Normal Risk

N/A: Not Available

*Refer to complete laboratory report for full gene details.