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Challenges to Integrating Pharmacogenetic Testing into Medication Therapy Management

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Abstract

Background—Some have proposed the integration of pharmacogenetic (PGx) testing into medication therapy management (MTM) to enable further refinement of treatment(s) to reduce risk of adverse responses and improve efficacy. PGx testing involves the analysis of genetic variants associated with therapeutic or adverse response and may be useful in enhancing the ability to identify ineffective and/or harmful drugs or drug combinations. This “enhanced” MTM might also reduce patient concerns about side effects and increase confidence that the medication is effective, addressing two key factors that impact patient adherence - concern and necessity. However, the feasibility and effectiveness of the integration of PGx testing into MTM in clinical practice has not yet been determined.

Objectives—In this paper, we consider some of the challenges to the integration and delivery of PGx testing in MTM services.

What is already known about this subject—While the addition of pharmacogenetic testing has been suggested, little literature exists exploring the challenges or feasibility of doing so.

Introduction

Medication therapy management (MTM) and comprehensive medication reviews (CMR) have been shown effective in reducing inappropriate medication use, adverse events due to drug-drug interactions, and medication non-adherence.[1–3] Pharmacist review of a patient’s medication regimen, including indications for the medications, adverse event profile, and pharmacokinetic and pharmacodynamic properties, may identify ineffective and/or harmful drugs and drug combinations that can be changed and lead to improved health outcomes.[3] Some have proposed the integration of pharmacogenetic (PGx) testing into MTM[4,5] to enable further refinement of treatment(s) to reduce risk of adverse responses and improve efficacy.[6,7] PGx testing involves the analysis of genetic variants associated with therapeutic or adverse response and may be useful in enhancing the ability to identify potentially ineffective and/or harmful drugs or drug combinations. This “enhanced” MTM might also

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reduce patient concerns about side effects and increase confidence that the medication is effective, addressing two key factors that impact patient adherence – concern and necessity.[8] However, the feasibility and effectiveness of the integration of PGx testing into MTM in clinical practice has not yet been determined. In this paper, we consider some of the potential benefits and challenges to the integration and delivery of PGx testing in MTM services.

Overview of MTM

As the safe and effective self-management of medications has become increasingly recognized as a key component to improving health, MTM services have transitioned from primarily patient education and counseling to systematic and coordinated processes for comprehensive medication management.[9] Patients with chronic medical condition(s) likely have numerous healthcare providers and medications and as a result, may inadvertently be prescribed multiple drugs within the same medication classes or drugs that may interact with each other, leading to increased risk of adverse events, failure to achieve therapeutic goals, discontinuation of medications, or reduced quality of life. Effective MTM aims to reconcile medication discrepancies and improve medication management.

Though practices can vary,[10] MTM services should include five core elements: 1) medication therapy review (MTR), 2) personal medication record (PMR), 3) medication-related action plan (MAP), 4) intervention and/or referral, and 5) documentation and follow-up.[11] Typically conducted by a pharmacist, MTM can serve as an educational tool for physicians and patients, and provide a personalized strategy for patients to improve adherence with their medications given their personal, economic, or other challenges with medication self-management. If modifications to a patient's current drug regimen are warranted, the pharmacist can also act as a liaison with the prescriber on behalf of the patient.

In 2003, the U.S. Medicare Prescription Drug, Improvement, and Modernization Act established a prescription drug benefit (Part D) that included a requirement for participating health plans to offer MTM services to eligible patients beginning in 2006.[12] Part D enrollees who had multiple chronic diseases, taking multiple Part D drugs, and likely to exceed $3,144 in annual costs (threshold for 2013) for covered Part D drugs (§ 423.153(d)(1)) were considered eligible for these MTM services. However, eligible enrollees in many plans initially had to opt in to receive the MTM services resulting in only a small proportion of eligible patients receiving these services on prescription medications.[13] This provision has now been changed so that eligible enrollees are offered MTM services unless they opt out with the hope that a greater proportion of patients will receive these services. As of 2013, there were 645 active Part D contracts with an approved MTM program.[14] In addition, several state Medicaid plans and private, non-Medicare health plans provide access to and payment for MTM services.

PGx Testing

PGx testing for patients' genetic likelihood for an adverse response or to determine suitability for a targeted drug is at the forefront of the personalized medicine movement and

gradually moving from specialty medications (e.g., oncology) to more broadly prescribed medications (e.g., codeine, statins, or warfarin). To date, the drug labels of 137 medications include PGx-related information[15] and it has been estimated that 16 percent of medications prescribed in primary care are impacted by PGx variants.[16] Knowledge of a patient's genetic predisposition for an adverse response or therapeutic response can augment current clinical predictors to improve drug selection and response at the time of prescribing. For example, testing for HLA-B*57:01 is currently recommended to identify patients at risk of experiencing hypersensitivity reactions linked to abacavir.[17–19] The Food and Drug Administration has issued warnings about potential codeine toxicity leading to adverse events or even death in those with a genetic variant of the CYP2D6 gene resulting in very rapid and complete conversion of codeine into morphine in children and nursing mothers.[20–22] The utility and hence, integration, of PGx information for other medications are still actively under investigation. For example, use of CYP2C9/VKORC1testing to inform warfarin dosing is currently under investigation for its usefulness in clinical settings to achieving INR goals and reducing potential adverse events associated with out of range INRs. [23–25]

At this time, the delivery model of PGx testing is unclear, with different approaches currently under investigation[26,27,28]. In general, PGx tests can be ordered at the time a medication is prescribed or preemptively for anticipated future treatment.[27] Health professionals involved in the delivery of PGx testing may include the laboratorian, prescriber, pharmacist, and potentially a genetic counselor. With development of new and cheaper testing technologies,[29,30] it is possible that patients' genetic predisposition for a panel of drugs will be ascertained through a single test and results consulted as new medications are prescribed.

Challenges to Integrating PGx into MTM Services

The addition of PGx testing to current MTM services would align well with the goals of MTM and fit within the scope of information discussed and reviewed between the patient and MTM provider. However, given barriers to the provision of current MTM services, it is important to consider the feasibility of adding this new element. In particular, the successful integration of PGx into MTM services likely faces multiple challenges at the health system, provider, and patient levels. Our discussion will primarily focus on challenges to the integration of PGx testing into MTM from the health system and pharmacist perspectives. We recognize that the extent and scope of some of these challenges may be heavily impacted by the type of health system (e.g., integrated vs. non-integrated) and the extent to which pharmacists are utilized or valued in the broader health care system. We identify and discuss six potential challenges to the integration of PGx testing into MTM services in the U.S. health care environment. These challenges were identified from a review of experiences encountered by implementation of MTM and other pharmacy services, the limited experience of early physician adopters and prospective users of PGx testing[31,32]. This list is likely not comprehensive and new issues may be identified as more pharmacies begin to offer this service. We will provide a general overview of the challenges rather than attempt to delineate challenges in different types of healthcare systems.

1. Timing of and Access to PGx testing

Pharmacists may provide MTM services in a range of settings, most commonly in a hospital, outpatient clinic, or community pharmacy setting.[33] As a result, each setting may present different challenges in integrating PGx testing into MTM services. As the majority of MTM services are currently delivered by community pharmacists or clinic-based pharmacists, we will limit most of our discussion to these settings.

As mentioned previously, PGx tests may be ordered at the time a drug is prescribed or preemptively when the patient is healthy and stored for future use. Regardless of when the test is ordered, a clinic-based pharmacist would likely have the most rapid and convenient access to the test results and patient's complete medical record. In contrast, a community pharmacist would have to rely on the patient to inform the pharmacist of their test result or obtain a copy of the results from the patient or physician. However, patient recall of PGx test results may be challenging for some given the novelty of testing and unfamiliarity with terms such as 'extensive metabolizer' or test outcomes such as "genotype." Acquiring a copy of the report from patients or providers may also be challenging as patients may not have been given a written report that they can share and physicians may be difficult to contact and reluctant to share laboratory reports with community pharmacists. A health information exchange (HIE) may be a feasible strategy for sharing test results amongst providers, including pharmacists, and could reduce duplicate testing by multiple providers [34,35], though a minority of states do not allow clinical laboratory results to be returned to a pharmacist.[36] Although patients are generally supportive of HIE, some have expressed concerns about their privacy and the security of the HIE [37,38].

Alternatively, clinic-based pharmacists could order PGx tests through collaborative practice agreements (CPAs), also known as Collaborative Drug Therapy Management. CPAs enable pharmacists to provide a variety of services in collaboration with other health providers (typically physicians) and may allow pharmacists to order PGx testing rather than depending on physician providers. Most states have enacted legislation permitting pharmacists to provide a range of drug therapy management services through CPAs, though the scope varies from state-to-state.[39,40] In 2013, 31 states permitted pharmacists to order clinical laboratory tests under a CPA (APhA).[41] In some cases, credentialing may be required; for example, only pharmacists certified as diabetes educators (CDEs) can order point-of-care tests.[42]

2. Extended MTM sessions

A typical initial MTM session may last between 30 minutes to one hour with follow-up appointments, as necessary.[3,43,44] If the pharmacist recommends PGx testing during the MTM, additional time will be needed to introduce PGx testing to the patient and discuss the purpose of the test, risks and limitations, and alternatives. In addition, a follow-up visit will be necessary to review the PGx results and their significance for the patient's drug therapy. While care may be improved for some patients with the inclusion of PGx testing, the additional time required to provide this service may result in a relative reduction in other MTM services. Even without PGx testing, it has been recognized that expanded patient eligibility for MTM consultations warrant additional service delivery options to address

potential workforce shortages in some geographic areas. The National Committee for Quality Assurance recommended that the 2006 Sound Medication Therapy Management Programs (Version 1.0) revise its position that the preferred delivery MTM model be face-to-face.[45] In 2013, 92% of Part D programs offered CMR consultation by phone, 42% also offered in-person consultations (up from 28% in 2012), and 16% of programs offered CMR consultations through tele-health (up from 1% in 2012).[14] Several studies have demonstrated the effectiveness of phone MTM in addressing medication-related issues[46–49] and patient satisfaction.[49] However, it is unclear whether MTM plus PGx testing can be fully delivered via tele-health, given the amount of new and potentially complex information that would be discussed.

3. Information Technology (IT)

The storage and portability of a patient's PGx results will impact level of utilization. Information technology can greatly enable rapid access to patients' prescription history and clinical test results.[50] A clinic-based pharmacist, as described above, could have access to PGx results through the clinic or health system's electronic health record. Likewise, MTM services could be documented in the electronic health record and recommendations based on the test results could also be contained within the electronic health record. However, the clinic-based pharmacist would likely have no to limited access to data on actual prescriptions filled or PGx tests ordered outside of his/her health system, except in a very small number of locations where these data might be accessible through an HIE.

Community pharmacists usually do not have access to a health system's electronic health record. Instead, community pharmacists often have a local (or pharmacy chain-specific) IT system focused on prescription fills with a separate IT platform for MTM services. The prescription database and MTM application can be locally integrated in order to facilitate completion of a medication reconciliation process that uses health plan prescription data and local pharmacy prescription data, especially for patients that use multiple pharmacies for their prescription medications. Currently, health IT tools for MTM services are primarily used to facilitate identification of patients eligible for reimbursable MTM services, complete medication reconciliation, and process reimbursement for pharmacists' MTM services.[51] PGx test results obtained from the patient or provider could be manually entered into most of the MTM systems; however, access to these data by pharmacists in other locations may be non-existent or very limited. Alternately, if testing is ordered by a pharmacist in the community setting, storage of the result in the community pharmacy database is also possible as community pharmacists already have experience storing other lab results for drugs such as clozapine. Therefore, a similar record of PGx results could be established and accessed for each new prescription. However, this also limits utilization of the PGx test results to that particular pharmacy. This discontinuity of care may particularly affect patients that obtain prescription drugs from multiple pharmacies for various reasons (cost, type of insurance, convenience).[52] In addition, the lack of connectivity with the prescriber with these IT systems impacts continuity of care.

In addition, even if pharmacists had access to PGx results, clinical decision supports (CDS) may be needed to promote appropriate interpretation and utilization of results. Some CDS

tools have been developed to assist physicians in considering testing or dosing/drug selection based on test results.[28,53] To our knowledge, no similar CDS has been explored for pharmacists.

4. Training & Workforce

In 2012, approximately 286,000 pharmacists are estimated to be practicing, primarily in community pharmacies (43%) and hospitals (23%).[54] Likelihood and interest in providing MTM services is predicted by pharmacist training and comfort level.[55] The Accreditation Council for Pharmacy Education (ACPE) currently requires colleges and schools of pharmacy to provide basic MTM training.[56] To fulfill this requirement, a range of training programs for MTM have been developed and implemented in pharmacy schools and continuing education programs.[57–59] If pharmacists are ordering lab tests, they will also require additional training on communicating test results. One of the issues raised by pharmacists with new testing programs such as HIV testing are discomfort with communicating positive results.[60]

The delivery of PGx testing as part of an MTM service will require additional training of pharmacists. Currently, pharmacists report low knowledge and confidence in using PGx information for adjusting dose or drug selection.[61,62] Several professional pharmacy organizations have called for the addition of PGx material into pharmacy curricula and schools have positively responded,[63] exploring numerous approaches.[64–66] For practicing pharmacists, continuing education will help promote awareness of PGx, but more intensive training may be required if pharmacists offer PGx testing given the complexity of the material.[67] Since decisions regarding changes to prescriptions must be approved by the prescriber, physicians, physician assistants and nurse practitioners must also be knowledgeable to understand the PGx-guided recommendations to act appropriately. Physicians have reported low knowledge about PGx[68–70] and are likely to have had limited exposure in medical schools.[71] Several professional nursing organizations have recommended PGx content in nursing programs[72] and genetics core competencies recommendations,[73,74] though more effort is also still needed to implement these recommendations into nursing programs.[75]

5. Standards-setting

Just as standards have been developed for MTM services in general, it will also be important to set standards for integrating PGx testing into MTM practice. In particular, given the relative novelty of PGx testing, it will be important to define what information should be delivered prior to testing and how to communicate the test results effectively and efficiently during the MTM session. Several factors may impact patient-provider communication about PGx testing, including provider knowledge, time, and patient interest. Since the genetics of drug response may be unfamiliar to patients, we suggest that a standardized teaching approach may be warranted to ensure the sufficient information is clearly presented to enhance patient understanding.

In addition, with the pharmacist's expanded role in interpreting and communicating PGx test results with patients and other providers, pharmacist liability would need to be addressed as

this expansion of current MTM services may be viewed as a potentially higher risk activity in our litigious society. Some have discussed the potential for liability and its potential adverse impact on provider behaviors regarding PGx testing.[76,77] When multiple providers are involved in treatment decisions, pharmacist liability appears to be limited to medication dispensation (Moore & Matlock, 2014).[78] However, courts have begun to recognize the broader roles of pharmacists beyond dispensation and applied a 'reasonable professional" standard.[79] Correspondence with the prescriber and patient are important elements in reducing liability[80] and a copy of the MAP including the PGx test results (or summary for patients) should be shared with both parties If the pharmacist has knowledge of a pateint's PGx test results, they may have a duty to warn patients of potential risks for current and future medications.[81]

6. Reimbursement

Another barrier to the provision of MTM services is reimbursement.[82–84] Depending on the setting, pharmacist billing can vary[33] and new models continue to be explored.[85,86] For example, in ambulatory care clinics, billing for pharmacist MTM services may be submitted as incident-to physician care charges.[87,88] With the establishment of pharmacists' Current Procedural Terminology billing codes (CPT codes 99605, 99606, and 99607), pharmacists may also directly bill for services. The variability in payer fee schedules and actual reimbursement rates [89] further add to pharmacists' concerns about appropriate reimbursement for MTM services. The current confusion regarding billing codes and additional time required to complete documentation and billing indicate pharmacists' need for additional support to obtain reimbursement.[84,90] Indeed, a survey conducted in 2011 found that a substantial proportion of pharmacists reported not billing for MTM services.[33,91] Others believe that Medicare Part D reimbursement is too low for pharmacy services including MTM.[92] The inclusion of PGx testing into MTM with the anticipated additional time needed to discuss testing, collect and ship the sample, re-contact the patient, and consult with the prescriber may further complicate reimbursement since pharmacist CPT codes do not account for complexity of MTM service and can only be used for in-person MTM.

Conclusion

The growth in PGx research and the readily available means for conducting PGx testing in non-traditional settings provides patients and clinicians with new ways to manage medications. Pharmacists are uniquely trained in using in-depth knowledge of drugs and their properties to safely and effectively select and manage complex medication regimen. PGx testing can provide a new level of detail for potentially even better drug selection and management decisions. Pharmacist-delivered services, especially in community practice settings continue to evolve to meet the demand from patients, payors, and other health care providers to improve medication management, including standardization and enhancements in MTM services. Now may be an opportune time to consider the feasibility of integrating PGx testing into MTM and to establish a niche for pharmacists in the personalized medicine movement. As with any new service, the integration of PGx testing into MTM conducted by pharmacists faces several challenges. In this paper, we explored some of those challenges to

stimulate discussion on potential next steps. Agreement from multiple stakeholders on the feasibility and value of this service, tested and proven models for implementation and dissemination, and an established business case are needed to advance this potential new method of medication management. This will likely require new partnerships between pharmacists and physician groups, diagnostic laboratories, and software vendors and engagement of professional societies and/or consortium of pharmacies to develop this potential new opportunity. Despite the challenges, we envision community pharmacists are uniquely poised, with respect to their expertise of drugs, frequent interaction with patients, and interface between prescribers and patients, to play a key role in delivering PGx testing. We believe that patient engagement through a service like MTM will be necessary, particularly during the early stages of implementation of PGx testing in general, to increase patient familiarity with testing and understanding of the results for current and future medication needs. As additional tests may be performed for a given patient, the level of engagement needed may be less. As the practice of MTM and PGx testing matures, early integration of the two tools may benefit all stakeholders

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Table

Summary of potential challenges to provision of MTM plus PGx testing service by community pharmacists.

1	**Timing of and Access to PGx Testing**
	• Timing PGx testing for making optimal drug decisions
	• Access to PGx test results done in various clinical care settings
	• Ability of pharmacists to order PGx testing
2	**Extended MTM Sessions**
	• Pharmacist time constraints in community practice
	• Uncertain added time needed for Initial and follow-up session needed to introduce testing/discuss test results
	• Uncertain feasibility of discussing PGx testing by phone versus face-to-face
3	**Information Technology**
	• Potentially limited access to patient's electronic health record
	• Need to integrate PGx test information into health IT tools for MTM
4	**Training & Workforce**
	• Limited PGx education in pharmacy curriculum
	• Need for continuing education as PGx field grows
5	**Standards-Setting**
	• Development of standards for integrating PGx testing into MTM practice to provide consistent and documentable added value
	• Consideration of pharmacist liability
6	**Reimbursement**
	• Obtaining adequate reimbursement for MTM plus PGx testing service