EDITORIAL AND COMMENT

Laboratory Monitoring for Pharmaceuticals: Familiarity Does Not Breed Contempt

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Laboratory monitoring helps ensure safe and effective medication therapy, especially for medications with increased risk of drug-induced toxicity. Indeed, many potential problems are readily detectable and preventable by common laboratory assessments. Unfortunately, suboptimal use of laboratory monitoring tests for detecting potential drug toxicity puts many patients at unnecessary risk of adverse medication effects.¹ Gaps in test ordering may be due to several factors, among which are lack of knowledge, lack of time, uncertainty regarding the importance of monitoring or timing of tests, disordered workflow, and lack of patient engagement in medication management. Further understanding factors that influence the appropriate monitoring of medications would help inform development of suitable interventions for improving monitoring practices.

In this issue of *JGIM*, Fischer and colleagues report on their retrospective study of 31,417 adult patients and 278 providers in a large, multispecialty group practice within a New England-based health plan. The study examined predictors of laboratory test ordering for 34 medications deemed as high risk for potential adverse effects.² This study specifically and uniquely evaluated the process of provider ordering rather than simply considering test completion by the patient. This is key to isolating the impact of the specific factors that may be influencing providers at the time of test ordering, apart from whether the patient follows through, an important, yet separate step in the process.

Among their findings, the authors noted that physician test ordering was associated with patients' increasing comorbidity burdens and older age and with providers having higher patient volume (measured in two different ways). Less frequent physician test ordering was associated with older providers, new use of medications, and medications requiring more frequent or multiple laboratory monitoring tests. Black box warnings were associated with increased monitoring rates, but these findings diverged substantially according to physician

specialty: specialists did better than generalists. Although Fischer and colleagues did not study the impact of laboratory monitoring on patient outcomes, this study contributes important insights into process of care issues associated with test ordering.

While laboratory test ordering rates in this study are clearly not perfect, they may be higher than rates in other settings and/or studies. Orders for laboratory testing ranged from a low of 9 % for primidone-phenobarbital levels to a high of 97 % for a complete blood count for azathioprine. In general, less commonly prescribed medications such as primidone, quinidine, and lithium had test ordering rates less than 50 %. More commonly prescribed medications had higher rates; for example, laboratory monitoring for angiotensin converting enzyme (ACE) inhibitors reached 91 % for a basic metabolic panel. Previous research conducted across a range of ten health maintenance organizations across the US found much lower rates (60 to 70 %) for similar monitoring tests for angiotensin-converting enzyme inhibitors.¹ Therefore, findings of the present study may represent optimistically high estimates of test ordering in relation to comparable studies. This may, in part, reflect that the current assessment focused on test ordering, a metric of physician performance, rather than test completion, which represents a combined metric of patient adherence and overall system and provider performance. In addition, in certain instances, the study attributed successful test ordering for a test(s) completed either before or after the index prescription, such as for the aforementioned ACE inhibitors, which will tend to overstate some ordering rates, though this was not the case for most drugs (personal email communication with Shira Fischer, MD, on September 11, 2014). Of note, the vast majority of medications included in the current study are older drugs, so how monitoring rates for newer drugs (e.g., creatinine monitoring for the novel oral anticoagulants) compares is uncertain.

Even so, the general lessons are important, and the study highlights potential gaps in safety. More specifically, Fischer et al. identified that providers with higher patient loads or prescription volume (regarding study medications) were more likely to order a recommended monitoring test. Moreover,

specialists performed far better than generalists for drugs with black box warnings. In aggregate, this suggests that those with greater expertise and/or experience with certain drugs have greater familiarity with ordering recommended monitoring tests. This is quite similar, as the authors also noted, to the volume-outcome relationship demonstrated in surgical and interventional settings.³ Along the same lines, specialists may be more aware of black box warnings within their typical prescribing domain. Prior studies have evaluated the impact of black box warnings on medication prescribing and monitoring, but have not extensively evaluated the impact of these warnings by physician specialty.⁴ This study importantly adds to the knowledge base in that regard.

So, what then is to be done? The findings of this study suggest that, first and foremost, systems being developed to improve prescribing safety should particularly focus on clinicians less familiar with ordering the monitoring tests for certain medications. Fischer and colleagues notably recommend targeting providers with lower prescribing frequencies and for patients who have lower comorbidity burdens or less interaction with the health care system. These are sensible recommendations. They also recommend increasing black box warnings as a tool to improve test ordering, although in this we are not too sure since black box warnings were also associated with less optimal test ordering by generalists. As such, these black box warnings do not appear to be the “silver bullet” solution, and we are concerned that aggressively adding more black box warnings may dilute the impact of such warnings, as is the concern with numerous drug-drug interaction alerts in computerized medication-prescribing systems.^{5,6}

In any event, we feel, as do the authors, that there must be a variety of additional solutions. As the authors have noted, improved monitoring definitions and guidelines are fundamental to improving the quality of monitoring. We anticipate that the stronger the evidence base for specific monitoring, and the more transparent the rationale for monitoring, the more likely clinicians will be to order recommended tests. Two relevant questions to consider for both new and old drugs are: (1) Is good evidence available for currently recommended laboratory monitoring, and (2) should there be levels (beyond expert opinion) of recommendations for monitoring? As an example, while it was historically standard practice to routinely check liver function tests for patients prescribed statins, this is no longer recommended except at baseline and not thereafter unless patients have symptoms of potential hepatotoxicity.⁷ Excess monitoring distracts prescribers from more crucial test ordering, but also wastes time and money, and it risks false-positive findings that may cascade into further testing. By reassessing and then reasserting the necessity and frequency of laboratory monitoring, we can ensure prescribers can focus on high-value testing parameters. Furthermore, we agree with the authors that vague

recommendations in guidelines or prescribing information, such as using the term “periodic,” are ambiguous and create uncertainty. Greater specificity is crucial if variance is to be decreased.

One promising method to improve prescribing is to utilize automated decision support systems, analogous to drug interaction order checks,⁸ that can help optimize test ordering at the time of medication prescribing, perhaps with enhanced alerts at the time a patient is first prescribed a medication, and for those drugs requiring frequent monitoring or multiple tests. Facilitating appropriate laboratory test ordering by integrating this into the clinical workflow of medication prescribing may prompt greater adherence, although this would need more formal assessment.

Additionally, implementing a team approach to laboratory monitoring may prove beneficial. There is potential synergy to working within patient care teams, such as those recommended in the patient-centered medical home model. Integrated health care systems, such as the Veterans Health Administration and Kaiser Permanente, have taken the lead in team-oriented patient care. This general model can be more widely applicable, however, and we advocate for utilizing pharmacists as key team members with expertise in necessary ancillary monitoring for drug therapy.⁹ Pharmacists already frequently use prescribing protocols in institutional settings for anticoagulation and antibiotic dosing, and expanding their roles to include routine medication monitoring may improve drug test ordering. This may be particularly useful for newly started medications and drugs requiring frequent monitoring, areas identified as especially suboptimal in the current study. Indeed, some states, including California, have enacted legislation granting increased responsibilities for pharmacists with advanced training, regardless of practice setting, to collaborate with prescribers on ordering and interpreting laboratory monitoring parameters.¹⁰ We suspect that expansion of this type of team-based approach with advanced practice pharmacists acting in collaboration with prescribers in non-academic or non-institutional settings will make strides in reducing gaps in medication monitoring, but the impact is as yet unclear and will need formal evaluation.

While Fischer and colleagues' study advances pharmaceutical safety research by providing greater focus on providers, we would be remiss in not mentioning the patient's role. Non-completion of tests by patients defeats the best of provider intentions. Hence, we must also find better ways to engage patients. Certainly, explaining the need to monitor to patients is crucial, but other steps in our technological age could include computer-generated reminders, or electronic mail or smart phone applications.

Overall, Fisher and colleagues have brought important attention to gaps in test-ordering rates in medication management, especially among providers who perhaps have less experience and expertise with the medication-monitoring recommendations for selected drugs. A singular solution to the problem is not clear but logically we must strive to develop systems and engage personnel that facilitate clearly delineated,

evidence-based laboratory test ordering, in concert with exploring technological tools that empower providers and patients to optimize safe and effective prescribing.

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