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Striking a Balance in Communicating Pharmacogenetic Test Results: Promoting Comprehension and Minimizing Adverse Psychological and Behavioral Response

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Abstract

Objective—Pharmacogenetic (PGx) testing can provide information about a patient's likelihood to respond to a medication or experience an adverse event, and be used to inform medication selection and/or dosing. Promoting patient comprehension of PGx test results will be important to improving engagement and understanding of treatment decisions

Methods—The discussion in this paper is based on our experiences and the literature on communication of genetic test results for disease risk and broad risk communication strategies.

Results—Clinical laboratory reports often describe PGx test results using standard terminology such as 'poor metabolizer' or 'ultra-rapid metabolizer.' While this type of terminology may promote patient recall with its simple, yet descriptive nature, it may be difficult for some patients to comprehend and/or cause adverse psychological or behavioral responses.

Conclusion—The language used to communicate results and their significance to patients will be important to consider in order to minimize confusion and potential psychological consequences such as increased anxiety that can adversely impact medication-taking behaviors.

Practice Implications—Due to patients' unfamiliarity with PGx testing and the potential for confusion, adverse psychological effects, and decreased medication adherence, health providers need to be cognizant of the language used in discussing PGx test results with patients.

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1. Introduction

Pharmacogenetic (PGx) testing assesses variation in genes associated with drug response, providing information about a patient's likelihood to respond to a given medication or experience an adverse event. Since the result of a single test can be important for several different medications due to shared mechanisms of drug metabolism, PGx testing may be relevant over the course of a patient's lifetime. In particular, understanding of one's drug predisposition and its impact on dosing or drug selection may result in improved outcomes, medication adherence, and patient satisfaction [1]. Therefore, patient comprehension of the test result becomes both critical but challenging due to a number of factors including varying provider and patient knowledge and experience with testing, limited time during an office visit for discussion of results, and patient health literacy and numeracy.

The psychological impact of genetic testing has been broadly examined for several conditions. In general, the impact appears to be minimal even for diseases without clinical interventions such as Alzheimer disease [2–4] and even when testing for multiple conditions through panel or array-based testing [5–7]. In contrast, PGx testing is believed to raise even fewer risks of psychological harms and stigmatization or discrimination compared to genetic testing for disease [8–10]; however, no evidence supports this presumption. It is possible that these risks have been underestimated when considering the challenges of effectively communicating results, particularly given the language used to report PGx test results and the potential long-term and recurring use of PGx test results. Furthermore, it is not clear if psychological harms from predictive genetic testing for inherited disease and PGx testing are comparable as individuals with a personal or family history of a disease may cope with test results differently than individuals with no prior personal or family history or expectation for need for testing, as may be the case for PGx testing. Additionally, a patient's psychological response to a PGx test result may be compounded by the nature of the condition for which treatment is needed.

It is anticipated that PGx testing is likely to become more widely used with more than 100 medications containing PGx information in their label and increased development of companion diagnostics [11, 12]. Therefore, it is important to consider the effects of PGx testing and the manner in which it is discussed with patients. In this paper, we consider potential risks of the language currently used to report PGx results and suggest alternatives with less risk of psychological effects. To our knowledge, there is little research or literature specific to communication of PGx test results. Therefore, the suggestions proposed in this paper are based on our experiences and the literature on communication of disease-based genetic test results and the broad risk communication strategies. As a best delivery model of PGx testing has not yet been determined, any provider including but not limited to physicians, pharmacists and genetic counselors may consider incorporating these suggestions when using PGx testing.

1.1. PGx Testing

Among other factors such as environment, body habitus, and drug-drug interactions, response to medication is affected by variation in genes encoding the drug target or involved in metabolism, transport, and other essential functions. For example, several genes encoding

liver enzymes, known as cytochrome P450 (CYP) genes important to the metabolism of many commonly prescribed medications, are highly polymorphic, resulting in a range of enzyme activity levels in patients [13]. PGx testing can provide knowledge about a patient's level of enzyme activity or presence or absence of a genetic variant for a targeted drug can inform medication selection or dosing to improve treatment response or reduce risk of an adverse event [13]. Testing may be ordered when a drug is prescribed (point-of-care) or preemptively [14]. In addition to physicians, nurses and pharmacists may play a role in delivery of PGx testing [15–17], particularly with respect to promoting patient understanding of the test result [18].

Clinical laboratories conducting PGx testing often report the test outcome in the lab report in multiple ways: the molecular genotype (e.g., T/T) and by its allelic abbreviation (e.g., *1/*5) and phenotype (e.g., poor metabolizer). The phenotypic descriptors of the level of enzyme activity used in clinical laboratory reports are standard terminology accepted in the medical research literature and clinical guidelines. Additional text may or may not be included to explain the phenotype: e.g., 'poor metabolizer' status means that the patient has low or no enzymatic activity, whereas an 'ultra-rapid metabolizer' refers to a patient with extremely high metabolic activity ('intermediate' and 'extensive' metabolizer refer to normal or moderately increased levels of enzyme activity, respectively).

2. Concerns with Using Standard Reporting Language to Communicate PGx Results

For communication of any test result, the primary goal is to optimize patient understanding about the test outcome and how the information impacts medical management. However, communicating PGx results may be more challenging than previously considered for many reasons including the type of test outcome (genotype) and interpretation (phenotype), limited patient knowledge about genetics and the role of genes in health, and the differing impact of results for each medication prescribed (e.g., for one medication, dose may be reduced based on the PGx test result, but for another, the dose may be increased based on the same test result). Patient factors such as health literacy [19], genetic literacy [20, 21] and numeracy [22] may also affect their ability to understand PGx testing and the results. Additionally, provider knowledge of PGx is one of the most common barriers reported [23–26] and is associated with limited experience with testing [27, 28]; similarly, limited knowledge and experience may affect communication about PGx testing [29]. Though participants have reported their informational needs for PGx testing in a research setting [30], to our knowledge, there are no recommendations regarding what information should be discussed with patients (pre or post-testing) and/or the language to be used during these discussions in a clinical setting. Based on our experiences with PGx testing in a primary care setting, we published a paper identifying key information to be discussed pre and post-testing, though did not review in detail the importance and impact of effectively communicating the test result [31]. Given the range of literacy levels of patients and even for those highly literate but unfamiliar with PGx testing, the language used to describe a patient's genotype or phenotype for drug response must be carefully considered not only to promote comprehension, but also to avoid risk of adverse psychological responses such as

feelings of hopelessness due to the immutability of the result (genes cannot be changed as cholesterol levels can), perceived inferiority of their genotype and perceiving themselves as different [32, 33].

2.1 Effects of Language and Terminology

As with other genetic test results, the communication of PGx test results will likely focus more on the phenotype instead of genotype, (i.e., what is the interpretation or meaning of the result for the patient?). When describing a genetic test result, it is generally recommended to avoid stigmatizing terms such as “mutant,” “defective,” or “abnormal” as such terms generally have a negative connotation [34–37]. Instead, neutral terms regarding the function of genes should be used, such as “working” and “non-working” genes. Additionally, some evidence suggests that “typical” is preferred when discussing normal results (i.e., intermediate metabolizer) to avoid stigmatization of presenting results as “abnormal” [38]. Use of categorical labels such as “poor metabolizer” may be easier for patients to understand than comparative terms like “high risk” [39, 40] and therefore, patients’ recall and likelihood to share the information with other treating providers may be higher. However, the potential for patient misinterpretation and adverse psychological responses may outweigh these advantages. For example, such labels may be interpreted as a bad outcome by patients, though the term ‘poor’ actually refers to the level of enzyme activity and not health outcome.

Since probability (numerical) statements are not typically included with the phenotype on PGx test reports, patients may assume that being a poor metabolizer for a given gene means that they are 100% likely to experience an adverse event or will metabolize *all* medications poorly. Similar confusion may ensue for patients falling into the normal metabolic range (an intermediate or extensive metabolizer) as they may develop a false sense of security and assume that they are not at risk for a side effect or non-response. Rapid and ultra-rapid metabolizers may pose similar risk of an adverse response or failure to respond to some medications as patients who are poor metabolizers. Thus, discussion of the estimated overall risk of adverse events may be important to enable patients to gain some perspective of what it means to be at increased risk for an adverse event. However, this information may be challenging to understand for patients with low numeracy [41, 42]. Use of different formats to convey risks may be necessary to improve comprehension (e.g., 30 percent or 1 in 3 patients) [41, 43]. Furthermore, patients may associate the term ‘metabolism’ with how the body breaks down food rather than medications, as this may be a more familiar context of the word, potentially leading to some confusion.

2.2 Effects of Health Status

Patients’ potential confusion about their PGx results may be further exacerbated by their current state of health. For example, patients may already be struggling with a new diagnosis or recurrence of a prior condition, and adding results from a PGx test indicating that they are at increased risk of an adverse response or potential non-response may impair their ability to cope. Patients diagnosed with conditions that are socially stigmatizing such as mental illness may be particularly vulnerable to the burden of an abnormal PGx result. Several drug classes commonly prescribed for mental health conditions are known to be impacted by PGx

variants [44]. For example, selective serotonin reuptake inhibitors (SSRIs) are metabolized by the highly polymorphic genes CYP2C19 and CYP2D6 [45, 46]. Given the challenges in achieving therapeutic efficacy with minimal adverse responses for mental illnesses, patients may consider PGx testing to be extremely helpful in medication selection/dosing and reducing the number of medication alterations to achieve an effective therapeutic plan [47]. A genomic test is under development to predict suicidal tendencies associated with use of several antidepressant treatments [48, 49]. However, communicating an abnormal PGx result to patients with vulnerable mental states may worsen their condition and lead to non-adherence [50], although such risks could be offset by more rapid identification and titration of a safe and effective antidepressant.

2.3 Effects of Patient Understanding

Ultimately, knowledge and understanding of one's PGx status can impact patients' perceptions of medication risks. As health behaviors are impacted by risk perception (e.g., theory of planned behavior [51]), a patient's likelihood to adhere to a prescribed medication may be affected by perceptions of higher risk of a side effect associated with an extreme level of enzyme activity (either very low or very high) as well as their understanding of how their provider can adjust the dose or select a different medication to increase likelihood of response or reduce risk of an adverse event [52]. During the patient-provider discussion, framing the test result positively (e.g., as an opportunity to improve their treatment) may promote feelings of control and reduce those of hopelessness or stigmatization [53]. Furthermore, even if patients attempt to adhere to their medication regimen, they may be overly sensitive to symptoms presumed to be a side effect of the medication, resulting in partial or complete non-adherence and therefore, potentially adversely affecting health outcomes. In addition, patients found to be a poor or ultra-rapid metabolizer may perceive themselves as 'difficult-to-treat,' [54], a label they will be reminded of each time a medication is prescribed [55–57]. These behavioral consequences of PGx testing have not been explored in-depth, but could have substantial costs and health consequences [58–60].

3. Promoting Comprehension while Minimizing Adverse Psychological and Behavioral Response

3.1 Essential Information Patients Should Understand about PGx test results

Regardless of the PGx result, without informing patients that the significance of the level of enzyme activity must be determined on a drug-by-drug basis, PGx test results could negatively influence patients' medication adherence behavior. We suggest that three types of information are necessary to promote patient comprehension of their results and minimize adverse consequences: 1) description of the actual test result (phenotype with or without genotype); 2) the significance of the result for the medication that the patient is currently being prescribed; and 3) that the results may also be important for future medications as drugs can be broken down by the same pathways in the body. Understanding how the test result may impact current treatment is important to allay concerns and help patients to better understand why they may be prescribed an alternative medication or dosing or if additional monitoring of side effects is warranted. At a minimum, it is essential that patients understand that they have been tested for drug response so they can inform other prescribing

providers and avoid duplicate testing. Patients or providers can then obtain a copy of the test report to confirm results. This may be difficult for some patients if they do not clearly understand or recall the purpose of testing, or if they do not realize that the test results for one medication may also be applicable for another medication.

3.2 Appropriate Language and Terminology

We suggest that terms such as ‘poor’ or ‘ultra-rapid’ metabolizer should not be used by providers or included in the interpretation section of a PGx clinical lab report without explanation of the actual meaning of the results written for a general audience. Both words may increase risk of misinterpretation and adverse psychological response. There are a few alternatives that providers may consider. For example, in a current ongoing study, the authors are defining metabolism, then using “slow” and “fast” metabolizer to help patients understand results (NCT#01970774). Alternatively, since it is still difficult to quantitate the exact level of metabolism based on the patient’s test result or estimate risk of an adverse response or non-response, use of familiar terms such as ‘low, moderate and high’ may be used to convey enzyme activity level instead. However, even these terms may be confusing as they may conflict with the overall level of risk. For example, a low enzyme activity level indicates a high risk for an adverse response for a given medication. A numerical scoring system has also been proposed to correspond to the level of enzyme activity [46, 61]. For example, a patient with no functional activity for CYP2D6 (poor metabolizer) would be assigned a score of ‘0’ and a patient with normal activity would be assigned a score of ‘1.’ Preferred language and terminology has yet to emerge; therefore, providers will need to be cognizant of the effects of their word choice and consider the most appropriate language and terminology for each patient.

3.3 Supplemental Information for Patients

Written information may be given to patients as well to promote comprehension and encourage sharing of PGx results with other providers. For example, the testing laboratory may consider developing a summary of the results written specifically for patients using terminology suggested here. Furthermore, given that patients increasingly will have access to their clinical laboratory reports through their electronic medical records, links can be embedded throughout the report. It may also be helpful to supplement text in the lab report or the discussion of results with figures or graphics to promote comprehension of the patient’s PGx results [62, 63]. Many genetic counselors use instructional aides to help patients understand test results and their clinical implications [64]. For example, a graphic of a bar representing the spectrum (range) of enzyme activity levels could be used, with a marker indicating where the patient falls within that spectrum. Patient-friendly online or mobile health applications could also greatly facilitate patient comprehension and the differing outcomes for medication selection/dosing based on the type of medication needed. As mentioned previously, patients should be encouraged to discuss the results with other providers and/or their pharmacist given the potential significance of the PGx result for multiple medications. Providing printed materials (e.g., a PGx results card) for patients can facilitate recall and sharing of results.

3.4 Promoting & Assessing Patient Comprehension

Anticipating patients' unfamiliarity with PGx testing, providers may consider incorporating methods to assess patient understanding such as teach-back [65, 66]. In addition, utilizing patient communication techniques recommended for low health literacy patients during this initial period of use of PGx testing may help promote comprehension such as limiting use of medical jargon, speaking slowly, using pictures, and limiting information conveyed [67–71]. There are many patient education resources including medication instruction sheets, personalized medication calendars, streamlined pictorial bottle labels, and simple reminder systems that can inform patients about their medication at a level aligned with their health literacy level. Technology provides many tools and resources which may facilitate improved adherence including pill monitoring systems, mobile health technology, only resources and social media, and electronic health records, among others [72].

4. Conclusion and Practice Implications

4.1 Conclusion

PGx testing has great potential to improve the care of patients by informing treatment decisions to minimize risk of adverse events and improve likelihood of desired clinical outcome. But in order for PGx testing to be useful to the patient and future treating providers, it is important that patients understand their test results or at minimum, the purpose of the test, so that they may share that information with other providers. The language and terminology used as well as health status of the patient will influence their comprehension of PGx test results. Therefore, we recommend that providers avoid stigmatizing terms to describe results and use supplemental learning aids to promote comprehension and educate patients. Laboratorians can greatly assist with provider communication of results by including a patient summary of the result in the test report as well as a list of patient resources.

In summary, we propose that when discussing PGx results, providers should focus on 3 key points: description of the result, health implication of the result for the current medication, and potential importance of the result for future treatments. Using appropriate language and supplemental written information can help relay these essential points.

4.2 Research Implications

To our knowledge, only one study has examined psychological response to PGx testing [73]. However, there are a number of limitations to the study: reporting of results was in a research setting by the research team rather than in a clinical setting by a provider, PGx testing for a single gene/drug was performed on healthy volunteers, the language used in communication was not examined or described in detail, and psychological response was assessed using only a single question (How do you feel after receiving this information?) [73]. Additionally, only one participant was discovered to have "increased risk" results. Therefore, it is difficult to predict the psychological impact on study participants and ascertain its relevance to a general patient population. Because PGx testing is considered different from disease-related genetic testing [74–76], it is unclear if risk communication practices used for other types of genetic tests, which are the basis of recommendations

provided here, would be appropriate or useful. Thus, research in this area will be important to identifying effective communication strategies and minimizing potential harms, including evaluation of our suggestions to avoid stigmatization and promote patient understanding.

4.3 Practice Implications

Promoting patient understanding and sharing of PGx test results is key to utilization of those results in therapeutic decisions throughout a patient's lifetime. It is essential that providers minimize the potential for patient misunderstanding or psychological events when discussing PGx results. Use of terminology that is different from that used in the clinical lab report, medical research literature and clinical guidelines may help achieve this goal. As PGx testing becomes more widely used, increased provider education and provision of educational aids will be necessary to ensure effective communication and appropriate use of PGx results.

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Highlights

- Pharmacogenetic (PGx) testing assesses variation in genes associated with drug response.
- Communicating PGx test results may be challenging due to complexity of result.
- Categorical labels like “poor metabolizer” are often used and may be misinterpreted.
- Adverse psychological responses and medication behaviors may result from such labels.
- We recommend that providers avoid stigmatizing terms to describe results