

## How Pharmacogenomics Informs and Influences the Medication Experience

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### Abstract

Both pharmacogenomics (PGx) and the medication experience (MedXp) share a common purpose for their use, which is to optimally tailor medications to each unique individual. The former pursues this aim by using an individual's genetic makeup, while the latter considers the subjective experience of medication-taking in one's life. The different ways by which these fields of study pursue their shared aim have resulted in relatively little understanding of their relationship when utilized in care processes to produce health outcomes. This commentary explores this gap and identifies implications for future research that can help close it to improve person-centered care.

**Keywords:** pharmacogenomics, medication experience, person-centered care, Donabedian model, medication adherence, medication-taking behaviors

### BACKGROUND

The medication experience (MedXp) generally refers to the lived experience of individuals involving drug therapy that shapes their attitudes, beliefs, and preferences related to taking medications.<sup>1-4</sup> In a recent concept analysis synthesizing 40 years of research, Hillman et al formally defined MedXp as "an experience of ambivalence and vulnerability in which the patient is actively engaged in an ongoing process or negotiation, which is pragmatic to the ways in which patients live and experience life, contextualized and nuanced within the social construction of their individual realities."<sup>5</sup> In this way, the MedXp represents essential information and context for informing drug therapy choices best suited to an individual.

Pharmacogenomics (PGx), generally defined as the study of how an individual's genetic makeup contributes to their response to medications, also seeks to optimize drug therapy for each individual.<sup>6</sup> Although variation in drug response has been recognized for some time, the science and clinical implementation of PGx has grown substantially over the past few decades.<sup>7</sup> Published guidelines recommending how to utilize PGx information are available from the Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group, and several others.<sup>8,9</sup> While the primary focus on PGx has been scientific discovery and clinical implementation, it is also important to consider how PGx might influence an individual's psychosocial experience of medications.

The MedXp and PGx share a common goal of optimally tailoring medications to each individual albeit through different person-centered approaches. Considering the limited exploration of how they relate to one another, the objective of this commentary is to explore the intersection of PGx and MedXp.

### RELATIONSHIP BETWEEN THE MedXp & PGx

As approaches to care become more tailored to each individual from a whole-person perspective, a framework for linking care processes to outcomes is essential. One way of understanding the relationship between the MedXp and PGx is provided by a modified Donabedian model. The traditional Donabedian model has three sequential concepts: 1) Structure, 2) Process, and 3) Outcomes approached from the perspective of the clinician. Each preceding category informs the one that follows it, such that "good structure increases the likelihood of good process, and good process increases the likelihood of good outcomes."<sup>10</sup> For example, 1) Structure: a hospital with a policy in place about flagging drug allergies, 2) Process: hospital staff utilizing procedures to prevent drug-related allergic reactions, and 3) Outcomes: reduced incidence of patient injuries from drug allergies. The focus of this commentary is how the MedXp and PGx relate in connecting care processes to outcomes from the perspective of clinicians and patients. While not explored in this commentary, integrating the structure concept will be important in future thought and work for this research area.

For care processes, Donabedian differentiates between those that are technical, such as care activities based on clinical knowledge, judgment, and skills including diagnosis, and interpersonal, such as care activities rooted in information exchange including a person's experiences, goals, preferences, and/or self-efficacy.<sup>10</sup> Donabedian outcomes represent the effects of care processes on patients and populations such as changes in clinical outcomes, patient knowledge and behavior, and quality of life. The linkage between care processes and outcomes is also populated by factors that mediate (i.e.,

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variables that explain why or how an intervention produces an outcome) and moderate (i.e., variables representing the conditions in which interventions influence the magnitude and direction of outcomes). This commentary proposes that medication-taking behaviors, such as adherence from a healthcare/clinician lens, are a linking mediator between the care processes and outcomes, with the MedXp and PGx serving as moderators that mediate a variable (i.e., 'mediated moderators')<sup>11</sup> acting at differing points of the modeled relationship. Figure 1 depicts one plausible configuration of this with the relationship and positioning of the MedXp and PGx in the model reflecting their relevance between each other and applications around the medication-taking behavior mediator. While the Care Process, Medication-Taking Behavior, and Outcomes are important elements of this proposed model, the following sections will focus on how they relate to the MedXp and PGx.

#### *MedXp: Patient Perspective*

Figure 2 depicts a conceptualization of the MedXp from the perspectives of the person taking medications (i.e., the patient) and the clinicians prescribing, managing, or professionally advising on the medications being taken. The upper half describes the patient lens of the MedXp with corresponding outcomes and consequences from resulting medication-taking behavior. Of note, medication-taking behavior is intentionally used instead of medication adherence, given the latter is more reflective of health system interests and perspectives. The six MedXp attributes were developed through a concept analysis conducted by Hillman et al, which are identified and defined as follows:

- Ambivalence - simultaneous and contradictory attitudes/feelings toward their medications.
- Vulnerability - actual as well as perceived risks and concerns of taking medications.
- Socially Constructed - accepted and shared social as well as cultural ideas of medications.
- Pragmatic - how the use of medications affects the processes and experience of an individual's daily life.
- Contextual and Nuanced - the circumstances that form the setting of one's medication use that is critical to a full understanding of it.
- Active and Ongoing - a recognition that medication use is a dynamic process that involves a series of actions that require effort and resilience over time to be sustained.

Under the modified Donabedian model, these attributes serve as inputs to medication-taking behaviors that lead to outcomes or consequences. Gliklich et al<sup>12</sup> provide three useful patient-oriented categories for organizing these outcomes, which are identified and defined as follows:

- Patient Reported – patient's perceptions of their status and perspective on health and disease in light of

medication taking (e.g., functioning, quality of life, conceptualization of self)

- Events of Interest – experiences relevant to medication-taking that involved adverse events, exacerbations, complications, improvements, etc.
- Family, Friends, and Community – perceptions, perspectives, and impact of medication taking as it relates to the patient's relationships with persons in their life, the community they belong to, and the health systems they interact with.

Ultimately, what constitutes a good or important outcome from the MedXp through a patient lens is dependent on what is meaningful and valuable to each person. It is also important to note that the outcomes, both from the patient and clinician perspective, serve as inputs for a feedback loop that traces back to the MedXp (see dotted line in Figure 1), demonstrating the MedXp concept's dynamic and ongoing attribute.

#### *MedXp: Clinician Perspective*

The MedXp can also be understood from a clinician perspective that is primarily informed by biomedical knowledge and thought processes. The Pharmacy Quality Alliance framework for identifying, understanding, and addressing medication-related needs serves as a useful representation of the MedXp from the clinician's perspective.<sup>13</sup> The framework's four categories are identified and described below:

- Indication - Biomedical and physiological knowledge of a disease or diagnosis and whether a medication will work to treat it (e.g., removal of unnecessary medications, need for additional medications)
- Effectiveness - Medication will lead to a physiological or biomedical improvement of, long-term control of, or symptomatic relief from a disease (e.g., change to a more optimal medication or an adjustment to a medication's dosage, frequency, administration, dosage, or duration)
- Safety - Biomedical or physiological impact on the body (e.g., medication interactions, contraindications, allergies, side effects)
- Adherence - Consideration of patient factors that will lead to the patient taking the medication as prescribed (e.g., patient understanding of instructions, patient forgetting to take, patient difficulty swallowing or administering, availability of medication, affordability of the medication). It should be noted that other medication use frameworks substitute 'Convenient' for 'Adherence,' to better reflect the patient's lens of medication-taking behavior than a biomedical-oriented perspective.<sup>2</sup>

The outcomes and consequences of the MedXp that are tied to the clinician perspective are represented by more traditional healthcare outcomes, which Gliklich et al<sup>12</sup> categorize into three general groupings:

- Resource Utilization – patient interactions and use of health system services (e.g., hospitalizations, clinic visits, emergency department use, days of school or work missed, number of medications, procedures, care costs).
- Clinical Responses – assessments by the clinician of how patients are responding to treatment(s) (e.g., status improvements, exacerbation events, stable progression).
- Survival – key endpoint for most biomedical conditions (e.g., all-cause mortality, cause-specific mortality, disease-free survival).

#### *PGx Fit*

If the MedXp represents an individual's subjective experience of taking medications in their daily life, then PGx can be thought of as the objective responses of an individual's body to a medication based on their genes that serve as input to this subjective experience. PGx helps to inform clinicians about an individual's ability to metabolize and eliminate medications, resulting in reduced adverse effects and improved efficacy through improved medication dose and selection.<sup>6</sup> This relationship is represented in the proposed modified Donabedian model (Figure 1) by the unidirectional arrow connecting PGx fit to the MedXp.

PGx may impact the MedXp at multiple time points, depending on whether testing is obtained preemptively (i.e., before a medication is prescribed) or retrospectively (i.e., after a medication(s) has been trialed). Individuals bring a wide range of beliefs and attitudes regarding genetic testing based on understanding and past experiences. Previous work suggests many patients find PGx testing useful and valuable but there is needed improvement in patient-clinician communication and the overall patient experience of care involving PGx.<sup>14–18</sup> Specific aspects of PGx testing relevant to patient-clinician communication and the patient experience fit into several of the aforementioned MedXp attributes, which we have categorized as negative, neutral, or positive (Table 1).

Preemptive PGx testing may help providers in medication dose and/or selection with the ultimate goal of improving clinical response as well as reducing the likelihood of adverse events. Patients may view the benefits of PGx testing similarly, rooted in the belief that if they undergo PGx testing before initiating a medication it is more likely to work for them. Several actions prior to this may also improve the likelihood of a positive outcome, including realistic expectation setting (i.e., clearly explaining how PGx testing can and cannot be useful), knowing in advance of the testing what the cost will be, and understanding the timeframe for the return of results.

Retrospective PGx testing is generally ordered after a patient has struggled to find a medication and/or dose that provides them symptomatic relief with minimal adverse effects. When

ordered retrospectively, PGx testing can 1) potentially explain the reasons for non-response and/or adverse effects, and 2) guide future medication therapy. Expectation setting is equally important when PGx testing is ordered in this fashion, as some patients may be disappointed if results are ambiguous or run counter to their MedXp.

Each individual's own MedXp may shape their attitudes, knowledge, and beliefs regarding their own PGx testing. In the case of parent/child relationships, the parent's own MedXp may impact whether or not they decide to obtain PGx testing in their child. A previous case/control study found that parents of children exposed to opioids were more likely to share the child's CYP2D6 results with their primary care provider as compared to children not exposed to opioids, and believed their child's doctor could use that information for improved care.<sup>19</sup> Additionally, the disease state that is being treated may influence the likelihood or the extent to which parents or individuals pursue PGx testing. Diagnoses such as attention deficit hyperactivity disorder, which can be challenging for the parent, patient, and provider, have PGx panels specifically marketed by companies for this disease state.

Given that PGx is a relatively novel offering in healthcare, some prescribers may be hesitant to order testing that is not yet considered a standard of care or they do not feel adequately educated/trained in the area. The vast majority of surveys of healthcare providers show that most see the potential for PGx, but also do not feel comfortable ordering, interpreting, or applying results.<sup>20–23</sup> While having a dedicated clinician (in most cases a pharmacist) oversee PGx activities within a healthcare system may mitigate some of these barriers, not all health systems have such a service in place. In contrast, other providers may order PGx routinely for use in their patients depending on the practice setting and medications most commonly prescribed. PGx testing is also available to some extent through direct-to-consumer testing, which may create situations where patients present to their provider with results in hand that the provider may not feel adequately prepared to apply. Furthermore, in some clinical scenarios one specialty provider may order PGx testing without realizing or knowing those results may impact medication therapy outside of what they prescribe. For example, CYP2C19 activity impacts clopidogrel as well as commonly prescribed SSRIs such as sertraline, citalopram, and escitalopram.<sup>24,25</sup>

#### **IMPLICATIONS FOR FUTURE RESEARCH**

The relationship between the MedXp and PGx has important implications for several aspects of healthcare, including but not limited to care quality metrics, practice implementations, health professional training, ethics, and health equity. Future research in each of these areas is necessary to enable care approaches that can be tailored to each individual person.

### *Care Quality Metrics*

Quality of Care refers to the degree to which health services increase the likelihood of desired health outcomes and patient satisfaction with the care received, representing areas of measurement that have become tied to health system service reimbursement by payors such as the Centers for Medicare and Medicaid Services.<sup>26,27</sup> Medication adherence is one of these metrics and refers to whether patients take their medications as prescribed. The use of PGx to tailor the selection of the drug, dose, and frequency to each unique patient may improve medication adherence, maximizing the clinical effectiveness of medication therapy for a patient while reducing the likelihood of an adverse event. However, it is also important to recognize that medication adherence represents an often (over)simplified endpoint that assumes alignment in health goals between the prescribing healthcare system and the person taking the medications. These goals have clinical elements (e.g., targets for blood pressure or blood sugar), but also extend to a person's process of healing and coping in daily life (e.g., dizziness, headaches, use of needles, weight gain).<sup>5</sup> This often involves the person adopting new routines, behaviors, or skills that are often underappreciated by healthcare providers, some of which may not fit well with the person's life and goals.<sup>28–30</sup> Thus, providers must pay attention to these aspects of a person's medication experience in light of PGx information, rather than just whether or not patients are taking their medications. A similar approach can be incorporated with adherence measures, which are most often indirect measures like pill counts, claims databases, and self-reported questionnaires, to improve both the fidelity and explanatory value of this information.<sup>31</sup> Adopting these approaches also aligns well with the rise of shared decision-making in healthcare practice and the growing recognition of the effects of self-assessments that patients make about the appropriateness, effectiveness, and safety of their medications.<sup>32–34</sup> The Donabedian model provides a framework for better conceiving, developing, and testing structure, process, and outcome measures for these approaches such as the model proposed in Figure 1.<sup>10</sup>

### *Health Professional Training*

PGx education is a required component of pharmacy curricula and is typically taught within basic sciences, pharmacotherapy, and/or as a standalone course.<sup>35</sup> Additionally, the American Association of Colleges of Pharmacy PGx Special Interest Group recently updated the Core Pharmacist Competencies in genomics, aligning them with the Core Entrustable Professional Activities for pharmacy practice.<sup>36</sup> While adequately covering the foundational science and clinical recommendations as they pertain to PGx is crucial, how PGx moderates the MedXp should also be considered. Patients and providers bring their initial knowledge and understanding of PGx before obtaining testing. Providing pharmacy students with the opportunities and simulations to practice explaining PGx to a patient, interpreting results within an EMR (e.g., EMR Go), and formulating and explaining recommendations will better prepare them to

understand the science around PGx and how best to apply it. How and where PGx and the MedXp fit into the Pharmacists' Patient Care Process can also inform the best approach to curricular integration.

### *Practice Implementation*

Implementing care approaches that integrate MedXp and PGx into real-world practice is another important area of research. Even the best innovations in healthcare can fail without adequate awareness, planning, engagement, resources, and incentives that align with priorities, training, and more.<sup>37</sup> This raises several questions that relate to patient and clinician awareness, perceptions, and use of MedXp measurements<sup>20,21,38–43</sup> and PGx testing<sup>44,45</sup> to identify key facilitators, barriers, and expected outcomes when they are brought together. Such efforts can also build the foundation for developing a viable workflow and business model to sustain a care approach that integrates the two concepts.

### *Ethics*

Adherence to ethical principles is necessary in healthcare. The number and complexity of ethical considerations in care grow as that care is tailored to an individual's genome, social determinants of health, values, and other factors of personhood. These considerations extend to privacy, confidentiality, autonomy, informed consent, fiduciary responsibility, and respect. The use of PGx also raises questions about the burden of knowledge for both the patient and healthcare provider, such as a clinician's role in PGx-testing. Infusing a patient's lived medication experience into PGx-based discussions of treatment can optimize the ethical, person-centered application of PGx testing to patient care.<sup>46</sup>

### *Health Equity*

Health equity, PGx, and the MedXp are intertwined.<sup>47</sup> Of note, two reviews addressing health equity and PGx as well as taking a community-based participatory research approach are reviewed elsewhere.<sup>48,49</sup> While PGx as a tool has the potential to reduce existing health disparities, it also has the potential to worsen them if minority and underrepresented populations are excluded from PGx research or if PGx is not widely accessible. The MedXp is impacted by socioeconomic and environmental factors, and accounting for how and where PGx fits will largely depend on the individual.

### **CONCLUSION**

The pathway and magnitude by which PGx moderates the MedXp is a relatively understudied area and should be a focus of future research given both are essential for tailoring medications to each individual. PGx also moderates the MedXp as it relates to the clinician's role in care processes that produce health outcomes. In order to achieve optimal patient outcomes, clinicians should consider the MedXp when PGx testing is being considered or utilized.



**Acknowledgements:** The authors gratefully acknowledge Lisa Hillman, PhD and Tim Stratton, PhD for their correspondences that greatly improved the quality of this work.

**Funding Support:** This commentary did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Disclaimer:** The statements, opinions, and data contained in all publications are those of the authors.

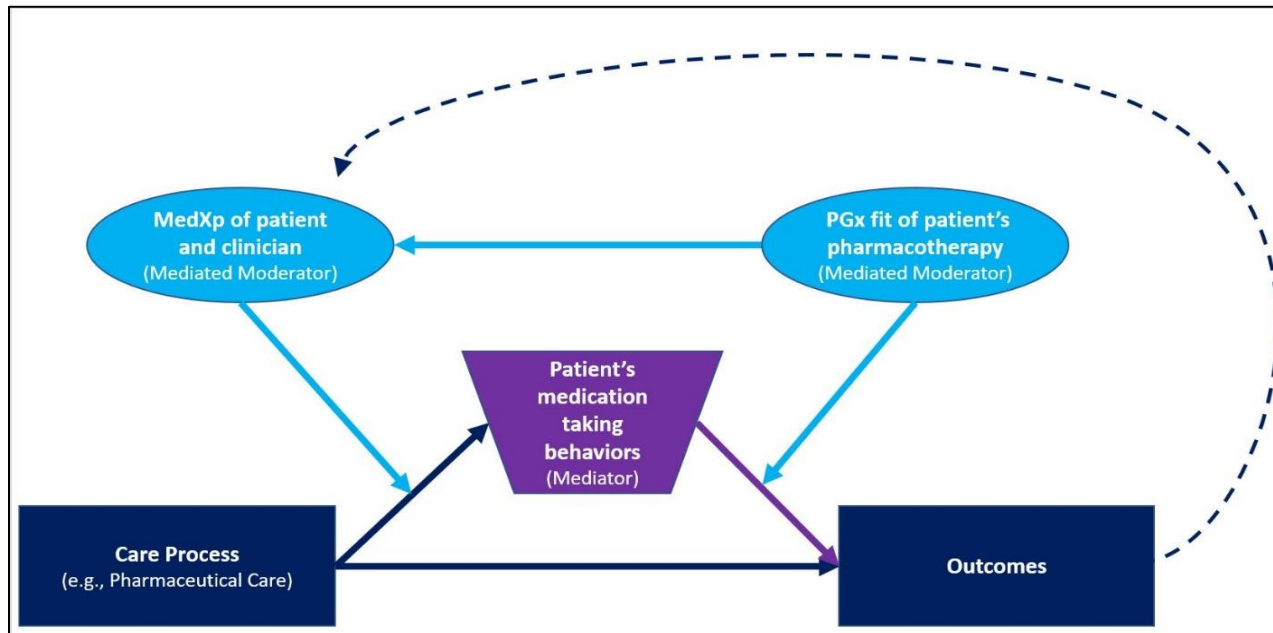
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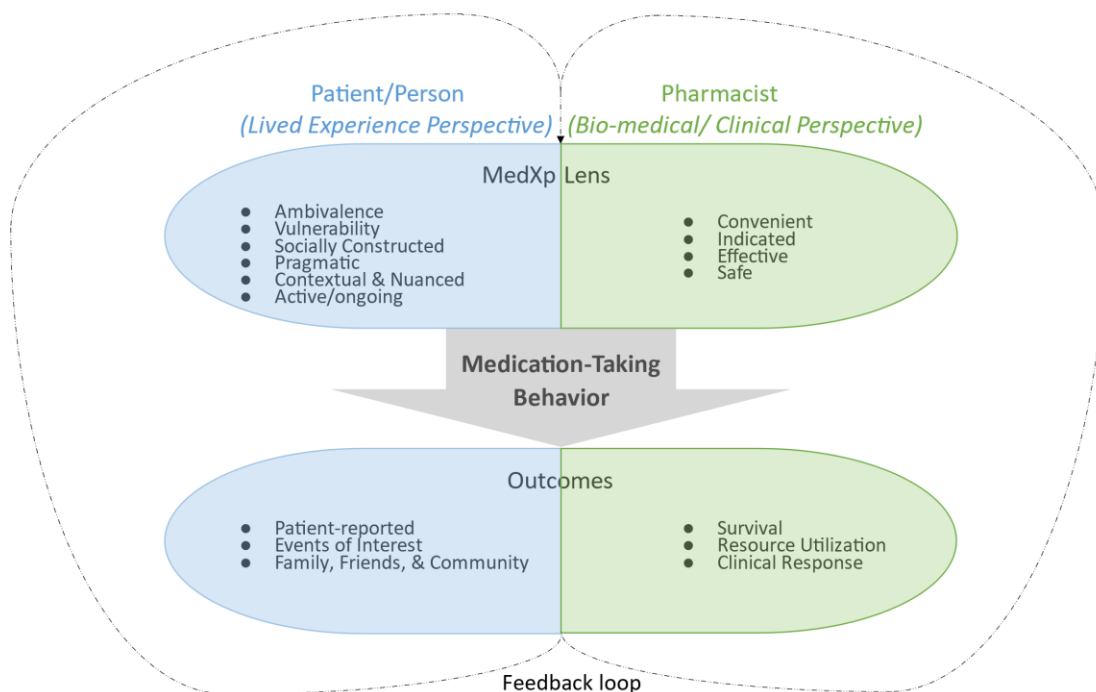
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**Figure 1.** Proposed Modified Donabedian Model for Medication-Taking Behaviors informed and influenced by MedXP and PGx.



Note: The organization of this figure is not meant to imply that a patient's medication-taking behaviors are separate from the other factors linking care processes with outcomes, and is only presented as such to highlight the focus on this particular factor for this paper.

**Figure 2.** The MedXP from the perspective of patients and clinicians with corresponding outcomes (3)



Note: In Figure 2, the pharmacist's bio-medical/clinical perspective is highlighted, as they are most often the dedicated clinician) overseeing PGx activities within a healthcare system



**Table 1.** Moderation of MedXp by PGx

MedXp Attributes	PGx Valence (Moderators - effects on strength and direction)		
	Negative	Neutral	Positive
<p>Ambivalence (<i>simultaneous and contradictory attitudes/feelings toward meds</i>)</p> <ul style="list-style-type: none"> <li>• Resistance</li> <li>• Necessary evil</li> <li>• Cost/benefit</li> </ul>	<ul style="list-style-type: none"> <li>➤ Concern of sharing genetic info and distrust of how it will be used</li> <li>➤ Belief information may not be useful</li> <li>➤ May be discriminated against by insurance</li> <li>➤ Differences in extent of testing/interpretation of results between companies</li> </ul>	<ul style="list-style-type: none"> <li>➤ Cost/benefit varies between individuals</li> </ul>	<ul style="list-style-type: none"> <li>➤ PGx maximizes biological fit efficiently with better outcomes</li> <li>➤ PGx may produce better quality of life, fewer adverse events that impact their life</li> </ul>
<p>Vulnerability (<i>perceived risks and concerns of taking meds</i>)</p> <ul style="list-style-type: none"> <li>• Perceived vs actual effect on body</li> <li>• Long-term use</li> <li>• Reliance/dependence on system/providers</li> <li>• Reliance/dependence on info/comm</li> </ul>	<ul style="list-style-type: none"> <li>➤ Industrialized/synthetic nature of drugs</li> <li>➤ Sub-optimal therapeutic changes due to drug shortages</li> <li>➤ Costs</li> <li>➤ Concerns over loss of privacy</li> <li>➤ Changing medication/dose without discussing with clinician</li> <li>➤ Fear of learning genetic results</li> </ul>	<ul style="list-style-type: none"> <li>➤ Confidence, competency, and relationship with PGx provider</li> </ul>	<ul style="list-style-type: none"> <li>➤ Reduces actual likelihood of harm and side effects</li> <li>➤ Improves actual likelihood of effectiveness</li> <li>➤ Only take as much as needed</li> <li>➤ May increase confidence of patient taking the medication</li> </ul>
<p>Socially Constructed (<i>social and cultural ideas of medicine</i>)</p> <ul style="list-style-type: none"> <li>• Meds as symbols</li> <li>• Norms, perceptions, beliefs</li> <li>• Social/environmental influence</li> <li>• Healthcare context/biomedicine</li> <li>• Sense of self</li> </ul>	<ul style="list-style-type: none"> <li>➤ Unrealistic expectations of PGx</li> <li>➤ PGx disinformation (e.g., commercial companies or individuals overpromising on what PGx can and cannot do) and misinformation (e.g., misinterpreting PGx results)</li> <li>➤ Not offered by all health systems/providers</li> <li>➤ Access and care quality inequities</li> </ul>	<ul style="list-style-type: none"> <li>➤ PGx news/headlines in media</li> <li>➤ Cultural views/beliefs with genetics</li> <li>➤ Availability of direct-to-consumer tests</li> </ul>	<ul style="list-style-type: none"> <li>➤ Positive attitudes toward precision medicine</li> <li>➤ Increasing trust in providers and health systems</li> <li>➤ Increased effectiveness and decreased adverse events from PGx restore previous self-identities (e.g., frequency and severity of seizures barrier to an occupation) or activities</li> </ul>

<p>Pragmatic <i>(how med use affects process and experience of daily life)</i></p> <ul style="list-style-type: none"> <li>● Evaluation from pt perspective</li> <li>● Prioritization of feeling well</li> <li>● Daily living barriers</li> <li>● Practicalities of med use</li> </ul>	<ul style="list-style-type: none"> <li>➤ Misinterpreting their results</li> <li>➤ Regret after undergoing testing</li> </ul>	<ul style="list-style-type: none"> <li>➤ Dosing modifications</li> <li>➤ Variants of unknown significance (i.e. results without clinical practice guidelines)</li> </ul>	<ul style="list-style-type: none"> <li>➤ May reduce the time to response</li> <li>➤ Increased effectiveness/safety</li> <li>➤ May increase adherence</li> </ul>
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<p>Contextual and Nuanced <i>(context/circumstances of med use)</i></p> <ul style="list-style-type: none"> <li>● Illness experience/health context</li> <li>● Daily life circumstances</li> <li>● Specific medications</li> <li>● Patient beliefs/attitudes/desires for involvement</li> </ul>	<ul style="list-style-type: none"> <li>➤ Fear that testing may increase anxiety due to results</li> </ul>	<ul style="list-style-type: none"> <li>➤ Personal testing can impact family members</li> </ul>	<ul style="list-style-type: none"> <li>➤ Belief that with PGx testing a medication is tailored to you</li> </ul>
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<p>Active ongoing process <i>(preservation/resilience/sustainability of med use)</i></p> <ul style="list-style-type: none"> <li>● Resistance and acceptance</li> <li>● Evaluative process</li> <li>● Control and self-regulation</li> <li>● Process takes time with no end</li> <li>● Burdensome and requires effort</li> </ul>	<ul style="list-style-type: none"> <li>➤ Testing may be cost prohibitive</li> <li>➤ Delay between sample and availability of results</li> <li>➤ Sometimes requires multiple appointments</li> </ul>	<ul style="list-style-type: none"> <li>➤ Need to account for new data potentially changing recommendations</li> <li>➤ New testing companies with additional genes/SNPs</li> </ul>	<ul style="list-style-type: none"> <li>➤ Results can generally be used for an individual's lifetime</li> </ul>
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Note: The term 'valence' refers to an individual's potential positive, negative, or neutral evaluation of PGx's moderation of a MedXp attribute.

\*Some qualities may overlap between cells. Organized by best fit rather than comprehensiveness.