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Pharmacogenomics

Synthesis of major pharmacogenomics pretest counseling themes: a multisite comparison

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The accessibility of pharmacogenomic (PGx) testing has grown substantially over the last decade and with it has arisen a demand for patients to be counseled on the use of these tests. While guidelines exist for the use of PGx results; objective determinants for who should receive PGx testing remain incomplete. PGx clinical services have been created to meet these screening and education needs and significant variability exists between these programs. This article describes the practices of four PGx clinics during pretest counseling sessions. A description of the major tenets of the benefits, limitations and risks of testing are compiled. Additional tools are provided to serve as a foundation for those wishing to begin or expand their own counseling service.

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For many patients and providers, knowledge of pharmacogenomic (PGx) concepts and testing are often limited [1–4]. Some patients have reported limited familiarity with PGx while others have reported a lack of perceived knowledge regarding genetic testing [3,5–8]. Despite these barriers, patients and providers report that PGx testing has potential value and increasing numbers of patients are participating in PGx testing programs [3,9,10]. Pretest counseling of the potential benefits and risks of PGx testing is paramount in order to ensure that patients are properly informed [3,11].

As PGx testing data become more readily obtainable, providers are requiring instruction as to how to best utilize the new data in their clinical decision process. Several organizations have created guidelines to provide recommendations based upon the results of PGx testing [12–24]. These guidelines contain instructions on interpreting PGx results and detail which medications should be modified or avoided altogether in the presence of specific genetic variations. However, current guidelines primarily provide recommendations as to how to interpret the results of a completed PGx test and do not generally describe which patients should be tested or how to counsel patients on the test. Without a clear delineation for whom testing is most impactful, it falls to the patient and provider to weigh the potential benefits and costs of PGx testing.

Due to the novelty and complexity of PGx testing, some health systems have begun establishing pharmacogenetic programs [25–32]. Some of these have included a dedicated PGx clinic to provide education and testing resources [25–29]. A common structure that has emerged within these clinics is the use of a two-visit clinic model. Patients are counseled on PGx testing at an initial visit and a follow-up visit is arranged to discuss test results [25–27]. General health information including medications, personal health history and familial health history are also gathered.

Frequently cited in the documentation of the implementation of these clinics is the need to address several key issues related to PGx testing with patients: the benefits of testing, the limitations of the test, and potential concerns

Table 1. Minimum pre-test patient counselling points.

At a minimum, the process should be designed to ensure the following points are addressed:
• The patient's health and medication history are obtained.
• The patient is asked about their rationale for seeking PGx testing and whether there are any pending therapeutic selections for which it may be used.
• The patient is counseled on:
• How genetic variations and their DNA can affect their body.
• How these genetic differences can influence the effect of medications.
• Limiting factors of PGx testing including which genes and medications will be covered by the test and the type of information that will not be covered.
• Potential risks of genetic testing, including genetic discrimination.
• The Genetic Information Nondiscrimination Act, the specific protections it provides and how their privacy is ensured.
• How the test is to be performed and when they will receive their results and recommendations.
• What to do with their results when they arrive and how they will be integrated into the health system.
• The patient is provided opportunities to ask questions throughout the session.
• The patient is prompted to ask clarifying questions through open-ended prompts by the counselor.
• The patient and pharmacist discuss a follow-up plan. This could include when the patient is to receive their results or discuss scheduling appointments with the PGx program or their primary care provider.
• The patient should also be advised where to direct questions or concerns that arise following the counseling session and directed to any other educational resources that are pertinent based on the discussion.

PGx: Pharmacogenomic.

associated with genetic testing [11,25,26,33]. However, there has not yet been a resource that codifies the specifics of what patients should be counseled on prior to testing [34].

This article summarizes the pretest counseling experiences of clinicians at four PGx clinics within the USA: the NorthShore University HealthSystem Pharmacogenomic Clinic (NorthShore), the USF Health Clinical Pharmacogenetics Service (USF), the Mission Health Personalized Medicine Clinic (Mission) and the Children's Minnesota Pharmacogenomics Clinic (Children's). The institutions involved in this project are overseen by a group of PGx practitioners that developed one of the first PGx clinics in their respective states placing them in a unique position to convene and compare their respective practices. These clinics by no means represent an objective authority or pinnacle of PGx practice but do include geographically and structurally distinct programs. While the resources available and architecture may differ between these clinics and those in other settings, the needs of patients serviced by these clinics are consistent.

NorthShore University HealthSystem's program is the US's longest operating PGx clinic. It currently provides care through a multigene panel covering most Clinical Pharmacogenetics Implementation Consortium and US FDA actionable genes. The clinic sees approximately 200 patients annually. USF initiated services in 2015 and steadily grew to seeing close to 45 patients annually. Pharmacogenetic testing is ordered through a commercial laboratory. The Mission Health Personalized Medicine clinic was started in 2016 to provide a resource for local providers and patients desiring PGx testing. Details have been published previously [32]. Children's Minnesota opened their clinic in 2017 and sees patients by referral chiefly from cancer and blood disorders, behavioral health, developmental pediatrics and primary care services. Approximately 100 patients were seen in the clinic in 2019 and 2020 and a transition from commercial laboratories to in-house testing is planned for 2021.

At each site, care is provided primarily by a clinical pharmacist specializing in PGx. Additional personnel are also incorporated, such as the use of a nurse practitioner by NorthShore, the inclusion of a medical geneticist at USF and Mission and the use of a genetic counselor at Children's. The nature of these additional team members can greatly change the workflow of the clinic and the ease of performing some tasks: such as medication reconciliation or counseling on broader genetic health topics. While the optimal composition for a PGx program has not yet been defined, consensus among the surveyed sites would suggest a structure with at least one pharmacist and one or more clinicians based upon the goals and design of the program. Clinicians further interested in program design should review Dunnenberger *et al.* and Arwood *et al.* for their descriptions of program formation [25,29].

Regardless of the specific structure of the clinic there remains key educational items that patients require before undergoing PGx testing. The objective of this article is to describe the commonalities in the pretest education provided at the four PGx clinics and what can be learned from the experiences of each program. Table 1 is a summary of our consensus minimum pretest patient education points.

Table 2. Benefits of PGx testing.

	NorthShore	USF	Mission	Children's
Adverse effects	"If there is a change in your DNA that causes the gene to produce fewer proteins then your body could break some medications down slower leading to a higher chance of side effects as the medications 'builds up'."	"PGx testing can help us predict whether you may be more likely to experience side effects to certain medications. For example, if testing reveals that you breakdown a medication much slower than the average person, this can result in higher drug levels in the body that may cause you to experience the side effects associated with the medication."	"If you don't break down medicines in a standard way then you could be at higher risk for a side effect."	"Changes in your DNA may slow down how medications are broken down in your body. This can result in too much drug in the body causing side effects."
Therapeutic efficacy	"If your body is producing too many of these proteins then you might work through medications too quickly to really get a benefit from them."	"PGx can help us predict the dose for certain medications or identify whether you're likely to respond to a certain medication." (go over basic metabolism and use an example of medication patient is currently on to explain active → inactive and *vice versa*)	"Alternatively, if you break down medicines more than we would expect, then you might not have enough of the medicine in your body for it to work properly."	"If the changes in your DNA cause medications to be broken down too fast, you may not get to a therapeutic level and the medication may not work for you."
PGx results are Life-long results	"These results are life-long results. However, as tests change and new genes are researched you may be asked or want to perform further PGx testing in the future. The laboratory reference sheet at the end of the report will be your best resource for determining if other testing could provide benefits."	"Pharmacogenetic results can have lifetime implications meaning the results can be used by your doctor or pharmacist to check for drug-gene interactions in addition to drug–drug, drug–food and drug–condition interactions throughout your life. For example, you may be getting pharmacogenetic testing today to guide antidepressant medications, but those same genes may apply to cardiovascular or pain medications as well. You may need additional PGx if you are prescribed a medication in the future linked to a gene that was not originally included on the test panel."	"Pharmacogenetic test results can be used over your life to help choose the medication that will give you the best chance of working. Because Personalized Medicine testing is a new and rapidly advancing area of medicine, current tests may not give you all the information to predict how you will respond to a particular medication. We have thousands of genes and we are only using a handful to help with medications right now."	"The PGx test we use looks at many genes and gives us information that can be used right now. These results will be valid for your child's entire life. New research may yield information that is not included on this test. If new information is learned, we may need to do more PGx testing in the future."
Benefit outside of initially ordered indication	"Some genes, like *CYP2D6* and *CYP2C19*, can provide information on multiple drug classes. For instance, these same genes can be involved in antidepressant medications, opioid pain medications, antipsychotics, proton pump inhibitors and nerve pain medications." (Most patients don't cite a specific disease state or gene of interest)	"While you may have originally undergone pharmacogenetic testing to predict your response to _____, these same genes may be used to guide other medications as well, such as _____. The US FDA Table of PGx Biomarkers provides a searchable database by gene or medication that you can reference for any future medications prescribed to you. Just keep in mind that the PGx-guided approach for each medicine varies."	"Variations in these enzymes can affect other medications that you might take in the future for other conditions."	"Right now you are interested in testing to help treat _____ (depression, anxiety, etc.…). The results of this test will also help guide possible future medications decisions like high cholesterol, heart disease, blood thinners or some types of cancer."

PGx: Pharmacogenomic.

Benefits

While patients may be interested or amenable to PGx testing, they may not necessarily understand how the information can improve their care. Many patients have limited health literacy and even more limited genetic health literacy [35,36]. Thus, we have found that it is important to specifically address the clinical benefits of using PGx data to guide therapeutic selection.

Four main benefits to PGx testing were consistently discussed among the PGx clinics and include the ability to limit adverse effects, improve therapeutic efficacy and utilize PGx results throughout the patient's life for multiple health conditions should they develop in a patient in the future. These discussion points focused on how pharmacogenetic testing can drive changes in health outcomes and provide additional value beyond the original indication for which the test was ordered. Specific language used to counsel on each main benefit of pharmacogenetic testing at the four clinics are presented in Table 2.

In our current counseling practices, the benefit of minimizing adverse drug effects and optimizing therapeutic efficacy are commonly discussed in tandem as they often can be illustrated with a reversal of the same example. PGx testing looks at variations in the genetic code that influence the pharmacokinetic and pharmacodynamic properties

of a drug. Patients may need education regarding how genetic alterations in genes encoding biological factors, such as drug metabolism and drug transporters or receptors, can affect their response to medications. To illustrate this point, counselors may focus on how changes in metabolic activity increase or decrease the amount of active medication available in the patient or how changes in the number or function of transports or receptors impact the function of their medications. This also serves as a prime time to educate the patient on foundational genetic concepts they will need to understand PGx. In particular at USF, Mission and Children's there is a concerted effort to address background information related to basic molecular concepts. Patients are informed of how DNA is used to create proteins and how these proteins can cause effects within their bodies. The teams then use examples and patient friendly language to detail how variations in their DNA could cause downstream changes that affect their health. Mission and Children's provide specially designed visual aids to their patients to assist in visualizing these concepts and improve their education.

Due to the unique nature of genetic testing, it is also important to discuss the additional value patients can derive from their genetic results. PGx results are life-long results in that a patient's genetic structure should not meaningfully change throughout their life and the results themselves will continue to be valid throughout the patient's life in the event future medications with pharmacogenetic associations are prescribed. Given the potential future application of pharmacogenetic results, consideration should be given to counseling the patient on accessibility and storage of results for future use. Additionally, patients should be counseled on the potential value in reduction in trial and error in terms of time and cost savings. While patients may not see immediate, direct financial return of their test cost, patients who utilize the results to guide therapeutic selection are associated with reduction in healthcare expenditure [37,38].

Finally, each clinic counsels the patient on the potential implications of their results to multiple health conditions. In the quote provided by USF, an example is given that a test originally ordered to guide antidepressant medications, may also provide information to guide antiplatelet medications [14–16].

Limitations

After discussing potential benefits, clinicians at each site counsel the patient on the limitations of PGx testing; what the tests cannot do. Some examples of the wordings used at each of the contributing clinics are detailed in Table 3. Some patients may be more familiar with medical genetic testing and might expect diagnostic results or those related to disease risk. All four institutions emphasize the differences between traditional genetic tests and pharmacogenetic testing. Additionally, some may have unrealistic expectations of what PGx testing can accomplish due to lack of widespread education regarding genetic medicine and the 'futuristic' appearance of the technology. In order to ensure that the patient is properly informed about the test they are undergoing, these discrepancies in their understanding must be addressed.

To counteract the perception of genetic testing as an infallible mechanism, all four institutions explain that PGx testing is only one of many clinical factors that can be used by providers to choose medications. Depending on the medication, patient-specific factors, such as age, weight, health history and interacting medications can also have a major impact on the medication prescribed. For patients with a long history of past medication intolerances or concurrent interacting medications, alternative treatment options may be significantly constrained regardless of what is reported by the pharmacogenetic test.

In our collective experience, a subset of patients is under the impression that PGx testing can predict their response to all medications, including over-the-counter medications. The use of PGx information is relatively new and extensive studies have not been done for all medications. For this reason, each site informs the patient that not all medications have PGx-linked recommendations. For certain medications, PGx association studies have not consistently demonstrated a genetically driven impact on medication safety or efficacy, but the potentially impactful genes may be reported on certain comprehensive pharmacogenetic testing reports. In these situations, we must explain that there is not enough clinical evidence to support how treatment will be altered based on a particular gene, but in the future more information may be uncovered. For some medications of interest, genetic testing may not be able to provide directly actionable information but may provide guidance on ancillary or alternative medications.

Additionally, some patients may have a key side effect that they are wishing to avoid, such as weight gain or nausea. PGx testing generally cannot predict which specific adverse effects a patient may encounter, only that a patient may be at an increased risk of experiencing adverse effects with the medication [12–24]. USF and Children's discusses at this point that 'normal' gene results (i.e., wild-type or those not associated with a change in function)

Table 3. Limitations of PGx testing.

	NorthShore	USF	Mission	Children's
Does not cover all medications	"We do not have studies and literature linking genes to all of these medications."	"Pharmacogenetic testing cannot guide all medications just yet, including over-the-counter medications and herbals. For example, if we take a look at your current medications, there is a gene linked to _____, but not to _____. We may know more in the future as scientists continue to research genetic predictors of drug response."	"There are not tests for every medication or all types of conditions."	"This test does not tell us about all drugs, only certain drugs that are broken down in the liver. Some medications are not broken down and are removed from the body by our kidneys. Others are broken down by enzymes not evaluated by this test."
Negative predictive test	"Another limitation of the test is that it cannot guarantee that a medication will work for you. We won't be able to look at the test results and say 'We should use drug x at dose y.' What the test can tell us is which medications we can remove from our initial list of options."	"There is a potential that when the pharmacogenetic test results return it may not find any changes in your DNA code that affect your response to _____ or explain how you responded to _____."	"It is possible that the results of the testing will not help you and your physician in managing your care." "Even if we narrow down the choices based on the results, it doesn't guarantee that those medicines will work for you. There may still be some trial and error."	"We cannot use this test to tell you which medication you SHOULD be on. We use these results to select medications that may have a better chance of treating _____ (depression, anxiety, etc…)."
Only one part of the medication selection process	"This is testis only one of several tools that you and your provider may use to determine which therapies may be best for you. Diet, exercise, health conditions and other medications may affect how a medication will work for you."	"Keep in mind that genetics is one of many factors taken into consideration when selecting a medication. Depending on the medication, drug–drug interactions, kidney and liver function, age, weight and diet, just to name a few, can also play a role."	"It is also possible that the results of the testing will not help you and your clinician in managing your care. Personalized Medicine testing is one of many factors that affect how your body responds to medications. Other important factors include age, weight, health and the other drugs you are taking. Personalized Medicine testing is used in combination with your other clinical findings."	"There are many factors that determine how medications work - (show visual aid graphics if available). Some of these factors will help us decide which medication to use. Genetics is only one of these factors."
May not catch rare variations	"Here is a sheet that describes what genes we tested and which spots on those genes we looked. You may want to do another genetic test in the future and this information can help you determine whether our test may have missed something that the new test would be able to find."	"For each gene, the test captures most of the known and common changes that may occur in an individual's DNA code. There is a potential that you may have a certain change in your DNA code for a gene that is not detected by the lab because it is rare or has yet to be discovered. In these instances, the result will reveal you have no changes in your DNA code and additional testing may be considered in the future."	"Most current testing panels include the most common genetic variations associated with medication response; there may be other known rare variations not included."	"PGx testing does not evaluate the entire gene. We look for changes that are known to affect how you respond to a drug. You may have a change in your genes that we are not looking for. If that happens, you could have a "normal" test result, and still have changes in how you respond to medications. As more research is completed, different tests may be available in the future."
Genes with limited evidence	"Some genes have not been studied well enough for us to make recommendations based upon their results. This may change as more studies are done and we learn more about the links between gene variations and medication response."	"There are _____(insert number) genes included on the panel and not all of them have enough evidence to guide treatment at this time. We may know more about these genes in the future as the research advances. You can check in with us periodically if you would like an updated interpretation."	"The Personalized Medicine tests we use today to help make decisions about your medications could change or grow in the future as new information is learned."	"The PGx test we use gives us the results for many genes. Our clinic will only make recommendations for genes that have enough research to help us select medications. The genes we do not talk about today may become important in the future as research develops."

PGx: Pharmacogenomic.

do not indicate that a medication is guaranteed to be side effect free or effective for a patient. Such patients would still be at standard risk of adverse effects when treated with the medication. Even patients with significant histories of intolerance to a medication may have a 'normal' genotype and that genetic result should not override their past experiences with the medications. At Mission Health, they also inform patients that PGx panels typically include the most common genetic variations and may not find rare variations. Children's highlights that most PGx testing predicts drug levels in the body and how this relates to side effects/medication failure. More research is needed to understand how PGx changes at the site of action affect drug response.

Risks & concerns

Despite the many uses of genetics in transforming our approach to patient care, apprehension for the possible misuse of genetic information, including confidentiality and genetic discrimination concerns exist [39–41]. Genetic testing inherently involves information that is intrinsically personal to the patient. More so than a metabolic panel, microbial cultures or an x-ray, genetic testing necessitates assaying the fundamental building blocks of what makes a person who they are. Due to the intimate nature of genetic information, all four clinics devote time to specifically addressing potential concerns and risks associated with pharmacogenetic testing. The two main areas of discussion center around protections against genetic discrimination and the implication of genetic test results for family members (Table 4).

Some patients express fear that genetic tests results, including PGx testing, could be used against them by insurance providers or employers [3,42]. To assuage these concerns, patients are educated on the protections provided by the Genetic Information Nondiscrimination Act (GINA) [43]. This federal law makes it illegal for health insurance companies, group health plans and most employers (those with 15 or more employees) to discriminate against you based on your genetic information. This protection does not extend to life, long-term care or disability insurance. Patients are also reminded of the privacy protections offered by the Health Insurance Portability and Accountability Act [44]. It is important to also address at this time whether any of the tested genes have prognostic impact or are associated with disease risk. While PGx panels are designed to detect potential drug–gene interactions, some of these genes may also indicate health risks irrespective of the patient medication regimen. For instance, some genetic variations are sex-linked and can potentially illuminate a chromosomal condition.

Patients undergoing PGx testing may have family members being treated for similar conditions and it is not uncommon for them to extrapolate how their PGx results may apply to their relatives. All four clinical sites explain the fundamentals of genetic inheritance [45,46]. Children and parents would be expected to share one of the patient's alleles for each gene, but we emphasize that only undergoing testing themselves would provide insight into their predicted response to certain medications.

Additional counseling points

There are several points to discuss with patients that are, by their nature, inherently specific to the program. These focus largely on the design of the program and its workflows but also financial and administrative consideration. It is important to discuss financial responsibilities and potential costs of testing with patients in the event insurance does not completely cover the test but this may not be a consideration for testing performed through grants or research initiatives. Patients should also be briefed on the sample that will be required and the process for obtaining the sample.

Clinic sites also discussed with patients how the data from the PGx tests would be handled. At each site, the PGx results are uploaded in some form into the electronic health record (EHR), and therefore, available to providers within the health system with access to the patient's EHR profile. This may be helpful to most patients as it simplifies the continuity of care process, allowing clinicians to integrate the review of PGx data alongside other pertinent laboratory and observed data. However, it may not be preferable to those wishing only a single provider to be able to review their results. For systems without direct result upload or for out-of-network providers, the patient is educated on their rights under Health Insurance Portability and Accountability Act and walked-through a release of information form. These steps are necessary so that the patient understands their privacy rights and who may have access to their genetic results. This is exceedingly important if the patient's data are in any way going to be connected to research or if their sample is to be placed into a biobank.

Coupled with a discussion of the privacy and storage of their data, it is also important to discuss with the patient how that data will be incorporated and utilized in their healthcare. Clinical decision support (CDS) systems are tools and workflows that assist providers in integrating information into their therapeutic process. These tools can include triggered alerts that prompt providers for action or passive reports and navigators that aggregate information. The extent and manner of these systems varied significantly among the surveyed clinic sites and may likely vary throughout the life and development of a program.

At NorthShore, patients were counseled that their results would be incorporated in their electronic health profile in several ways. They are available as a scanned copy of the report that they will receive as well as being directly put into their record as discrete or 'computer readable' results. Patients are informed that providers have several tools to view these results including a specific activity in the health record that will pull up all of the medications for which their genes might imply changes from the provider's standard selections. Furthermore, medications for which they

Table 4. Concerns and risks.

	NorthShore	USF	Mission	Children's
Genetic discrimination and protections provided by GINA	"There is also the potential concern for discrimination based on genetics. Currently, there is a law in place called GINA or the Gene Act that makes it illegal for employers or health insurance to discriminate based on your genetics. The law does not extend that coverage to long-term disability insurance or life insurance. We believe that this would be a larger concern for a genetic study looking into disease risk and we are not aware of any of those companies trying to use this information at present. However, it's important to know what the law does and does not cover."	"It is against the law for employers and health insurers to use a genetic test result as a reason to deny you employment or health insurance, or decide how much you pay for your health insurance as mandated by the GINA 2008. However, this does not apply to long-term care insurance, life insurance or disability insurance."	"All patient health information, including genetic test results, is protected through the institution's patient privacy policies and practices. In addition, a Federal law, called the GINA, generally makes it illegal for health insurance companies, group health plans and most employers (those with 15 or more employees) to discriminate against you based on your genetic information. Be aware that GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance."	Presented by a genetic counselor: "If you are concerned about the risks of genetics testing with respect to insurance coverage, we refer you to the GINA. This law bars employers and health insurance from discrimination based on genetic testing. GINA does not include life, long-term care or disability insurance."
Genetic results may be applicable to family members with similar health concerns	"However, whenever we do a genetic test we find out things about you but we also find out things about those you're related to. If you have siblings, parents or children then this test could potentially tell you something about their genetics as well. This test will not look at disease risk, like the chance of having a stroke or heart attack, so the conversations might not be terribly difficult but it's important to think about ahead of time how much information you want to share with your relatives."	"Sometimes patients will tell me that medication sensitivities run in the family and they've experienced it too. However, the only way to really know if someone is a carrier of a DNA code change in a gene predisposing the individual to an adverse drug response to a specific medication is for each family member to undergo PGx testing."	"Genetic variations related to medication response are inherited. This means that some of the variants you have inherited may be shared by others in your family. It is important to note, however, that your results may not be relevant for your other family members. To get the best picture of how genetics affects medication response in your family members, testing should be performed for each individual family member."	"Your child has this High Risk Result. This means that either mother and/or father also has some of these genes. Siblings may also have similar results. It may be a good idea for the parents and/or siblings to also get PGx testing."
Disease risk	"This test does not look at disease risk or other health factors. PGx testing only looks at genes and their relation to the response to certain medications."	"There are an estimated 25,000 genes in our body. We're only going to test a certain number of genes related to drug response. For the most part, many of these genes do not tell us anything about your disease risk, but there are a very few exceptions."	"Traditionally, genetic tests have been used to diagnose a disease or to predict if someone is likely to get a disease, such as Huntington's disease or inherited forms of breast cancer. These tests focus on disease risk. Personalized Medicine testing looks at genetic variants that relate to how a medication may work in your body, including the risk that you may have a bad response to a medication or the risk that a medication might not work for you. These tests focus on risks related to drug responses, not diseases."	"The PGx testing that we are discussing today is not intended to provide information about disease risk. However, we may receive some results, called incidental findings. These results may give us information about how your liver handles bilirubin (Gilbert Syndrome) or potential risks for clotting issues, especially girls taking oral contraceptives. If any incidental findings are discovered with this testing, we will refer you to an appropriate provider for additional follow-up."
Alternative option to testing	No specific wording reported.	"For certain medications, a PGx test is indicated prior to prescribing a medication (e.g., HIV), however, for _____ you don't have to and we will take standard precautions in prescribing the medication."	"Although some laboratories may offer this testing, currently we do not commonly recommend this testing for most ADHD medicines. We feel there is not enough information to act on the results."	"The PGx information related to ADHD is limited to a single medication, at this time and does not give us enough information to select between stimulants or other medications. If your primary interest in testing is for, it might be better to wait 1–3 more years for the research to mature."

ADHD: Attention-deficit/hyperactivity disorder; GINA: Genetic Information Nondiscrimination Act; PGx: Pharmacogenomic.

are predicted to have serious genetic interactions will trigger alerts to the provider to ensure that they have all of the information to decide, if it is still the best choice for the patient.

Children's does not currently provide in-house PGx testing (although it is anticipated by the end of 2020). As such, the Children's system is agnostic to the PGx lab which may test varying numbers of genes. During the follow-up visit to discuss results, patients receive a copy of the full lab report and a second Children's interpretive

report that focuses on those genes with sufficient evidence for implementation as determined by an internal PGx Oversight Committee. Similarly, to NorthShore, patients at Children's are counseled that their results will be used in the EHR in several ways. The original PGx lab report with all genotype results is scanned into the EHR. The genes that are included in the Children's interpretive report are incorporated into the EHR as discrete results and summarized for prescribers on a PGx specific results page. This page also presents medication information individualized to the patient that is relevant to their PGx results. Children's uses both passive CDS, displaying relevant phenotypes during the prescribing process as well as active interruptive alerts to prescribers for those results predicted to have significant gene/drug interactions.

At Mission and USF, a PDF report of the results of the patient's PGx testing are scanned into the EHR. These reports provide an easily accessible copy for providers throughout the system to review the results and allows for the growth of more CDS tools as new initiatives develop. Regardless of the specific process employed, it is important to discuss with the patient how, where and why their results will be held.

The counseling session concludes with a brief discussion of the follow-up plan and addressing any remaining questions related to PGx testing. As healthcare systems have become quite expansive, continuity of care has arisen as an area where patients may potentially 'fall through the cracks'. Thus, at several of the surveyed clinics specific attention was given to explaining how the results will be communicated to the patient and how pharmacogenetic-guided treatment considerations will be shared with other clinicians involved in the patient's care. The NorthShore PGx program serves patients both self-referred and referred by providers and this resulted in several options for the patients' next steps. Patients were informed that they could come back to the program for a visit to discuss their results, discuss them with their provider at their next appointment or simply leave the results entirely within the domain of their provider to act upon. At Mission, USF and Children's, almost all patients proceed to a follow-up disclosure visit once results are available. A visit note from this encounter is then sent back to their referring provider, primary care provider and any others requested by the patient.

Discussion

There were several commonalities observed between the four clinic systems. At each site, a majority of counseling was performed by pharmacist clinical specialists. Additionally, support personnel exist at each site in order to facilitate operations. All clinics utilized a genetic counselor at some point in their history, but some now utilize a nurse practitioner or medical geneticist. The divergence of these personnel may be due to variations in clinic structure and workflow.

The main tenets of PGx education including benefits, limitations and risks were fairly consistent throughout the clinics. However, differences were noted in the focus and specifics of some of these sections, such as whether GINA was directly discussed with patients. Variance was also found in the material covered beyond those major categories. For instance, USF, Mission and Children's have apportioned time to cover molecular background concepts. While information about molecular topics is provided to patients during the course of their discussion, NorthShore does not have a dedicated step in their process where this information is covered. One possible reason for this variety could be differences in institutional culture or patient populations. Different patient or provider groups may place higher value on a specific aspect of genetic testing, making them more germane to the counseling process.

Given the absence of a standardized PGx counseling structure, as evidenced by the comparison of our four sites, we created a reference sheet based upon our collective experience outlining the topics and themes discussed at each site. We organized these themes into the acronym PGX-DRUGS: Purpose, Genetic concept, X-ample, Drawbacks, Risks, Understanding, Game plan and Sharing (Figure 1). Clinicians who are beginning to utilize PGx testing in their practice can use this checklist as a basis for their own counseling efforts. It begins with discussing the purpose of testing (including the benefits of PGx testing outlined in this article) and basic genetic concepts to build an educational foundation for the patient. Then the limitations and risks of PGx testing are explained to the patient. Finally, the clinician should have a plan in place for completing the testing and coordinating implementation of any recommendations warranted by the results.

Within the climate of continuous quality improvement, it is necessary for any program to have benchmarks or metrics upon which it can be monitored and internally compared in order to ensure that progress continues to be made. While the 'core elements and structure of a PGx counseling session' contained in Figure 1 serves as an aggregate of the fundamental concepts and building blocks of pretest counseling, the more specific, discrete

After assessing patient's history of present illness, past medical history, current medications, social history, family history, etc...

Purpose and benefit of pharmacogenomic (PGx) testing

1. Gives extra information to help predict drug response
2. Helps with drug selection, side effects, efficacy, dose
3. Lifetime result
4. Future application of genotype results

Genetic concepts

1. Relationship between gene and drug response (DME, drug transporter, drug target)
2. Inherited basis of drug response
3. Provide visuals

X-ample ("example")

1. Use an example from patient's medication list to further help the patient understand connection between genes and drug response
2. Counselor may also use examples from their own genetic results if known

Drawbacks of pharmacogenomic testing

1. Research is incomplete. Not every medication is linked to a gene that can predict drug response, including herbals and OTCs. Some genes captured on panel may not have enough information yet to guide treatment.
2. Many factors affect drug response (kidneys, liver, age, weight, drug interactions)
3. 'Normal' (those with no change from the expected activity) or wildtype genotype results still warrant standard precautions and negative outcome are a possibility
4. While current testing captures the most common genes known to influence drug response and known variants in each gene, additional testing may be warranted if a new gene is discovered and not on the original panel
5. PGx testing cannot tell you with 100% certainty which medication will or will not work or whether you will get a side effect

Risks and concerns

1. Genetic Information Nondiscrimination Act (GINA)
2. Health Insurance Portability and Accountability Act (HIPAA)
3. How samples are stored and whether they can be used for any other testing or research
4. Pharmacogenomic testing does not tell us your risk of a disease
5. Other treatment or testing options that could eliminate the need for a genetic test

Understand patient's view of pharmacogenetic testing

1. Check in to see if patient has questions or needs clarification or to summarize their understanding

Game plan and process

1. Buccal or blood sample sent to lab
2. Turnaround time
3. Review of results at follow up visit
4. Financial responsibility

Sharing pharmacogenomic results

1. Patient summary to keep and share with providers outside of health system
2. Communicate results with pertinent providers
3. Coordinate care with clinical team as needed
4. Placement of results into electronic health record and tools available to providers
5. Availability of patient portals for access to test results

Figure 1. Core elements and structure of a pharmacogenomics counseling session checklist.
GINA: Genetic Information Nondiscrimination Act; HIPAA: Health Insurance Portability and Accountability Act; PGx: Pharmacogenomic.

elements included in Table 1 were created to be used by programs to track and quantify 'successful' pretest counseling sessions.

In addition to verifying that these criteria are met, programs may also wish to document more holistic metrics of their program's activity. All of the surveyed programs tracked the patient volume they serviced in order to establish trends and growth. Several also documented patient's primary indication or referring provider to ensure that services adequately covered the genes and medications needed by these groups. Programs may also be well served to keep track of common patient questions and review their process to improve areas that frequently lead to patient confusion or impaired understanding.

Identifying differences between PGx programs can illuminate areas where one size may not fit all due to variances in health system structure and culture. These differences represent areas for further individualization and development in order to ensure that each program's population is served as optimally as possible. Ultimately, it is hoped that this article may serve as a resource for those interested in implementing or modifying a PGx clinic.

While this article is intended to serve a wide audience of PGx clinicians, it is not without its limitations. With only four surveyed clinics there are invariably gaps in the scope of coverage in patient populations and institutional settings. The structure described here may not be feasible or optimal for all prospective clinics.

Conclusion

As PGx testing becomes an increasingly common element of the therapeutic decision-making process, counseling patients on the utility and results of PGx testing is only going to become more imperative. This article describes the experience of four PGx clinics in diverse health systems. The information conveyed within should serve as a reference to clinicians interested in starting their own PGx testing program and those discussing PGx testing with patients in more general settings. As these practices expand, further discussions and studies should be initiated to refine this process and continue to optimize patient care.

Executive summary

- Pharmacogenomic (PGx) testing is a growing part of the therapeutic decision process and pretest counseling is important during this initial phase as both patients and providers may not be familiar with genetic testing. However, guidance is lacking as to exactly what such counseling sessions should entail.
- This article summarizes the pretest counseling experiences of clinicians at four PGx clinics within the USA. Each of which developed one of the first PGx clinics in their respective states placing them in a unique position to convene and compare their respective practices.
- A summary of the consensus minimum pretest patient education points determined by the authors is presented in Table 1. This table could serve as a checklist to track metrics of 'successful' pretest counseling sessions.
- Three main categories have been identified as necessary components for effective pretest counseling: benefits, limitations and risks of PGx testing.
- Four main benefits to PGx testing were consistently discussed at each clinic: the ability to limit adverse effects, the ability to improve therapeutic efficacy, the ability to utilize PGx results throughout the patient's life and the ability to utilize PGx data in multiple health conditions.
- Examples of language used during counseling on the potential benefits of PGx testing is presented in Table 2.
- Limitations of PGx testing include that not all mediations have PGx linked recommendations and that PGx generally cannot predict specific adverse events.
- Additionally, patients should be counseled that PGx testing is only one of many clinical factors that can be used by providers to choose medications.
- Examples of language used during counseling on the limitations of PGx testing is presented in Table 3.
- Concerns regarding the security and use of test results are among the most commonly cited by patients. Discussion of the protections afforded by Health Insurance Portability and Accountability Act and Genetic Information Nondiscrimination Act may alleviate these concerns in some patients.
- It is also important to address whether any genes that will be tested have prognostic or diagnostic aspects and whether further genetic counseling may be warranted.
- Examples of language used during counseling on the risk or concerns of PGx testing is presented in Table 4.
- Additional counseling points may vary significantly between institutions due to differences in available personnel, visit structure and electronic integration.
- Patients should be counseled on where and how their data will be stored, who will have access to it, and how it will be utilized to improve their care.
- Counseling sessions should also contain a discussion of the follow-up plan and how to address future questions or concerns.
- Based on the variability seen in just the four programs samples, the major themes identified were organized into the acronym PGX-DRUGS: Purpose, Genetic concept, X-ample, Drawbacks, Risks, Understanding, Game plan and Sharing (Figure 1).
- This article can be used as a reference to clinicians interested in starting their own PGx testing program and those discussing testing options with patients in more general settings.

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