**Supplementary Table 4. Barriers and enablers – organised as per theoretical domains framework.**

We used thematic synthesis to analyse the data initially58, which is a widely accepted method for synthesising qualitative data.58 Thematic synthesis involved coding of the extracted data ‘line by line’, the development of descriptive themes and the generation of analytical themes. Initially barriers (and enablers) from each study were identified through generation of codes. Similar codes were then grouped together to generate descriptive themes and finally the descriptive themes were grouped into analytical themes. Coding and descriptive theme generation was carried out independently by two researchers (SQ, LC). Development of the analytical themes was undertaken by the main researchers (SQ).

Analytical themes were then grouped according to the 6 TDF domains (SQ, AL).

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| **Knowledge**  **(An awareness of the existence of something)** | | | |
| **Analytical theme** | **Descriptive theme** | **Illustrative quotes for participants (first order)** | **Illustrative interpretations from authors (second order - discussion section)** |
| Lack of genetic knowledge | Lack of knowledge  Harding et al 2019 | Provider-related  I haven’t had anybody say, ‘no I don’t want to go ’. I’ve had tons [of patients] come back and say to me ‘so now what I should do.’ They ask me what to do…not [the geneticist].Which puts you in a spot…. the biggest barrier for me would be not having the knowledge on enough of the appropriate diseases.(FG3)  It does take quite a bit of time…alot of time counselling patients…and if you were to think about how many other syndromes and conditions…might arise to start counseling…not to say that we shouldn’t be doing it… (FG1)  I think things change quickly and we’re not always aware of…which genetic tests…we can do…I would not know what to order… I don’t think we have a good enough understanding, at least I don’t, of genetics. (FG2)  A lot of patients I saw sometimes are a bit apprehensive. And may be with good reason… if they’re thinking, ‘what are the implications of finding this information out’, [or] if they don’t have insurances in place….Sometimes when I talk to patients about [testing] they’re hesitant. Sometimes family members don’t want to cooperate by participating…There’s a whole unknown for the patient…sometimes they [don’t want] to jump on board with finding out more. (FG1) | Perceived barriers to patient uptake of genetic counselling and testing included **apprehensiveness, lack of understanding of genetics,** limitations of genetic testing, implications of results, impact on insurance, and limited awareness about management options. Time, transportation, finances, and missed employment were deterrents, primarily for rural patients.  PCPs’ lack of confidence in their genetic knowledge may have resulted in missed opportunities for genetic care. Time to offer effective genetic care to patients, a perceived need to justify genetic testing, and costs for community-based genetic testing were considered problematic. These concerns influenced PCPs’ and patients’ decision-making about whether a genetics referral was worthwhile. Although telemedicine was useful, rural PCPs emphasized the value of face-to-face counselling. Due to delays in instituting new services, PCPs reported that rural communities have learned to manage "without." Thus, when expanded services become available, the service may not be utilized optimally for some time. |
| Lack of genetic knowledge | Lack of knowledge  Carroll et al 2016 | I think that even to have the conversation about genetic testing with the patient, it’s such a big conversation ’cause they’re going to ask us these questions that we don’t even have the answers to, like what is the benefit for me? … If you don’t know what the potential treatment options are with a positive [result] or the potential treatment options of a negative [result], how can I even have an informed conversation with my patients? (FP, FG4) | A pervasive theme was **limited knowledge of personalized medicine**. Primary care providers had little awareness of developments in personalized medicine, available tests, and triggers for appropriate referral for genetic counselling and testing. Knowledge affected practice, with some PCPs, based on responses provided, not referring when appropriate nor recognizing the benefits of genetic testing. A common example was lack of awareness of genetic tests for hereditary colorectal cancer and how results might change screening recommendations. Some PCPs acknowledged not knowing enough about personalized medicine and yet, based on responses provided, others were not cognizant of their incomplete or incorrect knowledge. Primary care providers who were aware of their lack of knowledge expressed concern and anxiety. Moreover, there was apprehension over the magnitude of knowledge that was required before they were confident to discuss genetics with patients. |
| Lack of genetic knowledge | Lack of Knowledge and awareness  Dressler et al 2019 | ”...more comfort in interpreting and applying results for future [drug/medication] use ”(P2) ”...primarily knowledge” ”...understanding of PGx, limits of testing”  ”Awareness that this [PGx]) is out there, it is not the future, it is now” |  |
| Lack of genetic knowledge | Lack of knowledge and awareness (Clinicians and pts)  Rigter et al 2020 | To me it [PGx testing] is all very new [… ], I don’t think about it [PGx testing]. This totally isn’t something that I am considering as a GP.” GP5, 5:54  “I am surprised by the list of drugs [you just showed] for which they know they could work differently for certain groups of people.” Patient FG5, 1:30 | In the (focus group) interviews, GPs and pharmacists expressed that pharmacogenetics is currently rarely considered or used by GPs.  Patients themselves said to generally be unaware of (potential usefulness) of the influence of genes on drug response. |
| Lack of genetic knowledge | Lack of knowledge and awareness  Rafi et al 2020 | ‘I’ve not heard the term (Pharmacogenomics), it’s something new to me’ (R15, Locum GP), and ‘I think those terms do make sense but even I don’t know the difference between genetics and genomics, so I wouldn’t know what pharmacogenetics is as opposed to pharmacogenomics’ (R11, academic GP). ‘I think one of the challenges is about what level of evidence we do need to justify using these tests in routine practice…. If you look at the randomised controlled trials, they provide a degree of justification in terms of informing those, but not so much in terms of reducing clinical adverse effects’ (R13, academic GP). | The key issues to emerge were a lack of knowledge and awareness and concerns around the evidence-base and utility of the data that might be used.  These data suggest that GPs may have little knowledge  around pharmacogenomics, and there is therefore a general  need for information about what contribution genomics could  offer to improve the safety and effectiveness of prescribing in routine clinical primary care. |
| Lack of genetic knowledge | Lack of awareness of PGx  Frigon et al 2019 | When asked by the interviewers, “When I tell you about PGx-guided therapy, what do you think of ﬁrst?” all four groups of PCPs and pharmacists referred to PGx’s use in cancer therapy. Three of the four groups mentioned the lack of awareness on PGx in clinical practice. One of the participants mentioned: “It’s something that is just around the corner, but we don’t know at all,” (PCP, group 1).  One of them shared this thought: “I am convinced that there is a link between genetics and drug treatment. Although historically, trains of thought were such that if an individual was not responding to a treatment, then it meant that the individual was having somatic symptoms. That was the term we were using. I am happy that you are bringing this up because this might avoid people being told that they are having somatic symptoms,” (Patient, group 2), while another patient mentioned, “I think, I am pretty sure in fact, that the link [for drug response] is genetic, but like many people, I can’t explain why,” (Patient, group 2). | Healthcare professionals interviewed had a generally broad idea of the deﬁnition of PGx. Most of them knew about it but had limited clinical experience.  When the interviewers explained to the groups of patients the concept of PGx, they had many opinions about it, demonstrating their interest with this science.  This study explored PCPs’, pharmacists’ and patients’ opinions on the imminent uptake of PGx testing in routine clinical care. A general enthusiasm toward the future implementation of PGx in clinics was perceived among the six groups interviewed. The findings from this study raised a lack of awareness on PGx among the health professionals interviewed. In fact, PCPs and pharmacists participating in the present study mostly stated they had very little knowledge on PGx outside its application to cancer therapy. |
| Lack of genetic knowledge | HCP PGx knowledge and awareness  Van Der Wouden et al, 2020 | “Well, I don’t think it’s very nice to say, but the GPs don’t know anything about it” (P5:15)  “I notice that the GPs are not interested in the details, they want to act upon the results but are not interested in anything with CYPs, that’s my perception” (P12:13)  “It really depends on the medical specialty, whether [PGx] is of interest to them. For example, the psychiatrists know quite a bit about [PGx], but I know how generalizable this is. On the other hand, I know a patient who was very proud of their PGx profile and showed it to their cardiologist, who had absolutely no idea what it was” (P8:31) | Pharmacists regarded themselves at a reasonable level of knowledge about PGx. They reported their PGx knowledge to obtained through both personal interest and participation in this implementation study. However, they noted that colleague pharmacists, GPs and medical specialists, who were not involved in a PGx study, had very little awareness and knowledge of PGx. Lack of knowledge of colleagues involved in the healthcare chain was often reported as a prominent implementation barrier. In particular cases, the inequality in PGx knowledge between the enrolling pharmacists and the treating physician hampered shared decision making and adherence to the DPWG recommendation. Pharmacists, however, did note a diversity in knowledge across medical specialists. Overall, pharmacists perceived the PGx knowledge of GPs to be lower than their own. A minority of GPs was reported to be knowledgeable and was able to request PGx tests.  In addition, pharmacists reported the lack of awareness of the possibility of PGx testing among the general population of pharmacists, physicians, and patients as being an important barrier. To stimulate awareness among pharmacists, many suggested more publications on PGx in the professional journal of Dutch pharmacists. To stimulate awareness among patients, some pharmacists proposed generating more media attention for PGx testing. Other pharmacists stimulated the initiation of pharmacotherapy audit meetings with their colleague GPs, to educate them on PGx and create awareness within the GP community. One pharmacist underlined the importance of sharing PGx success stories, for example of patients for whom PGx testing contributed to improved outcomes. |
| Lack of genetic knowledge | Profound lack of knowledge of direct-to-consumer genetic tests  Carroll et al | “If something goes wrong, someone is going to look for who is responsible and where you did fall through the gap.” (FP, FG3). | Most PCPs expressed an almost complete lack of knowledge about direct-to-consumer genetic testing (DTC-GT). There was much emotion associated with this area, with some PCPs describing it as “scary” and others worried about a potential deluge of patients requesting care after testing privately. Primary care providers with actual experience of patients with DTC-GT results voiced frustration at their delayed involvement and concern for patients who had been tested without prior counselling or thought of implications such as the privacy of their genetic information or the effect on their ability to obtain insurance. There was also concern for the provider. |
| Patients lack of knowledge | Unfamiliar with term PGx  (pt view)  Issa et al 2009 | ‘Well, the drug may not have caused the reaction. Something else may have caused the reaction. Something you ate, or what if the food does not agree with the medication you are taking? And it may cause a reaction also.’ (FG 2) | Most participants expressed an awareness and understanding of the term personalized medicine, which they had predominantly obtained through media sources including newspaper articles, radio, and television stories. There was less familiarity with the term pharmacogenomics. Following group discussion to probe for understanding, participants were presented with a lay definition of the terms pharmacogenomics (i.e., ‘the science that allows us to predict a response to drugs based on an individual’s genetic make-up. In other words, it is using genetic tests to determine how you will respond to a drug.’) and personalized medicine (i.e., ‘the application of pharmacogenomics to prescribe drugs that are tailored to patients based on their genetic information, as well as their clinical and family histories’) to clarify understanding and stimulate discussion. Participants in all 4 focus groups demonstrated a limited understanding of how genetic variation plays a role in drug metabolism, drug responsiveness, and toxicity, and how environmental interactions also play a role. Indeed, only 5 participants suggested that environmental influences may be relevant. |
| Limited experience with PGx | Personal unfamiliarity with genomic medicine  Chase et al 2017 | No direct quotes | Factors that influenced these lower priorities were the interviewee’s personal unfamiliarity with genomic medicine, a lack of compelling evidence for better outcomes, the increased cost of testing, potential work flow interruptions, and the need for other, higher priority, EHR related interventions. Clinicians across all sites were intrigued by the concept, but did not believe genomic-based precision medicine was ready for wide application. |
| Limited experience with PGx | **Limited experience with personalized medicine**  **Carroll et a**l 2016 | I wouldn’t say I’ve got tons of personal experience in my practice, other than that I’ve seen some of the commonly identified cancer screening, specifically BRCA 1, 2, coming back and being investigated within families, that’s probably the one being the most prominent …. I’m excited about the prospect of what personalized genomic medicine might offer us down the road, but my knowledge of it is pretty limited. (FP, FG5) | PCPs’ descriptions were vague but included phrases such as “wave of the future” and “what medicine will be.” Their personalized medicine experiences were mainly in cancer, particularly genetic testing for hereditary breast cancer, with some experiences in prenatal care. They described almost no experience with colorectal or other cancers. Patients were frequently described as the drivers of genetic testing and referrals, and PCPs sometimes believed that patients knew more about available genetic tests than they did. |
| Limited experience with PGx | Limited encounters with genetics in practice  Harding et al 2019 | Encounters with genetics in practice  The only time it comes up is if someone’s planning a pregnancy…or if suddenly a whole bunch of family members have cancer. Those are the only instances where I’ve had anybody raise any kind of genetic questions…. or if a baby’s been found to have some kind of abnormality than that kind of opens it up. (FG1)  Genetics impact on treatment  Genetics is becoming part of everything in family medicine. It’s just permeating everything you do…. It ’s going to be tricky for us to keep track. (FG3) | PCPs reported **limited encounters with genetics** in their practices, but had not explicitly identified some activities such as family history assessment as practicing genetic medicine. Most clinical exposures described by PCPs related to pregnancy or hereditary cancers; rare genetic conditions were less commonly encountered. PCPs were aware that genetics permeates many health conditions and used genetic information as a screening tool. Although knowledge about the genetic basis of a condition was considered beneficial, considerations about the interpretation of genetic test results, clinical utility, cost-effectiveness, and communication strategies were areas that PCPs felt needed additional clarification. Rural and urban PCPs had similar perspectives about the value of genetics in primary care |
| Limited experience with PGx | Level of comfort with genetic testing  Harding et al 2019 | Referral to genetic testing/counseling  Like so many areas of medicine, the role of the family physician is to help decide whether their concerns are legitimate or not. Make the appropriate referral if it is [or] try and reassure them that it is a misplaced concern. (FG2)  Patient care  People often times don’t understand the implications of [genetics]….You have to sit down and talk to them…. I want them to understand that there are false positives and false negatives… sometimes you have to spend more time with …people who aren’t familiar…. They haven’t talked about it, or they don’t really understand it and so it takes quite a bit of time. (FG1) | PCP **comfort with genetic testing varied depending** on personal training and experience. However, concern was raised that further genetic responsibilities would be downloaded to PCPs without sufficient support. One participant believed that genetic medicine was outside of a PCP’s scope and the responsibility of a geneticist or a non-genetics specialist who could refer on to genetics. Uncertainty about responsibility and the notion of specialist to specialist referral is important to acknowledge as it is counter to traditional views of practice, and may not be a consistent expectation so could result in gaps in care. |
| Limited experience with PGx | Varying level of knowledge  Chase et al 2017 | “we did some work when we were using Naltrexone for … so I’d be interested.” “Well, genomic information. Okay. So there’s -- and maybe I don’t know enough about it. … I don’t think there’s a specific place that I would find it except I refer a lot of people to medical geneticists.” “I mean I manage a lot of patients, you know, each month and I don’t know anything about, you know, whether their genes tell me to a do a certain thing.” | There was a wide range of familiarity with genomic medicine, from those who have worked in the field to those who profess ignorance. |
| Limited experience with PGx | Varying knowledge  Unertl et al, 2015 | Interviewers asked each subject, “How do you define the term ‘pharmacogenomics’?”, eliciting a wide variety of reactions and responses.  Several interview subjects laughed at the question, expressing uncertainty about the concept. For example, one respondent stated, “I don't know. Trying to identify patient-specific ways that patients use or break down or get rid of medications.” Other clinicians responded confidently and concisely.  For example, some subjects responded with a fairly simple definition, “I define it as understanding a patient's profile to help you make a better decision about the appropriate medication use.” Other subjects provided more detail in their responses, “It’s the use of genetic polymorphisms to determine even before first dose… potentially which drug, which dose of the drug, potential side effects, adverse effects from the drug. I guess in a nutshell… that would be my definition.” | The degree of precision and detail in definitions of pharmacogenomics varied widely. |
| Limited experience with PGx | Preparation and knowledge  Unertl et al , 2015 | One clinician described the uncertainties inherent in clinical knowledge by stating, “I feel like the things that I know, I know, but I'm fully aware that there's a much larger pool of what can … be applied to that I don't know. So, I know my ignorance" | Primary care providers in our sample had less prior exposure to pharmacogenomic concepts and expressed less confidence in their pharmacogenomics knowledge base. |
| Behavioural change | Reluctant to change current practice  Rigter et al 2020 | “In [current] practice they [GPs] will just play with the [medication] dose: we will increase it and see what happens, decrease it and if drug A doesn’t work, we will try drug B [… ]. It never really comes to the test. Even though that is the most likely cause of the problem.” Pharmacist, FG1, 3:35  “In general our profession is relatively conservative when it comes to new developments: first seeing what the effects are and what we gain from it and what the outcomes are and then getting on board. There are few people who then are pioneers [… ]” GP8, 10:3  “I think that more should be done with it [PGx] and that you should not wait until people develop all sorts of, euhm, just muddle along with their drugs. That we should be more pro-active.”Pharmacist, FG3, 5:2 | Although most participants of the interviews seemed to recognize the potential of pharmacogenetics—to reduce adverse drug reaction, increase effectiveness of treatment, and possibly indirectly increase adherence—not all seemed convinced of the urgency to press large-scale implementation. Especially general practitioners were perceived as reluctant to change their current practice of “trial-and-error” when prescribing drugs.  Especially pharmacists seemed supportive of the use of pharmacogenetics and were expecting more applications to be developed to optimize treatment for the patient. It was also expressed that it could be an opportunity to expand the current job responsibilities and accompanying funding structure of pharmacists. Consequently, most pharmacists showed disappointment about the current lack of use of the potential of PGx in primary care.  Although most participating pharmacists said to have both  the knowledge and infrastructure available to increasingly start  applying pharmacogenetics in daily practice, there was doubt as  to whether their peers would be as well-equipped.  It was acknowledged by both GPs and pharmacists that there  currently was a lack of knowledge and clear protocols for  effective implementation of pharmacogenetics in primary care,  in particular for GPs. |
| Training and education | Lack of genomic education - undergraduate level and also continuing education of healthcare professional6  Frigon et al, 2019 | “I will for sure want training to know what it is about and to know the pros and the cons,” (PCP, group 2). | PCPs and pharmacists were asked their opinion about the needs for training in PGx. Most groups stated that implementation of PGx in clinical practice should come with an appropriate training for health professionals.  Moreover, there was a general consensus among the groups toward the lack of training in PGx in medical and pharmacy programs and as part of continuing education |
| Training and education | Genetic education  Harding et al, 2019 | “If all the information about the expansion of genetic knowledge and testing capabilities is true, it sounds to me like it’s something I’d like to know about. There are lots of things that came up during my career that I didn’t learn about in medical school and yet it’s important to try and figure out what’s going on and be at least on the curve if not ahead of the curve.” (FG1) | PCPs identified a need for education, resources, and supports to aid them in improving the genetics care they could offer.  Foundational **genetic education** in undergraduate and postgraduate medical curricula was described as limited, resulting in PCPs’ feeling unprepared for genetic aspects of health care. |
| Training and education | PGx education  Lemke et al 2017 | For example, one participant (P02) mentioned: “I think it would be nice to have more in-servicing or more education on what all those things mean and why. I know there’s a clinical scenario and that’s important too, but I think a little bit more of the background into it would be helpful for physicians who are ordering this, so they really feel comfortable, not only with the clinical interpretation, but really understanding a little deep analysis of what that means for that patient. So, you know, I would like I think a little more education –[that] would even be that more valuable for clinicians.” | When describing PGx education needs, many different modes of training were suggested such as in-services, case studies, and online training |
| Training and education | PGx education13  Rafi et al, 2020 | ‘we are talking about different responses to drugs which will include a more detailed understanding of the genetic issues’ (R2, GP with informatics knowledge).  Practice GPs will seek education about it; ...another driver which is really crucial is the RCGP curriculum’ (R9, GPSI genetics).  ‘My patient cohorts are quite well informed – they educate me a lot of the time’ (R16, Clinical Fellow).  ‘always really grateful when someone came in to talk to us about say BRCA risk or something like that – it filled the gap’ (R16,Clinical Fellow).  Some people felt that ‘understanding of genetics is very variable, and people have all sorts of belief about the terms genetics and what genes and gene tests can tell them.’ (R9 GPSI genetics).  ‘The other aspect is to take it out of the hands of GPs, and delegate to nurse practitioners or pharmacists, they would do it, [so] wider MDT sharing of role, this might be something that a pharmacist do it in a practice [especially] if doing large numbers at a time’ (R12, a RCGP medical director).  ‘I mean from an educational programme, [would] have to put more through schools, universities, degrees you know, medical schools’ (R1,GP Principal). | Many felt that the level of pharmacogenomics knowledge that a primary care healthcare professional might need would vary depending on the level of complexity around clinical management they were responsible for,…  Professional differences and needs were also highlighted.  Patients knowledge and beliefs were considered by many,  Others mentioned the traditional approach of an expert opinion as the best source of information,  Some felt that involving other health care professionals such as pharmacists would be important, and it would require uniform dissemination of genomics education and competency needs.  Some focused on the vital role of education for successful implementation: indeed, education was often considered to go beyond the types of programmes aimed at either patients or professionals.  **Responses here highlighted the importance of skill-mix and delegation of roles which could underpin a strategic approach to the delivery of pharmacogenomics education.** |
| Training and education | Education  Harding et al 2019 | “If all the information about the expansion of genetic knowledge and testing capabilities is true, it sounds to me like it’s something I’d like to know about. There are lots of things that came up during my career that I didn’t learn about in medical school and yet it’s important to try and figure out what’s going on and be at least on the curve if not ahead of the curve.” (FG1) | Foundational genetic education in undergraduate and postgraduate medical curricula was described as limited, resulting in PCPs’ feeling unprepared for genetic aspects of health care. |
| Training and education | Resources /support  Harding et al 2019 | Resources  “I’m still not there… but you see the studies coming out, you keep it in the background and then eventually lose track. It would be nice to have a regular update of what’s in the pipeline and where it is and what’s the evidence behind [it].” (FG3)  “[A screening] questionnaire [could] be mailed out to the patient and they [could] do it virtually or online…. We as physicians could access a website that would allow us [to send surveys] for various conditions, or patients themselves could [access surveys], or be mailed [surveys] if they preferred that.” (FG2)  Support  “Prevention is concentrated on, is very mandated and very specifically pushed very heavily by the Ministry….If it doesn’t fall into the focus of the Ministry, it’s essentially ignored…. I’ll admit [that] I’m far more knowledgeable about things that are on the agenda than things that are not.” (FG1) | PCPs’ primary interests included information about current resources, tests, and referral guidelines. Participants emphasized a need for an array of CE options including email updates, pamphlets, mail-outs, and an online database of genetic conditions. Urban PCPs preferred in-person CE sessions. Timely access to an expert by telephone or email was suggested in rural settings due to limited opportunities for face-to-face sessions and informal interactions with colleagues. Industry sponsorship to attend CE was accessible, primarily for rural PCPs, but at risk for bias. |
| Training and education | Rapidly changing PGx knowledge and need for continuing education  Unertl | No direct quote  “I wish I knew more because sometimes I think we, I feel like we practice in a vacuum, especially on something so super specialized as this. So, you know it, and you learn it, and you know very well in six months what you know is not current. I mean, there's no way that it is." | The types of initial exposure to pharmacogenomics discussed by primary care providers focused more on general communication channels, such as electronic medical center newsletters and journal articles. Despite outreach efforts, questions remained about rapidly changing pharmacogenomics knowledge.  Because of the rapid evolution and expansion of pharmacogenomics knowledge, clinicians discussed the need for continuing education. Clinicians discussed concerns about their knowledge becoming quickly obsolete. One cardiologist summarized this concern by saying, |
| Training and education | Patient and provider education material  Lemke et al 2017 | One participant (P09) example included: “I think for patients it would be nice if we had pamphlets, nice, colorful, good pamphlets, that we could put in the office that patients can grab and look at themselves, because that would help them initiate testing. I don’t know how much having meetings and things like that will help, but definitely having a step-wise thing, how to order it. You know, ‘this is how to order. This is what you do with the results’.” | Along with the various modes of training participants mentioned, they also were interested in receiving both provider and patient education materials |
| Training and education | Pt education material  Unertl et al 2015 | “We might benefit from bullet-point thoughts of what patients are hearing because we're having to unravel some of their exceeding expectations when they get here.” | Providers expressed interest in a formal set of patient education materials that anticipated questions and concerns. “ |
| Training and education | Policies for responsibilities and ownership of PGx data  Unertl et al 2015 | “I think it'd be nice if there were some clarity about the responsibility for the ordering physician in terms of notifying the other physicians involved in the patient's care just so people know exactly what's expected of them when they order the test.”  “I think it's going to be important to come up with good processes to educate referring physicians as well as ordering physicians and specialists on how to handle this information. Who do you need to notify? Who's responsible for acting on the information? Who's responsible for educating the patients on it as well?” | Clinicians explained a gap between current policies and the range of data in the informatics intervention, with several clinicians exploring the need for formal clear policies to explain responsibility and ownership for pharmacogenomics data.  While clinicians felt clear lines of responsibility and ownership were necessary, they expressed concerns about the level of pharmacogenomics knowledge among referring clinicians outside the academic medical center environment. The need to educate busy community clinicians about the results and recommended action was an area that some clinicians felt needed to be explored in detail, |
| Miscellaneous | Relevance  Dressler et al 2019 | What did you gain by being in this study?  ”[with] so many PGx related meds are ID [infectious disease] or cancer, it was good to gain a better understanding of which drugs are related to my [primary care]practice ”(P3) | No interpretation |
| General interest in PGx testing | Greater role for genetics  Harding et al, 2019 | “I think technology will march on and there’ll be a lot more screening tests available. I hope [they] will have a lot more direction attached to them…we will certainly hear more as time passes.”(FG2) | Greater role of genetics in practice and increased demand for genetic care |
| Shifting patterns of work to allow new advances  Harding et al, 2019 | “There are a lot more things to do now then there were two years ago and somehow we managed to do that…. more work in teams, we use allied health professionals…share the load on a number of things…. one way of coping with the increased number of things there are to do…. giving up some stuff too – aren’t we? There are some things that we used to do that [we know] aren’t useful… we lose some things as we gain more knowledge.” (FG1) | Practice patterns were described as shifting such that new advances would replace prior standards. |
| General interest in PGx testing  Lee et al 2017 | The most popular reason cited among the pharmacogenomic group was to inform physicians’ decision-making, as evidenced in this comment: “It would give us more information…and better inform as to what medication to prescribe.” | The majority of participants in both groups expressed a strong general interest in the concept of pharmacogenomic testing.  The second most common reason was altruistic—the pharmacogenomic participants expressed a common desire (by their being tested themselves) to potentially help others find a more effective drug (i.e., more knowledge would be gained about how medications work in general if more people submitted to pharmacogenomic testing). |
| Potential of using PGx  Rafi et al 2020 | : ‘to be able to prescribe medicines with a confidence that [it brings]‘ (R4, informatics expert), and ‘To have a better outcome, target people more effectively’ (R1, GP Principal). ‘Anything that would help efficacy, it would definitely have the potential to be taken up by GPs.’ (R9, GPSI genetics’. | There was general agreement about the potential of using a pharmacogenomics approach |
| Positive attitude towards PGx  Barr et al 2008 | … in one case at least, would ‘have it straightaway’. | … a majority of participants in all the public focus groups felt that pharmacogenomics was a ‘good idea’, felt ‘positive towards it’ and, |
| PGx test results rapidly obtained to be valuable  Frigon et al 2019 | “If the tests existed and were available at a reasonable cost with above all, a rapid response, we would apply them for sure,” (PCP, group 1). | Most clinicians agreed on the fact that the results of PGx tests had to be rapidly obtained to be valuable. As one of the PCPs mentioned:  Some patients stated that they would prefer not to wait for the results of the tests before starting the medication. They preferred being prescribed a smaller dose of the drug while waiting for the results of the test and adjusting it accordingly. |
|  | Perceived role in delivering PGx   * Request PGx test   Van Der Wouden et al, 2020 | “We have a very important role because we should know most about it, at least in primary care.” (P4:37)  “[PGx testing] really is the task of the pharmacist because we are in the world of contraindications, interactions, and medication surveillance” (P10:26)  “The collaboration [with the GPs] is really good, but they think ‘this has something to do with the liver and can cause intoxications or ineffective plasma levels, you know what-this is your thing.” (P11:19)  “I feel that when I have done all the preparatory work, then its fun to report the results to the patient.  Especially when its something simple like “you will be getting another statin.” (P2:11) | Particularly, acting upon PGx testing results was a task that pharmacists felt very capable of doing, as they reported being experts in resolving drug interactions in medication surveillance. They additionally noted that they felt GPs did not have time for this additional task and that GPs expect this to be the pharmacist’s expertise. Most pharmacists, however, felt that following up on patient symptoms is a shared responsibility with the GP. |

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| **Social and professional roles**  **(A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)** | | | |
| **Analytical theme** | **Descriptive theme** | **Illustrative quotes for participants (first order)** | **Illustrative interpretations from authors (second order - discussion section)** |
| Skill mix | More access for pharmacists (and other HCP) to genetic information  Haddy et al 2010 | The pharmacist has a fairly good idea [of your medical history] if you go to the same pharmacist all the time. I think they should have a list of my medical conditions rather than just the drugs. (Group F >60 years) | Participants accepted that GPs, medical specialists, hospitals, and pharmacists would have access to both general medical and genetic information. The benefits of having 1 regular pharmacy were discussed with relation to minimizing interactions between medicines and disease states. One participant also suggested that pharmacists should have more access to this information than they currently have… |
| Skill mix | Pharmacists to have major role in PGx  Frigon et al 2019 | One of the PCPs described how pharmacists could be involved in PGx testing: “I would not do this for sure, I would not have time, I wouldn’t be able.[...]I would talk to the pharmacist about it. If you [pharmacists] know there is something wrong with one cytochrome, you could warn me if I prescribe something related to that.” (PCP, group 2).  “Our role is to follow the patient, to make sure our treatment is effective and well tolerated. So, to prescribe a [pharmaco]genetic test to prove it is effective[...]that’s what we do,”(Pharmacist, group 2) as well as the PCPs’ groups: “Maybe this could be a way of doing things; the physician makes the diagnosis and the pharmacist chooses the drug,” (PCP, group 1).  One of them mentioned: “They are the drug sellers, they lost me already” (Patient, group 1). Another patient speciﬁed “[The pharmacist] could give me a paper and I would pass a blood test. He would receive the result [...]contact my physician to see if a dosage modiﬁcation is needed, if it needs to be increased, but he wouldn’t necessarily be the one who makes the decision,” (Patient, group 2). | All six groups were asked to give their opinions on the role PCPs and pharmacists should play in the implementation of PGx testing. All four groups of health care professionals mentioned that pharmacists should play a major role in the implementation of those tests in clinical practice. Some participants suggested that pharmacists could review prescriptions made by the PCPs and the suggest a modiﬁcation to a treatment if a PGx test is recommended.  The idea that pharmacists could prescribe a PGx test and choose the drug according to the results of the test was also mentioned by the pharmacists’ groups.  Surprisingly, patients were more reluctant to the idea of having pharmacists prescribing PGx tests and choosing the drugs.  No clear consensus has been made on which health professionals should act as main actors in PGx implementation. ….when asked whether the PCPs or the pharmacists should be in charge of PGx testing, no clear consensus was observed between the two groups of healthcare professionals, yet it was reiterated that both of them should be involved. Interestingly, patients mostly believed that PCPs, not pharmacists, should be in charge of PGx testing. |
| Skill mix | Division of responsibility  Rigter et al 2020 | “[… ] I expect the pharmacist to know more than I know from pharmacokinetics and that sort of things and that he could advise me better in: this combination should be avoided in any case and this can go together.” GP8, 10:2  “But in that case I would actually want the doctor to only write down the diagnosis. [… ]. And that I come up with the pills for that.” Pharmacist, FG2, 1:167  “But I think a pharmacist in itself, is too commercial to do such things [order a PGx test and adjust treatment accordingly]. A blood drawing station or so [could do that], okay, or the GP himself, but a pharmacist absolutely not.” Patient, FG6, 10: 6  “Together [the GP and the pharmacist] we can make sure that the chosen therapy gets a very good chance of success when it, ehm, when the genotypes of the patient are known.” Pharmacist, FG1, 4:20 | Disagreement exists about the best division of responsibilities between general practitioners and pharmacists, and the patient’s role. GPs generally expressed the desire to be able to request the test themselves and want to remain end-responsible for the correct dosing of drugs. GPs mainly see the role of the pharmacist as signaling and advising on drug-prescription, including pharmacogenetic influences.  Pharmacists themselves seem to picture a more central role in pharmacogenetics for their profession; some even as partly responsible for all prescription of drugs in general.  However, pharmacists generally also seem to acknowledge that this role should be granted by GPs as well as patients.  Patients explicitly prefer the GP as having the final responsibility and being the contact person when it comes to applying pharmacogenetics, mainly because of familiarity and trust.  All participants emphasize that there is a need for cooperation and explicitness about roles and responsibilities between GPs and pharmacists.  To maintain the relationship of trust and give all stakeholders  the time to become acquainted with the new division of roles and  responsibilities, participants mentioned that it would be wise to  not act precipitately and implement pharmacogenetics in phases. |
| Skill mix | Primary care providers role in personalized medicine  Carroll et al 2016 | So, coming from personal life, my mom and my aunt both had breast cancer. Do I want to go and get tested, you know? Know what? I will go for the screening when it’s due and that’s what I will do, but do I want to know if genetically I would have that gene, that I’m more at risk, how will that affect the way I’m thinking, am I going to go for prophylactic [surgery]? No. So, I kind of … maybe I’m using my personal feeling, but I may apply it to my patients because, really, why do you want to know, like why, why? (FP, FG4)  “I think what has been missing in family medicine, as we’ve seen the growth and importance of genetics, is the ability to take a good history.” (FP, FG1)  “So as a physician, I would want to know exactly what I had to counsel my patients before even accessing the test and what the implications of that would be.” (FP, FG3)  I’m not sure that our role as a family doctor is becoming some kind of a specialist in genetic medicine. I think we come back to basic concepts as far as family medicine is concerned, which is taking a good history and physical … I’m not in a position to start trying to interpret the results. (FP, FG1) | Many PCPs described a context wherein their personal experiences sometimes informed personalized medicine clinical issues. Past personal experience or the experiences of family and friends also influenced PCPs’ attitudes toward and perceptions of personalized medicine. When relating personal stories, providers voiced that personalized medicine was helpful in diagnosing disorders but believed it made little difference to the patient’s outcome.  Initially, participants seemed uncertain what role they might have in personalized medicine, but as discussion proceeded, they identified that their role included taking family histories, conducting risk assessments, and referring to genetics clinics for genetic counseling or testing. They reported that taking a good family history was an important role for PCPs.  Primary care providers also described their role as being a resource to patients, answering questions and responding to requests for genetic testing. Currently, this was described as a more reactive role with patients driving the request for testing. Some PCPs questioned, however, whether they should more proactively identify patients who might benefit from genetic tests. Counseling patients on the risks and benefits of genetic testing was also seen as a responsibility, with some PCPs seeing themselves as gatekeepers, particularly in relation to DTC-GT.  A minority of PCPs did not want a role in genetic testing at all, describing lack of knowledge as an “out.” |
| Skill mix | PCP role - education, counselling, testing and referrals to specialists  Harding et al 2019 | Genetic care through family history  Patients with diseases that run in families… Figuring if they’re a baseline risk or if they’re an elevated risk… how to work that up is probably what I do most. (FG3) | PCPs endorsed a responsibility to take family histories, assess risk, determine appropriate management strategies, and facilitate referrals. PCPs viewed their role to include responding to patient concerns and educating and counseling patients about ethical, psychological, and medical aspects of genetics. |
| Pool of experts | Need for buddy or connection into a genetic service  Carroll et al 2016 | I think a buddy would be great …. It’s always helpful if you have a go-to person who can help you out. So over the years we all develop people that we can reliably get good opinions from and as you get to know them personally … you get a little bit better service I think, and sometimes a phone call will solve your issue and it won’t necessarily need to go through the whole process. (FP, FG3) | When asked about system changes that would facilitate personalized medicine integration, participants suggested having a “buddy” in a local genetics centre or an in-house nurse or FP with genetics training as an internal expert. |
| Pool of experts | Pool of experts in general practice  Rafi et al 2020 | ‘It will be rare to find a GP who is up to speed with pharmacogenomics... genomics whatever’ (R6, Academic GP).  ‘[it would] make sense to have a collaboration of Primary Care Physicians interested around pharmacogenomics‘ (R3, RCGP lead) or that ‘every GP would need some sort of training. Mainly brand new GPs would have enough knowledge but I suspect not – maybe in 5 years’ time when it’s more in forefront but not yet’ (R1,GP Principal). ‘But I think at the moment most GPs would need lots of training to use it’ (R1, Clinical Fellow) and inherent scepticism ‘..[just] think about trying to translate some of the apparent promise of the approach into practice’ (R10, Academic GP).  'this is new and yes, it will become mainstream, and it will become part of part of our clinical decision-making like everything else, because it’s going to be’ (R7, Digital lead). ‘It could revolutionise our practice, it’s hugely exciting for the future and GPs, rather than saying this is too much for us, we could be at the forefront of this’ (R12, a RCGP medical director). | The key challenge for the NHS was universally considered to be how the use of genomic information could be ‘mainstreamed’ (i.e. as part of normal practice) into general practice. It was clear that respondents thought that there would need to be a pool of GPs who could offer advice. However, the barriers to implementation included the fact that in General Practice at present, only small numbers of GPs understand the concepts.  Many felt that there was a need for both individual training and the ‘mainstreaming’ process facilitated through generating an expert pool in general practice:  Despite the obvious barriers, there was some acceptance that this was just likely to happen:  It was interesting that GPs perceived pharmacogenomics tests being used as tool as part of day-to-day clinical practice with the potential for General Practice to lead the way. |
| Professional relationships | Relationship with healthcare professional influencing PGx test  Lee et al, 2017 | “…if that had been my primary physician to suggest that…I would have said, ‘Well okay, let’s think about that. Let’s talk some more.’ But as far as me being in the emergency care, doctors I’m not familiar with…I know they got a protocol and Hippocratic Oath they must take…but, I’m not good with that in that situation.” | Both groups indicated that the nature of their relationship with the treating physician would influence their decision to undertake pharmacogenomic testing, as shown in this comment |
| high regard for physicians who adopted pharmacogenomics  Lee et al, 2017 | “My physician tell me based on my pharmaco-blood test…I needed my blood pressure medication changed…I was assured that this was a good idea to participate…I think it’s a real positive thing.” | Notably, the pharmacogenomic group expressed a high regard for physicians who adopted pharmacogenomics as a sign of staying at the forefront of medicine. One pharmacogenomic participant narrated his positive experience of receiving a pharmacogenomic-determined prescription, saying: |
| Relationship with healthcare professional  Lee et al 2017 | “It would make the pharmacist more informed and again another double, triple check before they’re handing me the medications.” | Regarding the relationship with their pharmacist, both groups agreed pharmacogenomics could help pharmacists identify problem prescriptions: |
| Opportunities for pharmacists  Rigter et al 2020 | “I think that more should be done with it [PGx] and  that you should not wait until people develop all sorts  of, euhm, just muddle along with their drugs. That we should be more pro-active.” Pharmacist, FG3, | Especially pharmacists seemed supportive of the use of pharmacogenetics and were expecting more applications to be developed to optimize treatment for the patient. It was also expressed that it could be an opportunity to expand the current job responsibilities and accompanying funding structure of pharmacists. Consequently, most pharmacists showed disappointment about the current lack of use of the potential of PGx in primary care. |
| Patient–doctor relationship  Dressler et al, 2019 | ”Allowing good conversations  between physician and patients” (P2) | No further explanation |
| Patient – Doctor Trusting relationship  Carroll et al 2016 | “If we don’t do it, who will? … [A]nd who’s going to know their history better than us?” (FP, FG4) | Despite infrequent experiences, PCPs speculated that personalized medicine might become increasingly entrenched in primary care.  Primary care providers’ relationship with their  patients was cited as an important reason for involvement in personalized medicine, with patients often seeking their advice because of this trusting relationship and because PCPs’ knowledge of patients’ medical and personal histories was valued by patients in decision making. |
| Acting upon PGx and reporting to patients  Van Der Wouden et al, 2020 | “We have a very important role because we should know most about it, at least in primary care.” (P4:37)  “[PGx testing] really is the task of the pharmacist because we are in the world of contraindications, interactions, and medication surveillance” (P10:26)  “The collaboration [with the GPs] is really good, but they think ‘this has something to do with the liver and can cause intoxications or ineffective plasma levels, you know what-this is your thing.” (P11:19)  “I feel that when I have done all the preparatory work, then its fun to report the results to the patient.  Especially when its something simple like “you will be getting another statin.” (P2:11) | Generally, pharmacists found handling PGx results enjoyable and felt appreciated for their work, both by GPs and by patients. A few pharmacists were extremely positive and noted that their added value by successful and beneficial reporting of PGx results to patients was the reason why they were in their profession. Additionally, the majority of pharmacists agreed that being the expert in PGx was of strategic value for the pharmacist profession, since it is a clear and concise example of how pharmacists contribute to  healthcare through medication surveillance. |
| Pharmacist added value and learning by doing  Van Der Wouden et al 2020 | “[PGx] is a great opportunity for pharmacists to show what we can do because a lot of people really don’t know that” (P8:38)  “[PGx] makes [pharmacist value] transparent for patients: What does the pharmacist actually do? What is the value of a pharmacy?” (P6:5)  “[PGx] gives a really good feeling. This is what I do this profession for.” (P11:15)  “This [added value] is the reason why I wanted to participate in this study because I want some experience with PGx testing, for the GPs too” (P7:33)  “The more [actionable PGx] interactions you encounter, the easier it becomes.” (P7:20) | Overall, the effects on professional interactions were very positive. Pharmacists felt that GPs perceived them as experts on the subjects and that they respected the initiative they had taken to implement PGx. Pharmacists also felt they could help GPs by taking this task upon them. Since GPs were perceived to be too busy for this additional task. |
| Professional interaction improvement  Van Der Wouden et al 2020 | “[PGx] brings you closer to patients, which really is an added value, and also to the GPs. So I really enjoy doing it.” (P2:56)  “[PGx] can give patients a certain feeling of trust in their medication when we say we are going to test your DNA to see if the medication fits your profile, then patients trust it more to start taking it.” (P6:26)  “[PGx] confirms what the patient most of the time already knows.” (P1:24) | All pharmacists reported that patient response to PGx was very positive and that they believed in the effects of PGx. A majority of pharmacists also perceived patients to be further interested and therefore were motivated to participate in the PREPARE study to receive their PGx results. Although pharmacists perceived patient interest, they also reported they felt a large portion of patients who did not understand what PGx was and how resolving a PGx interaction would benefit them. Nonetheless, lack of understanding did not prevent their perceived positive effects on the patient–pharmacist relationship. Pharmacists also reported that patients were rarely worried about privacy issues; only one pharmacist reported a patient questioning whether the DNA results would be shared with police officials. Interestingly, pharmacists did take into account which patient preferences were in their decision to adhere to the DPWG recommendation. The majority of pharmacists reported that if a patient were to disagree with a pharmacotherapy adjustment based on PGx test results, this would be a reason not to adhere to the DPWG recommendation. However, no examples of patient disagreement occurred during the study at the time of interview. |

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| **Behavioural regulation**  **(Anything aimed at managing or changing objectively observed or measured actions)** | | | |
| **Analytical theme** | **Descriptive theme** | **Illustrative quotes for participants (first order)** | **Illustrative interpretations from authors (second order - discussion section)** |
| Negative impact of PGx | Adverse impact resulting from negative results  Williams et al 2016 | One provider said, “I mean, it could go either way but it could motivate some patients to seek out those medications but it could be discouraging to other patients because I guess they could find out they wouldn't be as responsive.” Another said, “I think that nowadays, especially in the information age, they may just say, ‘Well I have the gene that would make me successful so it's worth a try.’ But others they may have a defeatist attitude and feel like, ‘Well I don't, the test says otherwise, and so I’m destined to be drinking or this probably wouldn't work.’ I think that would be a little bit detrimental.” | Providers also described concerns regarding the possibility of adverse impacts resulting from “negative” test results, including decreased patient motivation for and confidence in (or increased patient pessimism in) alcohol use disorder treatment. |
| Negative impact of PGx | Repercussions of positive test result – labelled, stigmatized, develop fatalistic perceptions  Park et al 2006 | This is, ‘‘The devil made me do it … I'm genetically programmed…"  I don't know if they (teenagers) could process this information appropriately, if they could put it into perspective. They are dealing with enough issues let alone saying, ‘‘Gee, son, the chances of you becoming a coke addict are 30 percent higher than the national average | Physicians worried in particular about patients’ response to positive status for genotypes associated with increased risk of addiction to substances such as nicotine, alcohol, and cocaine, fearing that they may become fatalistic or demoralized.  Physicians were apprehensive about the repercussions of a positive test result, fearing that children and teenagers who undergo testing might be labeled, feel stigmatized, or develop fatalistic perceptions. |
| Negative impact of PGx | Anxiety about genetic information  Frigon et al 2019 | “According to the test, it becomes negative for him [the patient] to know that he carries a gene, but that he may never suffer from the disease. It can make him anxious [...] ” (PCP, group 2).  "It’s better not to know about it [genetic information],” (Patient, group 1)… | Throughout the group discussion, some participants mentioned that revealing genetic information could cause anxiety to the patients…  When we asked the patients what they think they should know before doing the test, some patients believed they should not know everything about their DNA… |
| Negative impact of PGx | Ambivalence – depression and genetic research (targeted PGx research and meds designed to treat)  Barr et al 2008 | As one participant put it:  I have friends and colleagues who are taking antidepressants, and I think it has very different effects on them, there are some of them where I can’t tell the difference, but some of them have completely lost their personality, and some where it has helped them in a positive way, some of those who have lost their personality, you cannot ‘talk’ to them anymore, I think that is really sad (Danish Public Group 1).  Another indicated that:  I am actually quite morally ambivalent, because I can see that the individual needs it when that person gets out there, there is really a need for it, when you are completely desperate, when you look at a person with this illness etc. But generally speaking – when you look at it from above – then I think it is dangerous (Danish Public Group 2).  I think behind [genetic research] is such a conception of human being and also of the illness – now you will be ﬁxed, all will be all right. And I have to say my psychosis was also somehow a process of insight. It was also an experience and I know, not everyone thinks that way but I have undergone it and I didn’t want to be repaired at all costs (German User Group).  It is ambivalence. Only in the cases of small communities is it a sympathetic ambivalence, a positive one. We don’t get in your way, you don’t get in ours, but okay. You are a member of our community. Whatever happens, we’ll stick together. In a city, people are concerned with their own matters, they don’t want to think about, engage or look after people who are ‘relatively abnormal’ (Polish Public Group 1). | Feelings of doubt, uncertainty and ambivalence can also be seen in both public and users’ views – not only towards antidepressants but towards depression itself, and towards genetic research. Of course, to some extent this is not surprising since ethical issues surrounding genetics and debates over therapeutic enhancement are well rehearsed. But it seems worth reﬂecting on this issue since shifting views towards medication targeted for pharmacogenomics research and ambivalence regarding the condition those medicines are designed to treat may well have an impact on the reception of pharmacogenomics tests in the clinic. This is a factor that clinicians, psychiatrists, and health care providers will ﬁnd hard to ignore when consenting for and prescribing genome-based tests for antidepressants and then monitoring patients’ use afterwards.  Part of the ambivalence we are aiming to describe relates to depression itself. There was a sense amongst many that depression was ‘subjective’, that it was not always in need of immediate cure and could in fact be a source of personal growth:  A deep ambivalence regarding the use of anti-depressants. On the one hand, there is a strong hope, sometimes borne out of desperation as our data show, that new drugs will alleviate patient suffering. Pharmacogenomics may well be seen as part of what Novas (2006) calls a political economy of hope – where science, activism, and capital come together to promote expectations of success in biomedicine. Yet alongside these hopes for a cure, anti-depressant users consistently report that the decision to start taking the drug is not taken lightly, that they feel a sense of ‘giving in’ by having to swallow a pill each day to help manage their mood. Users also report, as our data showed, that anti-depressants sometimes affected one’s personality so severely that they began to question if they were really ‘themselves’ anymore. Again, the pharmacogenomics of depression cannot separate itself from these issues or from the political and economic context in which the drugs and genetic tests are developed and promoted. |
| Negative impact of PGx | Impact on patient perspectives and shared decision making  Rafi | ‘personalised medicine is about interpreting all the things in your context, the genetic element is one element, and it’s not the overriding element ’ (R4,informatics expert)  ‘I think GPs would be wise to understand, or at least be familiar with, the new role of genetic information in personalising medication’ (R2, RCGP clinical lead).  'So yes, it’ll definitely create more work I think both for us and for secondary care as well, and probably increase patient anxiety if they come wanting to know the significance of information’ (R15 Locum GP).  ‘Any interviewee mentioned, ‘there’s something a bit ethical about it as well in terms of exactly what genomic data you are getting and whether there’s any data that predicts future risk that you may or may not want to have known’ (R17, Clinical Lead).  'you have still got to develop a shared understanding of it between you; you have still got to have the same process of shared decision making’ (R10, GP Academic), and ‘I think it’s something about the general area around informed choice and rational decision’ (R5, Public Health Researcher). | Many interviewees made interesting observations around patient factors influencing pharmacogenomics, including the effects of personalised medicine and its impact on patient perspectives and shared decision-making. They valued patient-centred care but were anxious around extra workload pressures following implementation of personalised medicine. Genetics was seen as one of several elements contributing to ‘personalising medicine’.  The application of pharmacogenomics in personalised medicine was apparent to many.  Patient anxiety and workload pressure were also important considerations.  Presentation of the evidence to patients was considered important for a meaningful discussion, and the importance of shared decision making was raised by some, |
| Patient views | Consumer demand  Issa et al 2009 | ‘How many of us bought a 400 dollar VCR back in 1981? Now you can get one for 30 bucks. I mean, sooner or later Wal-Mart is going to open a clinic to test genetics.’ (FG 1)  ‘I guess if it were the only drug, I would want to try it anyway.’ (FG 2) | Several participants (about 68%) expect that there will be consumer demand for pharmacogenomic-based testing and prescribing. |
| Patient views | Conflation of disease risk and drug reaction  Barr et al 2008 | A good example of the conﬂation of disease risk and drug reaction can be found in the exchange below:  A: I would want to know that I was getting the best medication. I’d go for a genetic test if he thought I was depressed or is it, yeah, I would want to know. It’s in my interest I feel to be treated properly and I wouldn’t want to be depressed so you know, that’s just the way I feel. I’d want to be treated properly.  B: Another concern is well where all this genetic results get held, do they get held in a mainframe computer somewhere (multiple voices)  A: I couldn’t give tuppence, I couldn’t give tuppence where they’re held, stored my (multiple voices)  B: Or what they used it for?  A: Or what they used it for. If it’s going to beneﬁt me and my family in the long run, then I’m all for it. I mean I would hope you know, my granddaughters are going to be tested to show that they’ve not got the gene that I may well have passed on to them. And if there’s any medication they can take when they get to a certain age that would prevent them from probably getting the same disease, I’d be really happy. I’m only sorry that I didn’t know about it sooner (English Public Group 2). | Whilst focus group participants understood the difference between testing for drug response and testing for disease risk, this separation was nearly impossible to maintain in actual discussions. There was a sense that ‘at the end of the day, a genetic test is a diagnostic method that gives information on a person’ (German Public Group 3). There was a belief that various pressures would conspire to make it hard to keep testing at the level of treatability and that usages of test information could ‘spread like ripples in the water’ (Danish Public Group 3).  **A tendency to conflate the notions of a pharmacogenomic test for antidepressants with a genetic test for depression, a conflation which could cause patients to refuse a**  **pharmacogenomic test if they thought (rightly or not) that the results would have wider implications for themselves or their relatives.** |
| Patients views | Concerns when starting a new medication  Lee et al 2017 | “…if you went into this with more information that you may be more predetermined to have these side-effects. I think it would be even stronger notion that like if I throw up tomorrow that’s probably the medicine, whether it was or not.”  Is this drug necessary and effective?  Will my insurance cover it?  What other options are available?  What are the long term effects? “If it’s a new medication I’d have like the standard concern of what are the long term consequences…”(TC)  How does it interact with other drugs?  Is there sufficient research? “And they keep telling me it ain’t gonna get absorbed by your blood stream and stuff but, I don’t feel confident about that because there’s not enough, you know, research and stuff. This is a new disease and they don’t know how to deal with it. And they’re using me to find out…”(TC) | There were also heightened worries about side-effects… |
| Patients views | Therapeutic benefit  Lee et al 2017 | … “Is that the only reason that drug X was the preferred drug in the first place?…if there were other reasons I’d want to know what I was giving up, other than the cost. And then I’d be interested in who covers the cost.” | With the clopidogrel vignette, participants were concerned with insurance coverage of the expensive alternative and wanted to understand if the therapeutic benefit justified the higher cost incurred… |
| Behavioural change | Patients use a positive test result as rationalization for giving up  Park et al 2006 | "She might not be motivated to stop, because she might say, ‘‘Oh, it’s in my genes, I’m predisposed to it. None of this is going to work.’’  "If she doesn’t have this genotype, then she could think, ‘‘Well, that’s going to work for those people, but it’s not going to work for me.’’ | Physicians also appreciated the difficulty of understanding the meaning of association studies and concepts of penetrance. They were concerned that patients could use a positive test result as rationalization for giving up trying to quit smoking.  Conversely physicians worried that patients not genotypically inclined to a certain treatment might be discouraged from trying any smoking cessation treatments at all. |
| Behavioural change | Managing results expectations  Lemke et al 2017 | A practitioner (P02) articulated the importance of this discussion with patients: “And, you know, it’s again, this test doesn’t encompass all drugs yet either, so you can’t use it as the ace in the hole, so to speak, that it’s going to get you out of trouble every time. It’s just one aspect of the patient that you’re analyzing that will hopefully yield some benefits for that patient. It’s not going to be 100% of the time where you’re going to have a successful outcome, but it’s probably got limited or no downside to hurt the patient.”  Another physician (P13) commented on managing patient expectations; she stated: “Not as long as you set the expectations. I think you can’t bill it as, ‘We know exactly what drug to use and how much to use,’ but we can say, ‘It’s a guide.’ So setting those expectations, because if you don’t set the expectations and they’re saying, ‘How come this didn’t work for me?’ It’s just a guide. It’s not all the answers. Also, the expectation of really what drugs we’re looking at. Making sure that they’re clear with that. That it’s not like in a test for breast cancer risk or things like that, so it’s always setting the expectations.”  This primary care physician (P08) described a patient who required additional reassurance after receiving her results: “I had one patient that reacted only more in panic. All the things that were red-flagged like ‘Never take Plavix, never take this.’ More ‘what if I need it? What do I do then?’ You’re 30, you don’t need Plavix, but one day when you do, hopefully there’s a drug out there that you can use instead. I only had one patient that reacted more alarmist, anxious, about the results, and was not as thrilled that she got them.” | One of the findings that emerged was the concept of managing results expectations with patients.  In addition to managing patient expectations about what kinds of information PGx testing can and cannot provide, one participant also brought up a patient’s concern about potentially not being able to use a certain medication. |
| Reliance on genetic testing | Reliance on genetic test rather than patient history  Park et al 2006 | "I wonder if a lot of this could be obtained by talking or getting a history as opposed to going after a gene … So I think we probably could get a lot of information clinically without ordering a test." | Many physicians questioned the benefits of immediate treatment matching based on genetic test results relative to merely cycling through available treatments according to patient preference. Moreover, some physicians expressed concern that practitioners would rely on the genetic test rather than take a comprehensive history of the patient. |
| Reliance on genetic testing | Undermining the importance of psychological and behavioural determinants of smoking/quitting.  Park et al 2006 | "Just doing the test focuses on the test and not the patient himself. The patient is the key part of it. Eventually they are going to have to stop whether or not they are positive or negative for this gene." | Physicians voiced significant concern that overemphasizing the biological factors associated with nicotine dependence would undermine the importance of psychological and behavioral determinants of both smoking and quitting. |
| Reliance on genetic testing | incentive to use medicines instead of conversation therapy  Barr et al 2008 | As one member put it:  But the question is whether one should not invest all this money that is used to develop these tests and drugs in other things, like . . . I don’t know . . . like social structures that would make people less sick in the ﬁrst place . . . What is important is that more people start thinking more about these themes and that they maybe have the idea that it is maybe not necessarily the solution to ﬁnd more efﬁcient drugs. Rather [the solution is to] try to live in another more human society so that one gets less sick and less depressive in the ﬁrst place (German Public Group 3).  If I got this questionnaire, going back a couple of months ago, when I was quite unwell, I would have jumped at the chance of a blood test to make me better. But when I would be getting a bit better and I’d start thinking about it more logically, I’d realise that I’m going back into the medical model again and I’m going back into all this, you know, taking drugs (ENUSP). | For all the support in our focus groups for pharmacogenomics, criticism of the medical model was reﬂected in a number of responses. There was a feeling that pharmacogenomics represented an extension of the medical model that already pervades the diagnosis and treatment of depression and that ‘there might be a bigger incentive to use medicine instead of conversation therapy’ if genome-based therapies reached the clinic (Danish Public Group 1).  Some service users in the ENUSP organisation (European Network of (ex) Users and Survivors of Psychiatry) explicitly used the term ‘the medical model’ thus tying their discussion into user/survivor politics…  This quote highlights a related theme that a number of people expressed – that is, a continual fluctuation and/or contradiction in attitude towards their condition and medication. For some users at least, desperation gets entangled with hesitation, depending where/when in the process they are confronted about the possibility of pharmacogenomics.  **Doubts about the medical model of depression, a model which in the minds of some people at least does not adequately explain life events as causal factors. More importantly for the uptake of pharmacogenomics, there is a related view that the treatment**  **of depression has been overly medicalised, leading to a neglect of alterative therapies which could be just as efficacious.** |
| Medical mistrust | Medical mistrust by marginalised population (pt. view)  De Marco et al 2010 | ‘I think there would still be a trust issue though with the medical community. I think that’s the, that’s the problem that we get into when we start talking about personalized medicine.’ (FG5) | …there was much agreement in one AA focus group that even with personalized medicine medical mistrust would still be an issue.  We also found that medical mistrust by marginalized populations, as discussed in particular in the AA focus groups, may affect the acceptability of personalized medicine when it becomes widely available. |

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| **Beliefs about consequences**  **(Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)** | | | | | |
| **Analytical theme** | | **Descriptive theme** | **Illustrative quotes for participants (first order)** | | **Illustrative interpretations from authors (second order - discussion section)** |
| Reduces adverse drug reactions | Avoid adverse drug reactions  Lemke et al 2017 | | One participant (P04) related his thoughts about PGx testing for his patients: *“I think of patients who’ve had difficulties with different medications, classes of medications, and potentially utilizing this information to prevent using time poorly in terms of starting patients on medicines that probably won’t work or putting them on doses that probably won’t work.”* Another participant (P07) said: *“It will help me decide what medication to give to the patient, say if it’s a patient with depression that I’m having a hard time figuring out what medica­tion I could use due to side effects or lack of response.”* | ….helpfulness to patients in poten­tially avoiding medication side effects and guiding decision-making for patients who are starting a new medication. | |
| Reduce side effects  Lemke et al 2017 | | “*His results showed that Plavix was not likely to be beneficial to him, so it affected, actu­ally, his treatment plan.*” Another interviewed physician (P15) detailed her patient’s outcome: “*Yeah, he’s been struggling with depression. He’s been very against medica­tion, antidepressants specifically. A lot of anxiety related to side effects. He went on Lexapro and after two days he had horrible, horrible side effects that took a week to ease off of, mostly GI-related. You hit that point where you finally get him to the threshold, and all the things he was afraid of happened…But now [after PGx test results] he’s on Effexor, and a month later he’s a totally different person.*” | In addition, participants cited specific examples of how PGx test­ing results were used to adjust patient medications to increase effectiveness and reduce side effects. A practi­tioner (P11) explained: | |
| Improve compliance through less side effects  Lemke et al 2017 | | “*…like my patients who are on antidepressants, cholesterol medi­cations-we can actually do the testing and find out which medications either work the best or produce the least side effects. And then hopefully that would lead to better com­pliance. That’s the problem with all these medications-nobody takes them.*” | A number of primary care physicians talked about the complicated dynamics that occur when patients try medications that either do not work or cause adverse effects. Patients may or may not want to embark on another medication trial and one physician (P05) talked about how PGx testing could be used to improve patient compliance in these situations: | |
| Reduction of adverse events  Frigon et al 2019 | | “All drugs that were given to me, going to the hospital, having adverse effects, drug rejection […], I could have had fewer adverse effects, fewer visits paid to the emergency room and my quality of life could have been better,” (Patient, group 2). | Unanimously, all groups mentioned the reduction of adverse events as being one of the main benefits of PGx testing  Moreover, clinicians stated that PGx could enable them to spend more time on other aspects of their practice by saving them time on dealing with drugs’ adverse events. | |
| Concept of individualized medicine  Chase et al 2017 | | *“I’m a little wary of it but I’m also excited because I think it will help us get closer to having an individualized plan for people that really is about who they are.”*  *“if there’s a way to pinpoint what medication would really be the best for the patient based … genetic makeup or, you know, whatever is going on, then I think that would be great… I have seen a lot of patients where we try one, two or three different types of IV treatments and it just doesn’t work and you have to wait so many months for it to kick in and if it doesn’t, then switch over. ..if there’s a way to narrow it down to … find … that best drug..”*  *“I think it’s important to try to identify future risks for people, not just-- which you can get at with cancer risks but-- so what are the future risks of you developing diabetes?”* | The concept of individualized medicine was appealing to the interviewees.  This knowledge could then translate into more effective treatments  And they also thought it might help with risk assessment.  This positive attitude was consistent across clinics. | |
| Adverse effects  Haga et al 2012 | | ‘‘With warfarin, probably because of just the difficulty of use, getting the dose adjusted properly and people being high or being low and we can’t explain that, I think that makes sense. I don’t see the delay in that as a big barrier.’’ [Male-PCP-FG#3] | Overall, discussants were interested in PGx testing and recognized the immediate benefit to improve drug therapy outcomes.  For severe adverse effects and drugs with narrow therapeutic windows, PCPs indicated that they would be more inclined to consider ordering PGx testing.  PGx tests hold great promise to improve outcomes through tailored drug treatment based on patients’ genetic risk of adverse effects and/or likelihood of drug response.  …. professional attitudes toward PGx testing in general, interest among our participants was positive, though less so with PCPs, potentially due to geneticists’ greater familiarity with the field and/or favorable biases. | |
| Tolerate adverse effects  Lee et al 2017 | | “…if I know it could be really effective…even if there might be some side effects then I might be more willing to push through, knowing the benefits.”  “…if you went into this with more information that you may be more predetermined to have these side-effects. I think it would be even stronger notion that like if I throw up tomorrow that’s probably the medicine, whether it was or not.” | Interestingly, participants expressed high expectations of drug efficacy with a pharmacogenomic-determined medication with the preparedness to tolerate side-effects, as exemplified by this comment:  There were also heightened worries about side-effects, as in this example: | |
| Value of PGx testing in primary care  Rafi et al 2020 | | I think it will be more important for things like anticoagulants, side effects, cancer therapies, less so for antihypertensive and statins’ (R5, Public Health Researcher). | Many interviewees discussed the value of testing in primary care, including examples of application, improving efficacy whilst reducing toxicity and confidence in the use of such approaches. There was some discussion about how pharmacogenomics could offer value, and it was generally deemed to be dependent on the available expertise: | |
| Reduce adverse effects  Barr et al 2008 | | I don’t think I would have minded if I, when I was, quite just before I was pinned down, and injected, if they’d have just done a quick swab and actually got me something that wouldn’t have been so horrific in its side-effects because my metabolism contradicted it  or whatever it is that they use, I don’t think I would have minded that actually in a way  (English User Group 2).  We realise that our members often do not die of psychiatric disease but of other diseases which they got in effect of the prolonged use of psychotropic drugs, for example liver diseases, stroke, heart failure and many others. It is not unusual for a psychiatric patient to die between the age of 30 or 40. They die because their body can no longer stand so many drugs and it gets ruined. So what most patients dream of is that a medication is formulated that will not bring about side effects. And it is really not important whether it will be developed based on a patient’s genotype or in another way. What we really want  is that we stop dying prematurely because of the medications we have to take (Polish User Group 3). | There was an overwhelming desire to eliminate adverse drug reactions, as the following excerpts show: | |
| Reduction of adverse drug effects  Issa et al 2009 | | *‘*When you’re trying to find the right treatment, you’re wanting results immediately and here you are going through side effects and things, and that just adds on the time that it’s taking to try to get rid of your symptoms. So you try another one and that just takes more time. So I think it’s very time consuming as well.’ (FG 4)  ‘My biggest problem was the fatigue. It was wearing me out, I mean, by four o’clock every afternoon I was ready to go to sleep. I mean, it took 2 or 3 different ones to get me where I need to be without feeling like I need to go to sleep whenever I need to be working or whatever. That was my biggest problem.’ (FG 2) | Approximately 68% of patients generally indicated a preference for the use of pharmacogenomic-based testing for the purpose of improving drug prescribing and associated health outcomes. Discussion centered on concerns related to experiences with adverse drug reactions and the potential for pharmacogenomics to overcome or minimize the problem of adverse drug reactions. | |
| Reduces adverse effects  DeMarco et al 2010 | | ‘Like you say with joint problems, stomach upset, the medicine may be able to more synthesize with your system so that you’re not experiencing all of these different emotional ups and downs, um, sickness, diarrhea, constipation … all the other symptoms, all the other side effects.’ (FG5)  ‘And, it’s not as time consuming as it is if you keep going back and forth to the doctor trying to figure out what’s gonna work.’ (FG6) | All focus groups held generally positive views of personalized medicine. However, participants in the AA focus groups spent a greater amount of time discussing positive views than did the white focus groups. These positive aspects included fewer side effects and less trial and- error when prescribing. In contrast, white focus groups concentrated more on the view that while personalized medicine is an exciting prospect it will take time before the full potential is realized. | |
| Reduces adverse drug reactions | Pharmacotherapy improvement  Van Der Wouden et al, 2020 | | “Being able to select those patients at higher risk for adverse drug events before initiating the drug, that is very beneficial” (P13:17)  “I think [PGx] may improve drug adherence, I think so.” (P6:25)  “I think [PGx] will prevent a lot of healthcare costs related to hospital admissions.” (P15:31)  “[testing diagnostically] may not always give a definitive answer, but at least we will be able to cross-out genetics as being the cause [of the adverse event].” (P5:31)  “We are now able to fine-tune pharmacotherapy.” (P3:20)  “I don’t know if we are saving lives with it, but [PGx] is beneficial and fun.” (P2:50) | ..all pharmacists reported to strongly believe in the beneficial effects of PGx guided pharmacotherapy on a number of domains:  pharmacotherapy, pharmacist added value and knowledge, and professional interactions.  When delivered in a pre-emptive setting, pharmacists reported that they believed that PGx guided  pharmacotherapy would be particularly beneficial for identifying patients who are at higher risk for adverse drug reactions. A number of beneficial downstream effects were reported by pharmacists:  improvement of drug adherence, prevention of hospital admissions, reduction of trial and error in finding the correct dose, and time-saving. When delivered in a diagnostic setting, pharmacists attributed the added value of PGx in being able to determine the cause of an aberrant response to a drug, although they noted to be aware that there will not always be a genetic cause. | |
| Reduces trial and error | Aid in therapeutic choice  Williams et al 2016 | | For instance, one provider commented that use of genetic testing would “probably save everybody…some headache of trying something that's less likely to work.”  Another said, “I think doctors in particular would respond well to having a test…it makes it [treatment decision-making] feel less nebulous.” | ….number of providers believed that the results of genetic tests could aid in therapeutic choice by reducing ambiguity in treatment decisions and reducing trial and error. | |
| Increase patients confidence in their care  Williams et al 2016 | | For instance one provider said, “If I were to have a test that would tell me, ‘hey,…this patient is not going to respond to that,’ then I wouldn't put them through A and B. I think they have confidence in me if I prescribe something for them that works the first time, instead of you know, trial and error.” | Additionally, providers thought the test might help them more strongly advocate for medication treatment and increase patients' confidence in their care. | |
| Reduce trial and error  DeMarco et al 2010 | | ‘Because that way they’ll know that will work for me and what won’t work for me, and … it won’t take me through the, you know, uh, thing of getting this prescription, trying this, you done spent your money on this, this doesn’t work. You don’t get a refund.’ (FG1)  ‘It will save you some other conditions too … Save you going through the, the sickness or sometimes you’ll be sick for 2 weeks while taking a pill.’ (FG5) | … both AA and white groups held similarly favorable views of genetic testing as a way to find the best medication.  Both groups saw genetic testing as a promising practice for reducing the risks in the current method of prescribing. Similar to the views of personalized medicine, participants believed that genetic testing would decrease side effects and reduce the trial-and-error nature of prescribing, thus saving money. | |
| Improved effectiveness  Issa et al 2009 | | ‘[Now] you have to take many different drugs. You  would take one, and then you would have to wait a month to see if it worked or whether or not you tolerated it, or whether or not it worked for you. Sometimes it did, and sometimes it was a series of kind of hunt and peck to find out what’s gonna work best for you. It was frustrating at times for me.’ (FG 2)  ‘If you could take one test and end up taking one pill,  and it’s going to work versus spending the next 6 months testing every pill that didn’t work, right there that genetic testing becomes worth it.’ (FG 1) | Other promising benefits identified include the potential for improved effectiveness of any targeted therapies and the possibility of reducing trial and error attempts at appropriate prescribing and dosing | |
| Patient benefit | Patient motivation  Park et al, 2006 | | “I think letting someone know this is earmarked to them and their uniqueness probably will have a better chance of breaking the cycle of failure.  Again, it adds something extra, whether it be placebo-like or whatever, encouragement.” | Physicians felt the greatest benefit associated with genetic testing to tailor treatment was the ability to better direct treatment for patients, therefore, increasing their probability of and motivation for quitting.  Physicians viewed patient motivation as the strongest predictor of successful smoking cessation and believed the possibility of tailoring treatment approaches to patients’ individual characteristics might enhance patient motivation. | |
| Patient motivation  Williams et al 2016 | | For instance, one provider shared,  “sometimes having a little feedback and pointing to a lab result is helpful for when you're discussing things with patients.” Another said, “some people are in the middle, and it might help tip them one way or the other.” Similarly, one provider said, “it would let us know if this medication would be more helpful to someone like you, then you might be able to forge some movement in that direction. Might be very powerful, I would think.” | Providers also perceived potential benefits for patients and thought that test results could be a catalyst of patient motivation for and engagement with/adherence to treatment. | |
| Benefit patients who had exhausted other treatment options  Park et al 2006 | | If she’s had multiple quit attempts before, then I would be highly more likely to want to get a test that helped me figure out what was the right treatment. | Physicians believed the test would be a beneficial option for patients who had exhausted other treatments and repeatedly failed to quit. | |
| Improve patient adherence to treatment  Williams et al 2016 | | One provider explained, “If you tell the patient this medicine is much more likely to be effective versus it might be effective, I think it helps with compliance.” | Providers also thought genetic testing  could help improve patients' adherence to treatment | |
| Relieve patients of personal blame  Park et al 2006 | | If you’ve got somebody who you try to legitimize the problem with, you could suggest that there’s an organic basis, not just a psychological weakness or lousy habit…that there’s some other basis for her addiction. | In framing smoking as a disease, the test may relieve patients of personal blame and feeling that they are at fault for their inability to quit smoking, the burden of which may decrease chances of success. | |
| Use as preventative tool through raising patient awareness  Park et al 2006 | | And test patients who aren’t smoking … this part that says the genotypes are associated with a greater likelihood of becoming addicted to nicotine in the first place; maybe I can do something with that information to motivate folks not to begin smoking. | Many physicians also saw potential in using the genetic test as a preventive tool with non-smoking patients or early initiators, reasoning that awareness of elevated susceptibility to nicotine addiction might dissuade patients from initiating or continuing to smoke. | |
| Create a placebo effect for patients  Williams et al 2016 | | One provider shared that use of the tests “could give us a lot of hope…letting the patient know going into it that they're very likely to have a good success rate. I think that has some potential placebo effect, which would be good too.” Another said, “Offering a patient with alcohol difficulties a way to know if they would respond better would definitely make a difference….if I could do that test and be able to give that patient the feedback that they might respond better, then they have a good chance of responding better to this type of medication.” Another similarly expressed, “because if you think it's going to help you, it's probably going to help you.” | Providers also suggested that conducting genetic testing that resulted in an optimistic prognosis may, in itself, create a placebo effect for patients regarding medication use and treatment outcome. | |
| Quick access to results  Cost effective options  Park et al 2006 | | No direct quote | Physicians were hopeful that the test would provide new, cost-effective treatment by matching patients immediately to the most effective treatment. The fact that test results would be obtained quickly also appealed to physicians. | |
| Implications for future  medication management  Dressler et al, 2019 | | ”[how the test results] could impact future care.” (P3)  ”Looking at patients not responding to antidepressants” (P2) | No further explanation | |
| Competitive edge  Dressler et al, 2019 | | ”. . . provided a competitive edge [for the practice],” but that this interest in PGx was not shared by other colleagues in his/her practice (P2) | No further explanation | |

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| **Environmental Context and Resources**  **(Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)** | | | |
| **Analytical theme** | **Descriptive theme** | **Illustrative quotes for participants (first order)** | **Illustrative interpretations from authors (second order - discussion section)** |
| EHR implementation | Priority for EHR implementation  Chase et al 2017 | “We can’t do everything…right now the priority is to make the system work for us I think we are working too hard for it.” “I think [incorporating occupational health and social determinants of health] can help more right now than personalized medicine and at lower cost.” But there is a possibility that this could change in the future: “I probably don’t think about genomics, ... but in the future, if we have that kind of information, that would be awesome.” | Even if the providers wanted to incorporate genomic information into their CDS, there are many priorities that were viewed as more important, including work-related data: |
| EHR implementation | Clinical decision support in EMR  Dressler et al 2019 | “would like to see orderable in EMR” (P1,P3) | Common themes ……"and have this embedded in the EMR. Although participating physicians promoted having PGx clinical decision support in the EMR, some indicated that other physicians in their practice may not agree; again, highlighting the challenge of addressing differing perspectives within a single practice. |
| Workflow issues | Translating results into clinical decisions  Unertl et al 2015 | Clinicians expressed strong desires for, as one clinician described it, “decision support that's informational that doesn't disrupt the flow of the work.”  "I'm a very quantitative person… intermediate doesn't mean anything to me. So… can you tell me poor metabolizer? Could you quantify that in some way? 10, less than 10%? Some number that tells me or even something that's just color coded and it says, “Prescribe something else. Don't do these drugs,”  Another physician suggested,  “Most importantly, the information has to be pushed to the ordering physicians so that the ordering physician gets the information. With that push has to be very easy links to… written advisor statements invented by the experts that tell us what is recommended. And then, there should be another link to the original data for people that want to know exactly what the evidence is one way or the other.” | Once tests results were reported, clinicians integrated pharmacogenomics test data into their clinical decision-making processes to varying degrees. The need for CDS in general to be well integrated into clinical workflow has been a repeated theme of informatics research on CDS… so the extension of this perspective to pharmacogenomics CDS was unsurprising.  Interview subjects provided suggestions for several different approaches to CDS, focused on the idea that CDS needs to be clear and concise but also provide the ability to seek out more information quickly and easily if desired |
| Workflow issues | PGx integrated into EMR – integrating electronic alerts  Frigon et al, 2019 | In fact, one of the pharmacists shared this thought: “It would be essential to have it included into a software that can help us not to miss some information,” (Pharmacist, group 2).  The idea of integrating electronic alerts was suggested by one of the PCPs: “The prescriber should be aware that he [the patient] is a slow metabolizer and that when we prescribe this, it makes BEEP [alarm sound],” (PCP, group 1). | All professionals agreed on the fact that, in order to be implemented correctly, PGx data should be integrated into the software programs used by health professionals.  Most patients also agreed that results of those tests should be computerized and put into a universal electronic medical record (EMR), therefore all information could be easily accessible to any professionals. Patients also mentioned that tools to facilitate their comprehension of PGx such as information pamphlets, reliable websites, phone lines and books would be of great help. |
| Workflow issues | Workflow issues for CDS, unwilling to have interruptions on their workflow  Chase et al 2017 | “So that would involve additional blood work … I’m not sure how that would be incorporated into my work flow.” “It is not part of the flow.” | Without a significant perceived benefit, providers were unwilling to have interruptions on their workflow..  This was a concern for all clinics, and appeared to be more prevalent for clinicians with prior EHR implementation experience. |
| Reporting results | Clearer layout  Lemke et al 2017 | One participant (P03) said: ‘No, it [specific genetic/ metabolic details] could all be on the back end of the report, but I need the first page to be much more clinically relevant.” | A specific need mentioned by participants was potential changes in the results report to make it clearer. |
| Reporting results | Information overload  Unertl et al 2015 | As one clinician expressed, “One gets diluted, tired, and then ignorant of things that are posted on every single patient, especially if we're not using it very often.” | Due to the highly specialized content of pharmacogenomics tests, some clinicians expressed concern about the clinical relevance and information overload of reporting genomic information to the EHR. |
|  | Informatics - electronic capture of genomic information  Rafi et al 2020 | ‘it’s the record that is kept by the patient, follows the patient unlike hospital systems’ (R1, GP principal).  ‘I would be worried about would be the coding within the system to make sure we are correctly capturing the right information’ (R1, GP Principal),  ‘concerns about data security is higher with genetic data because it has implications on a criminal type of basis not just for the data subject’ (R4, informatics expert).  ‘The reality is we’re talking about genomic information [yet] we haven’t even got decent family history data so how are we going to use genomics if we can’t even incorporate family history?’ (R14, Locum GP).  ‘SNOMED CT codes, the one that are supposed to be integrated in primary care [soon], they are absolutely not adequate in recording genomic information. They are very patchy, [and] relate to only certain codes’ (R9, GPSI genetics).  ‘it is potentially a problem I think... if the implications of the genomics test affects family members, because we are very good at recording in one patient’s notes but actually because of confidentiality etc. it’s very difficult to ensure all the right people have cross referencing for that result.’ (R12, a RCGP Medical Director). | There was agreement about the importance of electronic capture of genomic information, anxiety around a new coding system and concern around the principles of data sharing.  Interviewees discussed the application of informatics to pharmacogenomics. In particular, the sensitivity of personal genomics information recorded on a patient’s primary care electronic health record:  Many felt that limitations around expertise in coding could be an issue:  ...with concerns that the information being recorded could be highly sensitive:  There was frustration that the recording of family history has not been a success, and some questioned whether genomic information be recorded more successfully.  Furthermore, new coding systems due for implementation do not appear to incorporate plans for recording or coding.  This point resiterates the issue was around data sharing." |
| Ordering/  interpreting tests | Ordering and reporting on tests  Unertl et al 2015  Interpreting PGx test reports  Unertl et al 2015 | “I think more information is always better about patients. So I believe that it's important to try to obtain this genetic information, pharmacogenomic information on my patients. That's step number one. Step number two is what do you do with the information? We're still learning.”  “There is so much information that comes back when [the laboratory test report] shows results that you say, “Okay, I don't know what this means. I'm going to go to [the EHR] where it's really simple and it tells me it's a poor metabolizer or intermediate metabolizer.” Those are words I can understand as opposed to getting all the genetic information.”  I think poor metabolizer is a good word, a good phrase… Indeterminate would suggest that we have no idea what the mutation does. Whereas, intermediate… a more suitable word might be partial metabolizer.”    As one clinician expressed, “One gets diluted, tired, and then ignorant of things that are posted on every single patient, especially if we're not using it very often.” | A clear theme across interviews was that clinicians understood the rationale for obtaining pharmacogenomics information, but integrating this knowledge into healthcare practices raised complex questions and concerns.  Standard laboratory reporting of genomic test results was sometimes unclear to clinicians, leading them to seek answers from the interpretive information present in other sections in the EHR.  Some clinicians felt that even these distilled phenotype terms were difficult to interpret, in part because the nomenclature that was familiar to the clinical genetics research community was not transparent to end-users.  Due to the highly specialized content of pharmacogenomics tests, some clinicians expressed concern about the clinical relevance and information overload of reporting genomic information to the EHR. |
| Ordering/  interpreting tests | Meaning of genetic test results and communicating results  Park et al 2006 | "It isn’t concrete. You are doing a test that is saying that you may be predisposed to this; you might have an increased likelihood. What are you going to treat? I don’t know what you are going to do with this information" | Many physicians were unclear about the meaning of genetic test results, how such information should direct clinical care, and their ability to effectively communicate genetic information to patients.  Prior to clinical integration, physicians agreed that they would need more information about the test, such as its **sensitivity and specificity.**  Finally, some were concerned that a **time-consuming** informed consent process would be needed. |
| Interpreting genetic test | Interpreting genetic information  Park et al 2006 | I think there is this sense in the public of genetic testing being absolute, without a good understanding … a genotype has a 55 percent prevalence [in one group] … what does this really mean? | Physicians were concerned that patients do not know how to interpret genetic information in general and that reported racial differences in the prevalence of certain genotypes across racial groups would compound the problem. |
| Ordering/  interpreting tests | Ability to understand and explain PGx test results  Unertl et al 2015 | “So, at the beginning, we started all this, I went through this detailed explanation of what we were ordering, and what I found from patients is that the response all along is, ‘Oh, please order it. It's stupid not to order this particular test. I definitely want to know the information.’ At this point, it's become a shorter conversation in terms of, ‘I want to do this. I think it's smart. This is why,’ and everybody says, ‘Fantastic. Please do and can my daughter get it? Can my uncle get it? Can my grandmother get it?’”  “I'm usually somebody that likes to simplify things an awful lot for understanding for both my patients and for me. So, you know, how can I make this as simple as possible so that they get the big picture of why I'm doing the test, but not overwhelm them with its purpose.”  “I think that you had a lot of clinicians who were blindsided because all of a sudden, patients start finding out they were intermediate metabolizers and this is before anyone knew what to do with that. And so, I think, you know, you had patients asking their doctors, ‘Well, I got this, you know, this is what they said I am. You know, what do I do?’ And the doctors would go, ‘Uh, I don't know.’”" | Initially, clinicians discussed pharmacogenomics testing in detail with patients before ordering tests, but reduced the amount of explanation over time.  Other clinicians felt that in-depth explanations of specific pharmacogenomic testing details were unnecessary in initial decisions to test.  When receiving test results, clinicians faced the challenge of interpreting and communicating the information to patients and families. Their level of familiarity with pharmacogenomics impacted this interaction. |
| Ordering/  interpreting tests | Ability to understand and explain PGx test results  Lemke et al 2017 | “Less comfortable. You know, looking at some of the results that were returned, that just kind of says ‘drugs to avoid,’ but doesn’t give a lot of science behind it or explanation. I think I would like some guidance with that.” | One of the main hurdles for providers was difficulty in understanding the pharmacogenomics test report.  Many of the participants described having a lack of understanding of how to interpret the pharmacogenomics results and that they were not adequately prepared to communicate complex results. |
| Ordering/  interpreting tests | Ability to understand and explain PGx test results  Haga et al 2012. | ‘‘I think the part that is daunting for me is having these conversations are so time-intensive, and trying to do it in a way that is understandable to the patient, and it’s like, oh, I’ve got to do this discussion now.’’ [Male-PCPFG#3]  ‘‘We are going to do this test, but we also might ﬁnd out information that we didn’t really want to know, and are you okay with that? It’s like, how to explain that to somebody who might have a high school education or something like that.’’ [Male-PCP-FG#3] | Many PCPs acknowledged that they themselves would be unlikely to understand the signiﬁcance of the ancillary risk information, given their limited knowledge and experience with genetic testing. Therefore, referral to a specialist may be most appropriate. In addition, PCPs believed that it would be challenging to communicate genetic disease risk information, particularly for patients with low literacy and given the **time constraints** of a typical appointment. |
| Ordering/  interpreting tests | Specific training to report PGx results  Lemke et al 2017 | She (P03) asked for an explanation to detail: “Say, ‘here’s the genes that we’re going to be showing you, here are the ones that are relevant, here’s what you tell the patients about these other ones that are irrelevant. And if you have trouble with this, you know, here’s a resource for them and for you.’” Another physician (P09) volunteered: “Maybe even if someone just sat down and reviewed my results with me, that would give me an idea of how to present it to a patient, or how to explain it to a patient, if someone treated me like a lay-person and read through my results and showed me how they would do it.” | One participant wanted further training specific to results report interpretation |
| Ordering/  interpreting tests | Unclear procedures outside of the study  Van Der Wouden et al, 2020 | “No, I don’t know how to [request a test]. There seems to be some kind of system where you can order tests electronically, but I don’t have access to it anyway.” (P3:16)  “Officially, a prescriber still has to request it and that is particularly irritating. I just want to arrange [requesting tests] myself.” (P12:9)  “Can the pharmacist also request [PGx tests]? I have to say that the reimbursement policy is really unknown to me.” (P15:23)  “... if there was clarity about reimbursement, what does it cost, which patients are eligible—sort of practical guidelines, that would be really useful.” (P14:16)  “Requesting a test wasn’t really complicated at all. However, it is still unclear what [genes] to request; do we request the full profile or are you going to request one gene specifically?” (P5:38)  “Well I know I can request a gene test in Leiden. If I request in Rotterdam, then the whole panel is tested. But how to make those choices, that is unclear to me.” (P10:30) | The majority of pharmacists reported that they were not sure on how to request PGx testing outside the research-setting. More specifically, they were not sure if test costs would be reimbursed by the insurance companies if requested by a pharmacist, when to request testing (diagnostically or pre-emptively), how to request testing, at which laboratory to request testing, and unsure about which genes to test or whether to test the entire PGx panel. One pharmacist reported being aware of how to request a test outside the study setting, because of being involved in a clinical project. Several pharmacists reported that for application outside the study setting a set of practical guidelines specifying which patients and genes to test, which is the responsible HCP for requesting a test and reimbursement procedures, would be very helpful.  A number of pharmacists expressed that they felt the assistance of pharmacist **professional organizations** would be very helpful in **creating both practical implementation guidelines, to clarify PGx testing logistics,** and information brochures to inform patients regarding PGx. Some pharmacists felt strongly that the **pharmacist professional organization should publish a PGx policy statement and coordinate implementation centrally**. One pharmacist suggested that this policy statement could help to advocate for the reimbursement of PGx testing. |
| Cost concerns | Cost of PGx testing  Issa et al, 2009 | ‘Ok, so maybe the testing is expensive but over a course of time you wouldn’t be going through the cost of the different drugs, the cost of the different office visits, so it might end up balancing out or saving money in the long run.’ (FG 2) | Participants expressed concern about the potential costs of pharmacogenomic-based testing and how this might influence access to and availability of testing among various populations |
| Cost of PGx testing  Lemke et al, 2017 | “I don’t think that any patients are really going to pay for that unless there’s really, truly a concern. You know, if someone’s tried multiple statins or multiple antidepressants and even then it’s hard for them, it’s going to be hard to convince someone to do this test that’s not covered. I think it’s different from paying out of pocket for a heart scan because it’s such a visual thing and people totally get it. I mean, we’ll see with time how it goes.”  “I know one person felt short changed that they did this test and they didn’t get any information from it.”  “…maybe the cost for some patients. If it’s not covered by insurance, it might be a bit much and patients may not have so much buy in to it if they don’t think it is really going to be a benefit.” | Physicians also described test cost incurred by the patient (as many insurance companies will not cover testing) as one of the most significant barriers to PGx testing.  The barrier to PGx testing that was most often discussed by participants was the cost to their patients. |
| Cost of PGx testing  Dressler et al, 2019 | ”. . . still wrestling with affordability” (P1).  ”a $99 test would be (a good price point)” (P1,2,3)  ”Good to know that with lab [x], Medicaid patients will not be balance billed” (P3)  Pricing continues to be concern and barrier for physicians as they were still "wrestling with affordability." At the time of the study, the cost of the clinical PGx panel testing was approximately $250 and physicians were informed of this price (and that a grant would be covering the test costs for the study). When the cost of testing came up during the interviews, physicians came up with the same price point, indicating that a PGx test, under $100, would be more inviting for them to routinely use in their practices and would have "little pushback." | Out-of-pocket cost for the patient is still one of the major barriers especially in regions serving underserved patients. Outcomes data and cost–effectiveness estimates are needed, but these data need to include impact over the course of a patient’s lifetime, not just during one episode of care or a limited 12 month period of time (a year time frame is often used to measure impact by health insurance providers). Estimation of long-range impact is needed to demonstrate to health insurers, policy makers, physicians and patients that PGx testing should be an accessible test routinely used in primary care. |
| Cost of PGx testing  Williams et al, 2016 | One provider summed up the potential for all of these barriers: “I mean it matters like how expensive is the test and how long, is it going to take three months to come back after it got sent off to wherever, the only lab in the country that processes those tests or something like that…as long as it wasn't a huge cost or take a really long time or huge burden on resources from a lab standpoint um then yeah, I think it's another aspect of the clinical decision making that would help inform us.” Another said, “Given cost issues uh why wouldn't you use the science that's available to make the best decisions?” | Providers …. expressed concerns regarding potential pragmatic barriers, such as cost… …these findings indicate that, for primary care providers, the perceived utility of genetic testing to guide prescription of medications for alcohol use disorders is likely to be dependent on the benefits and ease of the testing outweighing its costs, as well as comfort with treating alcohol use disorders.  Providers described several potential pragmatic or logistical barriers to use of pharmacogenetic testing. These included cost, turnaround time, and availability of laboratory facilities in which the test could be conducted. |
| Cost of PGx testing  Chase et al, 2017 | “Cost concerns appeared to be more frequently measured by the community clinics."  “It‘s the cost containment. I probably would not [use genomic testing] if there wasn‘t a huge difference in patient outcomes.” “I don‘t even know if MediCal [state insurance] covers things [DNA testing for breast cancers] like this.” | Cost concerns - Not only were the additional tests viewed as adding additional cost for limited value, there was also the questions of who would pay for them: |
| Cost of PGx testing  Frigon et al, 2019 | “Who will pay for this? The government? Will it be covered? Will the taxpayers agree with that?” (Pharmacist, group 1). Interestingly, patients seemed to be more inclined to pay for those tests. One of them said: “We have a financial concern but, above all, we want to be healthy,” (Patient, group 2).  One of them said: “We have a ﬁnancial concern but, above all, we want to be healthy,” (Patient, group 2). | Cost of PGx testing was seen as the greatest reluctance to its implementation for most of the participants interviewed. In fact, participants highlighted the fact that the decision related to the cost of those tests is one that needs to be taken by the society, as specified by a pharmacist:  Although the cost of PGx tests was perceived as a main barrier to the implementation of PGx by the participants in this study and many others, it is no longer considered as such. In fact, the development of multigene PGx tests considerably reduced the cost of PGx testing.  Interestingly, patients seemed to be more inclined to pay for those tests. |
|  | Cost of PGx testing  Harding et al 2019 | Patient that had a family history of... a genetic abnormality leading to a clotting disorder. I sent them out for the test and … it would have been $300 to the patient….A lot of [conditions], even if they come up, aren’t relevant to us as primary care physicians because they just aren’t on the public funds. [Patients] have to be referred to the hospital to be tested. (FG1)  We talked about [a resource] years ago, with the family health team, but the funding just fell apart. But [if] you had somebody that [could] check out [information sites on the web], make sure it’s valid information, [keep us] up to date…. (FG2)  I have come across patients that have been reluctant to travel … for a consult. (FG2)  There’s this phenomenon in smaller communities where, when certain services aren’t available for along period of time, you learn to get along without them….The availability of the service doesn’t necessarily mean more people will get better…. (FG2) | Systemic barriers included access to resources such as trained staff and up-to-date materials, costs to patients for community-based genetic testing, and access to timely communication from referrals about follow-up plans especially for rural PCPs. |
|  | Cost of PGx testing  Lee et al 2017 | ““There must be other information attached to whatever they found that made me genetically different from other people.”  Shouldn’t it be automatic when you go to the doctor, they try and do everything possible for a person?”  How expensive is it? | Participants asked about issues such as cost of the test and why the test was not routinely done. |
|  | Cost of PGx testing  De Marco et al, 2010 | Negative – attitude towards genetic testing  ‘I think that’s a win-win for everybody, but probably so cost prohibitive that couldn’t even be done in the near future, on any regular basis. But, sounds good.’ (FG4)  But, even if … you have private healthcare insurance … and the doctor wants to do this genetic testing to see whether that works best for you or not. The health insurance company may decide that it’s not necessary, and it’s too expensive, and they want to do the old trial-and-error way.’ (FG2) | White focus group members also agreed that insurance companies might not pay for a procedure to determine the best medication because of high costs.  …participants appeared to be most concerned about the receipt of inferior medications and expressed general mistrust of the motives of the medical community while white participants were concerned about cost.  … African Americans were concerned that these new technologies would cost more than they could afford to pay out-of-pocket while whites worried that the high cost meant that insurance companies would not cover medications prescribed via this method.  The white focus groups held positive views on genetic testing but expressed concern that the practice would be too expensive to be accessible.  … participants felt that, while promising, the use of genetic testing to personalize medicine might be too expensive to be accessible to the general public. |
|  | Cost of PGx testing  Unertl et al 2015 | “I mean it’s a huge financial burden on patients to make the change. So we have to prove that it actually changes outcome.” | Clinicians reported that making medical decisions related to pharmacogenomics data involved a complex effort to balance cost, risk, and benefit. Alternative medications suggested by the literature and adopted by the program for use within CDS could create higher out of pocket costs and new safety concerns in addition to the promise of improved efficacy. Clinicians discussed the challenges inherent in integrating program guidance with the social situation of the patient and uncertainties with how much genome tailored therapy would improve outcomes. |
|  | Cost of PGx testing  Rigter et al, 2020 | “It should be clear, practical and applicable, otherwise it won’t happen.” Pharmacist, FG3, 5:29 | Another impediment to the routine application of pharmacogenetics surfaced when discussing reimbursement. It was expressed that potentially investments are required in a different silo of health care than where the return on investment will appear. |
|  | Cost-effectiveness  Rafi et al 2020 | The balance between financial costs, cost-effectiveness and opportunity costs was mentioned by many participants:  ‘If all these things add up into patient benefits more than other interventions of a similar opportunity costs and similar financial costs, then good. But I wouldn’t want to [adopt it] just because it’s a wonder of biotechnology’ (R11, GP academic), and: ‘I think for primary care the key issues are going to be clinical utility and cost effectiveness. There are some barriers in terms of commissioning at the moment, and the way commissioning is siloed is going to be one of the main barriers and those are one of the main question marks over pharmacogenomics before it’s mainstream’ (R9, GPSI genetics).  ‘CCGs at the moment would be hugely concerned by the workload… it’s a major workforce crisis across the country and struggling to provide enough appointments to see people at the moment, and the thought of having extra work for GPs….’ (R1, a RCGP medical director).  ‘The Dutch Pharmacogenomics working group have published guidelines for the clinician based on genotype’ (R8, Scientist).  ‘I think it will be more important for things like anticoagulants, side effects, cancer therapies, less so for antihypertensive and statins’ (R5, Public Health  ‘to be able to prescribe medicines with a confidence that [it brings]‘ (R4, informatics expert), and ‘To have a better outcome, target people more effectively’ (R1, GP Principal). ‘Anything that would help efficacy, it would definitely have the potential to be taken up by GPs.’ (R9, GPSI genetics’. | Issues such as commissioning decisions based on cost-effectiveness were considered to be really important.  With current workload pressures in UK general practice, it was clear that incorporating genomics in practice with the potential benefits was welcome provided the implementation considered cost-effectiveness as a priority.  Issues such as commissioning decisions based on cost-effectiveness were considered to be really important. The balance between financial costs, cost-effectiveness and opportunity costs was mentioned by many participants:  However, the current working environment was not considered ideal:  Many felt that approaches to implementation built on established models would be crucial. One felt that the UK could learn about implementation from countries with differing healthcare systems.  Many interviewees discussed the value of testing in primary care, including examples of application, improving efficacy whilst reducing toxicity and confidence in the use of such approaches. There was some discussion about how pharmacogenomics could offer value, and it was generally deemed to be dependent on the available expertise:  There was general agreement about the potential of using a pharmacogenomics approach:  This point was important and relevant to the discussion about supporting implementation into practice. |
|  | Cost effective  Harding et al 2019 | Value of genetic care  We need to know what conditions are actually cost effective to screen for, because if we can prevent or manage then outcomes are better….You have to look at the big picture… is the test expensive?(FG1) | Although knowledge about the genetic basis of a condition was considered beneficial, considerations about the interpretation of genetic test results, clinical utility, cost-effectiveness, and communication strategies were areas that PCPs felt needed additional clarification. Rural and urban PCPs had similar perspectives about the value of genetics in primary care |
| Cost concerns | Who pays?  Haddy et al,2010 | "Who should pay?  The only arguments against the “government pays” model were the following:  Screening the whole population's genes (approximated in the focus group as $1000 per person) was a criminal waste of money. (Group F)  Tests must be elective—I have never agreed with total government control of knowledge, even if it will help me and my family. (Group F)  Genetic tests not directly related to disease diagnosis or drug choice—If you go to the doctor to determine things now, it's covered, as should genetic tests be covered. If it was a genetic screen for offspring of a certain type, that's different, and we should pay individually. (Group C)" | Who should pay?  Most participants indicated that they felt genetic testing should be funded by the government (ie, Medicare), because the information would ultimately reduce the cost to the community, for example, reducing sick days, minimizing adverse drug reactions, reducing drug wastage, and decreasing doctor visits. The “government pays” model was seen to minimize potential inequity between the low and high socioeconomic groups if only those who could afford the test received improved medical care.  “Significant barrier that needs to be investigated is the determination of an effective funding mechanism, to ensure equity of access to PGx approaches.” |
| Who pays?  Chase et al, 2017 | Cost concerns  “It‘s the cost containment. I probably would not [use genomic testing] if there wasn‘t a huge difference in patient outcomes.” “I don‘t even know if MediCal [state insurance] covers things [DNA testing for breast cancers] like this.” | Cost concerns  Not only were the additional tests viewed as adding additional cost for limited value, there was also the questions of who would pay for them:  Cost concerns appeared to be more frequently measured by the community clinics. "  *Costs: With effective data transfer from other institutions a*  *genomic test can be done once and shared across multiple*  *organizations, thus minimizing costs. There are already CDS implementations that have significantly reduced duplicate lab test, similar strategies can be used for genomic testing [15].* |
| Who pays?  Unertl et al 2015 | “Patients do not want to pay for testing particularly if it's not… if they don't see upfront the benefit of it. I think it's going to be harder to convince people that that is added value.” | Some clinicians expressed reservations regarding whether patients would be receptive to genetic testing once it was charged to their insurance plan and they were responsible for co-pays and deductions. For example, one specialty care provider stated, |
| Who pays?  Issa et al 2009. | ‘Some illnesses that, even for high cholesterol, I don’t think I would test for that. But as it gets more serious, it’s more likely that I would have it done.’ (FG 4) | Willingness to Pay  A number of participants expressed willingness to pay out-of-pocket for testing provided that pharmacogenomic-based testing could offer valid and reliable information that would influence treatment decisions. It should be noted that although willingness to pay is generally considered a structured health economic concept, in this study we are limiting use of this term to the more commonly accepted lay understanding derived from the questions, ‘Would you be willing to pay for pharmacogenomic testing?’ and, ‘How much would you be willing to pay for pharmacogenomic testing?’ Not surprisingly, willingness to pay was dependent on the severity of the disease or condition in question, with patients arguing that they would be willing to pay more for pharmacogenomic testing that would inform decisions regarding treatment options for colorectal cancer than for testing to inform decision-making regarding prescribing options for hypercholesterolemia |
| Cost of insurance | Insurance coverage  Lemke et al, 2017 | “Then of course that becomes a challenge of what you have to prove to them [insurance companies] in order to show them that a patient would benefit in order for them to cover. Are there any instances where insurance companies cover, can you answer that, or no?” | Another practitioner (P15) commented about test benefit and justification for insurance coverage: |
| Cost of insurance | Insurance coverage  Frigon et at 2019 | The insurance company will not be willing to pay anymore. You won’t be insured for depression because you are a slow metabolizer,” (PCP, group 2). | Concerns about insurance companies having access to PGx results were also mentioned by all groups interviewed: |
| Cost of insurance | Insurance loading (paying extra premiums based on personal medical data)  Rafi et al 2020 | ‘obviously it has implications for life insurance’ (R16, Clinical fellow).  ‘I suppose the genetic component that needs explaining is the repercussions for the family, any sort of genetic information can’t be seen in isolation from the family’ (R6,GP academic).  So I would want to put that in, it’s owned by society’ (R4, informatics expert), and: ‘there is social disparity in requesting of (genetic) testing and accessing the testing and that somehow that knowledge could have an effect on family relationships. I think the issues around genomic data is broader, and I think that’s around the impact it has on other people and someone’s future health’ (R2, Clinical Lead). | Many GPs were concerned about insurance loading for relatively minor conditions, and that genomic data may be used to make such decisions around insurance premiums that could have potential repercussions for family members.  Genomic information was generally considered to be different to other forms of clinical information. For example, ‘insurance loading’, i.e. paying an extra premium based on personal medical data is something that worries both patients and GPs on behalf of their patients, and was frequently discussed… Of importance was how many GPs anticipated insurance loading for what seemed relatively minor conditions.  The familial nature of genomic data was also frequently highlighted….  The tension between ownership of personal and family information and ‘societal’ ownership seemed problematic: ‘  **Reflections like these highlight the perceived familial importance of genomics and the considerations to be taken into account around sharing.** |
| Cost of insurance | Insurability and costs  Issa et al 2009 | "‘Who gets that information? I mean, that guy that’s paying the bill, the insurance company is gonna have full access.’ (FG 1)  ‘But the insurance companies ought to get on board. If we can cure your high blood pressure by finding the right pill, even if that pill costs 50 bucks a day, versus not finding it and not doing anything, and then you having a massive stroke, need 6 months of rehab and have to renovate your house so you can get around, the insurance companies ought to get on board. And say, “We can save ourselves a pile of money by finding out now how to treat him to prevent that.” ’ (FG 1)  ‘Ok, so maybe the testing is expensive but over a course of time you wouldn’t be going through the cost of the different drugs, the cost of the different office visits, so it might end up balancing out or saving money in the long run.’ (FG 2)  ‘If the insurance company is paying for it, the insurance company has the right to know.’ (FG 1)  ‘Let them know I had the test, I mean, they have to know to pay, but they don’t need to know my results.’ (FG 2)  ‘We know that the insurance companies don’t dictate what’s covered, it’s your employer that dictates what’s covered. Is your employer going to sit down and restrict access to this test because of the cost associated, and what that would mean in formularies for the pharmacy and access?’ (FG 4)  Will this affect insurance/employment? “If that were to be shared with the wrong people in the future, could that impact my insurance? Employment? … I trust you guys.” (PGx) | Discussion surrounding issues related to insurability and costs was also animated in all the groups. |
|  | Undetermined reimbursement for test and consult  Van Der Wouden et al, 2020 | “I don’t mind [the lack of reimbursement] in the experimental phase, but at a certain point, if it becomes more daily practice, then I think there must be something to compensate for [our time].” (P8:43)  “If it starts becoming routine practice, then yes, I would think it would be logical to receive compensation for the consultation—that our time is reimbursed by the insurance.” (P9:28)  “Well, what I really find a major obstacle is that we are not compensated for the consultations. When I look at how much energy we invest here, we get nothing at all for it. I think that is really a major obstacle because that is not feasible of course.” (P12:39) | All pharmacists reported the lack of reimbursement of the actual PGx test and lack of reimbursement of the time spent by pharmacists to record and act upon the PGx recommendation to be major implementation barriers.  Regarding the costs of the actual PGx test, many pharmacists felt strongly that the test costs were currently too high. The reimbursement status of PGx testing was unclear for the majority of pharmacists. Some believed it was covered by deductible expenses or that reimbursement was included in healthcare insurer’s optional insurance packages, while others believed that the patient had to pay out of pocket for testing. For some pharmacists, this uncertainty was a reason not to request testing outside the study setting, as they did not want to risk unplanned costs for the patient.  Pharmacists also felt strongly that the time they spent on recording and interpreting PGx test results should be reimbursed. One pharmacist noted that they did not mind the lack of reimbursement in a study-setting. Yet, reimbursement for pharmacist time would be imperative for routine implementation. Another pharmacist suggested a possible reimbursement route to be one comparable to the available reimbursement of medication reviews. Many pharmacists stated a number of approaches in acquiring reimbursement for PGx testing. These approaches included **advocacy from professional organizations, generation of convincing evidence for patient benefit and cost-effectiveness of a PGx panel test, a decrease in PGx testing costs, and increased PGx testing in routine care**. One pharmacist compared reimbursement of PGx testing to blood group typing, suggesting that as PGx testing becomes more routine and common, insurers will reimburse it over time. |
| Limitations | Limitations/implications of genetic testing  Harding et al, 2019 | It does take quite a bit of time…a lot of time counselling patients…and if you were to think about how many other syndromes and conditions…might arise to start counseling…not to say that we shouldn’t be doing it… (FG1)  I think things change quickly and we’re not always aware of…which genetic tests…we can do…I would not know what to order… I don’t think we have a good enough understanding, at least I don’t, of genetics. (FG2) | Systemic barriers included …. access to timely communication from referrals about follow-up plans especially for rural PCPs.  Perceived barriers to patient uptake …… limitations of genetic testing…. and implications of results. |
| Limitations | Concerns about consenting to a pharmacogenomic test  Lee et al, 2017  (repeated in accuracy of test, ancillary findings, cost and insurance) | “How accurate is this genetic testing related to medications? Is there enough track record? Is it on target?”  What will my options based on the PGx results?  What is the significance difference between the drug treatments?  Ancillary findings “There must be other information attached to whatever they found that made me genetically different from other people, and I want to know anything that is potentially understood based on that test…” (PGx)  How expensive is it?  Why isn’t this routine procedure? “Shouldn’t it be automatic when you go to the doctor, they try and do everything possible for a person?”  Will this affect insurance/employment? “If that were to be shared with the wrong people in the future, could that impact my insurance? Employment? … I trust you guys.” (PGx)  “…the television, if you see a certain medication, that you’re taking, or you’ve been prescribed to take, and they’ll say, real fast: ‘Side effects of such and such…’ Wait a minute, hold on, I’m gonna be dead by taking this stuff…or I’m gonna be crippled or something if I take this medication.”  “…if I was gonna do this genetic testing it would have to be over more grave circumstances…if I don’t do it, I’m gonna die.” One traditional care participant was skeptical of physicians’ knowledge of medicines as he felt like a “guinea pig” being tested with new medicines, while other participants felt overmedicated by physicians who kept adding new medications. | Both groups wanted to understand their underlying condition that prompted the pharmacogenomic test and subsequent prescribing of the pharmacogenomic drug. Participants were also concerned if pharmacogenomics would affect their insurance coverage and employment.  Unique concerns of the pharmacogenomic group included questions on accuracy of the test …  Some participants expressed deep mistrust in pharmaceutical companies for deemphasizing the serious side effects of their advertised medicines, as conveyed in this comment:  Another representative quotation from a traditional care participant was this: |
| Limitations | Population level benefits limited by reducing target population  Williams et al 2016 | One provider said, “it still could be…that the person [could] not have the genetics, [and] it [the medication] would work fine.” That provider went on to conclude, “I’d probably still try it on everybody and then if it works, it works.”  Another said they would likely try the medication regardless of results of the genetic test because, “I mean, I imagine in that cohort of people who are not [identified as] responders [based on test results], there were still a decent number of responders, right?” | Providers described several potential drawbacks regarding use of a pharmacogenetic test to guide treatment decisions. These included the possibility that the population-level benefits of pharmacotherapy may be limited by reducing the target population for its receipt. |
| Ancillary findings | Dealing with ancillary findings  Haga et al 2012 | ‘‘In a situation where it’s the Alzheimer’s, then I think you have to have a discussion with the patient ahead of time, before doing the testing, because there is a risk to having that knowledge.’’ [Male-PCP-FG#3] | …many PCPs felt that ancillary risk information would scare patients, they felt that it was their duty to disclose this information, particularly if the condition was treatable. However, geneticists felt that it was not always necessary to disclose the presence of PGx ancillary risk information to patients and that the decision depended on the type and severity of the disease as well as its penetrance. |
| Ancillary findings | Dealing with ancillary findings  Lee et al 2017 | “There must be other information attached to whatever they found that made me genetically different from other people.” | …question of ancillary information discovered, as illuminated in this comment: |
| Time constraints | Restricted time constraints  Park et al, 2006 | "It puts more burden on me to have to get the test results and make a phone call." | Physicians expressed concern that integrating genetic testing into their practice would add to their already **restricted time constraints** and that the test might provoke patient anxiety, leading to patient requests for additional genetic tests that might not be appropriate. Many physicians would be dissuaded from recommending the test if they could not get immediate test results or provide the test at their own office. |
| Time constraints | Time constraints  Lemke et al 2017 | “A lot of times when people think genetic testing, they think this is going to show them that they’re going to get cancer or whatever. We have limited time to be explaining this along with everything else that we talk about in our exams.” | …**time constraints** as a challenge and the need for an in-office follow-up appointment to discuss results. |
| Accessibility | Accessibility of PGx test results  Haga et al 2012 | ‘That may even make sense to put it on our medication portion of our EMR, under the allergy section..So anybody going to add a medication would see that up there in bold up the top.’’ [Male-PCP-FG#3] | …recognized the value of convenient access to PGx test results, believing that due to its importance, PGx test results should be stored somewhere easily accessible to other healthcare providers as needed. Pharmacists, in particular, may beneﬁt from having access to a patient’s PGx test results. |
| Accessibility | Easily accessible personalized med tools  Carroll et al 2016 | “Well I guess for me it would be point of care, it’d be right there … right in front of the patient … either online or downloadable … so that there’s a decision-making algorithm.” (FP, FG3) | Recommendations were also provided for personalized medicine resources. Primary care providers described needing tools that were easily accessible, up to date, from a reliable source, and reflecting local resources, both online and available at the point of care. |
| Accessibility | Flexible testing options  Lemke et al 2017 | “I just think some people are not technologically savvy and a simple thing, simple things become huge obstacles.” | The need for flexible testing options was described by physicians, in order to meet the needs of diverse patients. One physician (P04) described how technical issues could be an obstacle and that some patients might not be able to navigate the technical arena of going online to watch an educational video and submit payment; |
| Pragmatic barriers | Turnaround times  Williams et al | One provider summed up the potential for all of these barriers: “I mean it matters like how expensive is the test and how long, is it going to take three months to come back after it got sent off to wherever, the only lab in the country that processes those tests or something like that…as long as it wasn't a huge cost or take a really long time or huge burden on resources from a lab standpoint um then yeah, I think it's another aspect of the clinical decision making that would help inform us.” Another said, “Given cost issues uh why wouldn't you use the science that's available to make the best decisions?” | Providers described several potential pragmatic or logistical barriers to use of pharmacogenetic testing. These included cost, turnaround time, and availability of laboratory facilities in which the test could be conducted. |
| Pragmatic barriers | Turnaround time  Lemke et al 2017. | “So, I’ve been having problems. I really have not received anybody’s clinical results, as far as a notification goes, that it’s ready. I get the results of their phenotyping only and then later on I’ll find that the clinical [result] has been sitting there and it’s back, and it never comes at the same time. It comes later and it doesn’t alert us to when those results are populated.” | A delay (beyond typical 3 weeks) in receiving results was also described as a barrier in providing timely patient feedback. Difficulty with accessing the results report within the EMR was also mentioned. |
| Which patients to test | When and whom to test?  Rigter et al 2020 | “You should know: when do you want a test? Do you want it before therapy or when the therapy doesn’t work or when adverse reactions occur? Who will you test?” Pharmacist, FG1, 4:97  “I think something is going to change [… ] and that you will advise more proactively instead of reactively. Because that is a profile that is established since moment zero [… ], then you already know for the coming years what your patient is allowed to have and what not.” Pharmacist, FG2, 1:166  “The moment of testing… I think in the future we will go towards the moment a baby is born, that immediately a DNA-profile is made.” Patient, FG6, 4:2 | … protocols when to test a patient (see Figure 1) are considered essential to implement pharmacogenetics successfully.  When discussing the best timing of testing, there seemed to be a tendency to prefer preemptive testing because of the direct usefulness of the information at the moment of prescription of a relevant drug. |
| Which patients to test | Access to testing (pt view)  Issa et al 2009 | ‘But important too is: Who gets the test? Is it only people with money? Who is excluded from the test?’ (FG 3)  ‘The cost and availability. ... certain technologies may only be at certain places, like here at the medical center?  And not in more rural areas or something like that? It’s not like you can go to a community clinic with no insurance and say, “I want this test. Do it now.” ’ (FG 2)  ‘[T]here’s certain parts of the population that’s going to be disproportionately tested, you know. So maybe we’re not  looking for all the aspects that might, you know, if we might  have 5,000 West Virginia coal miners versus 5,000 innercity  Chicago youth, you know, versus 50 millionaires from  Houston.’ (FG 1)  ‘What happens if you’ve been on [a drug], and you’re doing fine, and they discontinue it?’ (FG 2) | Participants expressed doubt regarding access to testing and availability of pharmacogenomic-based diagnostic and associated therapeutics. |
| When to test | Pre-emptive testing  Rigter et al 2020 | “But if they are not going to use drugs, then there is no need to know it. You can also wait until the moment someone is going to use drugs.” Pharmacist, FG3, 5:62  “I would still argue to do it on indication alone [… ], so if you expect problems, but not standard with everybody.” GP6, 7:56 | …there was no consensus about the target population (e.g., newborns or specific subgroups later in life) and questions arose about the (cost)-effectiveness of preemptive testing. Therefore, some participants preferred companion diagnostic or reactive testing.  Deciding on most appropriate timing of testing proved complex and therefore participants expect it to be resolved at policy level, as well as clearly described in protocols. |
| When to test | pre-emptive vs reactive  Dressler et al 2019 | Doing it [pre-emptive testing] for every young patient [diagnosed] with depression would be awesome; if a Patient has a bad response right off the bat [to an antidepressant] we may lose them to follow-up” [I] would not test every patient, not pre-emptively, only if there is a good reason ... need to ensure medical necessity |  |
| Technical issues | Technical issues  Lemke et al 2017 | “I just think some people are not technologically savvy and a simple thing, simple things become huge obstacles.”  “*I actually took the kit to my patient and did the testing, because she happens to be somebody I also know, and I think if I hadn’t been there, she might have been a little rattled doing it. She’s a little older and taking care of a variety of different medical problems at once.”* | The need for flexible testing options was described by physicians, in order to meet the needs of diverse patients. One physician (P04) described how technical issues could be an obstacle and that some patients might not be able to navigate the technical arena of going online to watch an educational video and submit payment….  Having to mail in the test kit via FedEx was also mentioned as a barrier for some patients. A participant (P06) discussed how she might have to guide an elderly patient through the process, or that she might want to do the kit testing in the office setting, rather than have the patient do it at home. |
| Clinical utility | Lack of evidence - clinical utility  Rigter et al 2020 | “[… ] As long as you don’t know the effectiveness, but also the costs and benefits in primary care. I would think, that as a GP, you should be very careful in this matter.” GP5, 5:16 | Lack of evidence on **clinical utility** was mentioned as a general barrier to include pharmacogenetic dosing advices in guidelines for general practitioners.  FG interviews …indicate that currently the main barrier for implementation is the lack of insight into clinical utility of pharmacogenetics testing. Some stakeholders express they are convinced of the need to use pharmacogenetic information in primary care, but others state that necessary evidence for preemptive testing in primary care is lacking. |
| Clinical utility | Insufficient evidence of clinical utility  Van Der Wouden et al 2020 | “I still think so, yes, research has to show if it is at all cost-effective.” (P1:23)  “The insurer is only thinking about cost-benefit ratios. So we should show that its cost-effective or cost-saving so that patients do not receive ineffective means. But of course, we hope to demonstrate that in the PREPARE study. Nonetheless, those [genetic testing] prices really have to really go down.” (P12:21)  “We are still implementing in a research context, and investigating its added value. Similarly to implementing a new drug, it has to have demonstrated added value before prescribing it in the clinic. They must first prove that first.” (P5:53) | Pharmacists reported insufficient evidence for the clinical utility of a panel-approach outside of the study setting. Similar to the requirement for novel drugs to demonstrate a favorable benefit/risk ratio and cost-effectiveness, they also felt this is a strong requirement for the implementation of PGx panel-testing. In contrast, specific drug-gene interactions were deemed to be supported by convincing evidence by some pharmacists.  For example, multiple pharmacists reported that they would support the pre-emptive testing of  CYP2C19 in all patients initiating clopidogrel in their practice. Reasons stated for prioritizing this particular gene–drug pair were the relatively high prevalence of patients with aberrant genotypes and the strong evidence for patient benefit. However, practical constraints were preventing them from implementation. Additional drugs, for which PGx interactions were deemed important for pharmacists to implement, were statins and antidepressants, the reasons for this being that there was sufficient evidence and perceived patient benefit. |
| Clinical utility | Need for evidence  Chase et al 2017 | “We do that already. Like, if the patient when they come in for physicals, we ask them family history.” “nobody has actually linked any of those genetic markers to anything that we do.” | Some thought that they were getting enough “genetic data” by just reviewing the family history, while others cited a lack of trials showing significant benefits for primary care providers: |
| Clinical utility | Utility dependent on prognostic accuracy  Williams et al 2016 | For instance, one provider said, “If it's an accurate test that really identifies pretty well who might really benefit from treatment, um, then I think it would be useful…I think it would really depend on how much better, compared to someone who doesn't have that gene, what the difference is and how meaningful that is. I mean, I don't know enough about the test to be able to really, to say.” Another said, “I probably wouldn't necessarily use the test very often since it's not a yes and no, it's a ‘could be better’. So it still could be that the person [could] not have the genetics [and it would] work fine.” | the utility of a genetic test would be contingent upon test performance characteristics or other aspects of the clinical scenario in which it was used. First, providers acknowledged that utility would depend on prognostic accuracy (i.e., accurately predicting the relative likelihood of medication response) based on the outcome of the test. |
| Clinical utility | no incremental utility over standard care  Williams et al 2016. | One provider said, “It would be helpful but it's not—I don't think it would change [my prescribing practices] that much.” Another shared, “If I was leaning toward prescribing it anyway, and the patient was interested in that particular medicine, then I wouldn't order the test ‘cause it wouldn't change my outcome.” Some believed that “just trying the medication may be simple enough,” without the genetic test, particularly if the medication had a favorable safety and side effect profile. As one provider explained, “The side effect profile of naltrexone, I feel like, is pretty reasonable…so I think the more toxic the treatment, the more something like that [pharmacogenetic testing] would weigh into your decision [to prescribe].” | Some providers expressed uncertainty regarding use of pharmacogenetic testing because they believed it would provide no incremental utility over standard care. Some stated that results of such a genetic test would not influence their therapeutic choices. |
| Clinical utility | Clinical utility of tests  Williams et al 2016 | One provider explained, “It's one other tool that would help in the selection process, it wouldn't be the sole tool that I would use to decide whether or not to use the medication in an individual.” Another shared, “If there's a significant difference in treatment outcomes based on the data and the data would impact your prescribing pattern, then it would be another tool in your kit.” | While no substantial ethical concerns arose in response to the interview questions, providers described a need for more information prior to judging the potential clinical utility of such a test. Specifically, participants wanted to understand the safety and prognostic accuracy of the hypothetical genetic test, and to understand exactly how results could be interpreted. Finally, they believed that genetic testing would be “another aspect of clinical decision making that would inform [them]” though it would be unlikely to be the only factor in clinical decision making. |
| Clinical utility | Clinical utility of tests  Issa et al, 2009 | ‘This is all based on the premise: does DNA really tell us everything? I mean, that’s really a core thing. Does your DNA determine your absorption?’ (FG 1)  ‘How does it work for me? I would want to know how it would work for me. How is it going to work for me as opposed to something else you’ve shown through testing that isn’t going to work for me?’ (FG 2)  ‘Well, the only thing I really care about is how accurate the test is.’ (FG 4)  ‘I would want to know, what are the chances of getting a false positive or a false negative? Telling you that you can take this drug, and then the test be wrong. What are the chances of that?’ (FG 2)  ‘Say if there was only a 50:50 chance that the test results were true. I mean, I would think I would need at least 70:30.’ (FG 2)  ‘I’d be more concerned about where I was having the test run. I mean, what is their training, their experience?’ (FG 4)  ‘What we need to know is how many tests did they run before they sent the official results to the doctor? Because if you can’t get the same results at least 3 times, then there is something wrong with your procedures. ’ (F G 3)  ‘I think these tests should be really monitored. I mean, I think these tests would be the kind to be double-checked on. I mean you would do it and make sure you got the same results 2 times.’ (FG 2) | There was much discussion in all the focus groups surrounding a number of potential barriers and risks that the participants identified as being of paramount importance. In particular, as some of the quotes below demonstrate, **analytical validity, clinical validity, and clinical utility** of the information provided by testing to improve health outcomes were of paramount concern. |
| Clinical utility | Accuracy of the test  Lee at al, 2017 | “How accurate is this genetic testing related to medications? Is there enough track record? Is it on target?” | Unique concerns of the pharmacogenomic group include questions on accuracy of the test … |
| Guideline development/  accessibility | Accessible PGx guideline  Frigon et al 2019 | “[...]there are some studies, but we never heard about those. We never read them, nobody ever told us about them. Honestly, we’re waiting for a guideline or a deﬁned clinical approach,” (PCP, group 2) | Most groups of healthcare professionals mentioned that accessible PGx guidelines were needed before PGx testing could be used efﬁciently…  PCPs and pharmacists interviewed in this study also mentioned the lack of clinical guidelines as being an obstacle to the adoption of PGx. Yet clinical guidelines supporting the development of PGx have been developed by some institutions such as the Clinical Pharmacogenetics Implementation Consortium [52]. This finding might suggest that current clinical guidelines are not appropriately communicated to frontline healthcare providers, such as PCPs and community pharmacists. Easily accessible clinical guidelines should be provided to healthcare providers with details on the various steps of PGx test prescription (when to prescribe a PGx test, how to do it, where to send the samples and how to manage PGx test results). |
| Guideline development/  accessibility | Lack of genetic referral guidelines  Carroll et al 2016 | One participant described the referral process as, “You feel like you’re referring to the abyss.” (FP, FG2) “I speak to oncologists on the phone often, but I’ve never spoken to somebody from genetics before. I wouldn’t actually know where to start … I don’t know anybody in that field.” (FP, FG4)  “What do clinics need?” was a common question highlighting PCPs desire for detailed referral guidelines. | Primary care providers described frequently being unsure when a patient should be referred and, consequently, most referred liberally to genetics clinics. They reported it as erring on the side of caution but sometimes described “referring willy nilly” owing to lack of knowledge of referral guidelines. Participants recounted primarily positive experiences, with genetics clinics seen as “reliable go-to places” that provide outstanding care. Primary care providers appreciated genetics consultation letters and described them as an excellent source of education. However, they observed that relationships and communication patterns were different from those with other specialists. Few personal connections exist and many never connected directly with genetics specialists.  Another difference noted was that genetics clinics sometimes declined referrals, generally because the family history did not meet guidelines for genetic testing. When this occurred, PCPs reported no guidance on what should happen next and were left wondering about patient management. Primary care providers described feeling somewhat criticized because they had flagged the patient as concerning enough to require referral. ..PCPs’ desire for detailed referral guidelines. |
| Guideline development/  accessibility | Guidance document  Dressler et al 2019 | ”Who will really benefit from testing” (P2) ”Who to test is still a question” (P3) ”Even soft guidelines of who to test would be helpful” (P1) ”What is the drug–gene pair with highest likelihood of causing problems” (P1) | All PCPs agreed that the lack of guidelines was a barrier to adoption both before and after participating in the pilot. Although the PCP training included a discussion of CPIC, including how to use the online guidelines [26], our physicians wanted more situational and practical guidance. |
| Guideline development/  accessibility | Infrastructure inefficiencies  Van Der Wouden et al 2020 | “Well, I think it’s really important that clear and practical guidelines are incorporated into our EMR.” (P15:26)  “Not all recommendations are very clearly interpretable.” (P3:2)  “The DPWG recommendations really help a lot, even though they are not always very clear. So for example  ‘avoid clopidogrel’, well with TIA you do not have many alternatives than clopidogrel, and dipyridamole is unavailable at the moment - sometimes I want the guidelines to be more concrete.” (P15:9)  “Well, what I find the biggest obstacle is the limited automation in the pharmacy system.” (P11:37)  “The best thing would be if we received the data from the LSP from the lab, of course.” (P13:32) | Pharmacists considered the management of gene-drug interactions as a routine part of medication surveillance. They felt responsible for the recording of PGx results and the integration within their clinical workflow, to the same standards as that of acting upon other drug-drug interactions. Overall, pharmacists were not satisfied with the performance of the CDSS. Primarily, they reported that recording the test results for the 12 pharmacogenes in the EMR was time-consuming and error-prone. Moreover, a widely used computerized pharmacy system only supported the recording of 10 contra-indications per patient.  As a result, pharmacists were unable to record the 12 reported phenotypes as contra-indications and therefore information was lost. All pharmacists considered it their responsibility to record the results, as opposed to delegating it to pharmacy technicians. Additionally, the majority of pharmacists incorporated a quality check by a second pharmacist to avoid recording erroneous results. This was especially important to them because they noted that genetic test results persist throughout life. One pharmacist suggested a perfect IT system would automatically import the results from the performing laboratory, for example utilizing a nation-wide EMR sharing infrastructure.  The DPWG recommendations were considered clear and easily interpretable overall. However, a number of reported barriers were associated with clarity and interpretability of the SLCO1B1-statin and CYP2D6-metoprolol recommendations. A number of pharmacists reported DPWG recommendations, which they found unconcise and unclear. For example, the DPWG recommendation for the CYP2D6 poor metabolizer-metoprolol interaction has two potential actions which also depend on the indication of metoprolol use and the symptoms the patient may have experienced. **As a result of this perceived unclarity, pharmacists reported to be less confident in discussing the results with the treating physician and less likely to adhere to the recommendation.** |
| Decision-making | Another aspect of clinical decision making  Williams et al 2016 | One provider explained, “It's one other tool that would help in the selection process, it wouldn't be the sole tool that I would use to decide whether or not to use the medication in an individual.” Another shared, “If there's a significant difference in treatment outcomes based on the data and the data would impact your prescribing pattern, then it would be another tool in your kit.” | ….they believed that genetic testing would be “another aspect of clinical decision making that would inform [them]” though it would be unlikely to be the only factor in clinical decision making. |
| Guiding primary care medical decision-making  Lemke et al 2017 | One of the participants (P14) described his PGx testing experience with the take-home kit: “Oh, it is very useful. It was easy. And when I’m explaining it to patients I tell them exactly how to do it, not, ‘You’ll get a kit and then the instructions will be there.’ I tell them, ‘You’re going to swab for thirty seconds here, thirty seconds there, a minute over here. You’re going to let it [the sample] dry.’ I give them the full details.”  This provider discussed how going through his own PGx testing and results process was helpful to him in explaining patient results. He said: “I was my own test case, so I think that was a very good way to introduce physicians to this process, to actually do it. When you do it, you certainly learn a lot more. Then, you go through the report. Certainly makes it easier for me to explain a patient’s report when I have seen my own.” | Guiding primary care medical decision-making  Most participants felt that undergoing direct access PGx testing themselves was a useful teaching tool and that it was helpful for them to have first-hand knowl­edge of the testing and resulting process. To them, this translated into providing better and more concrete information to patients regarding testing and decision-making. |
| Individualize medication treatments  Lemke et al 2017 | One provider (P12) reported: *“I think it will be specific to certain patient populations… patients that I see that’ ll benefit from it are probably patients that are on some psychiatric drugs, antidepres­sants, SSRIs are a big one.”* Another participant (P14) described how having results from PGx testing could be beneficial in his patient population: *“One of the most valuable parts of this [testing] I think is the blood thinner. That’ ll be very valuable if they’re in the emergency room getting a stent and the decision is trying to be made as to which blood thinner they get put on. I think they are going to benefit tremendously from that bit of information.”* | Primary care physicians described how PGx testing could help them individualize medication treatments for their patients and, for many, how there is a context-dependent value for specific conditions or categories of patients. The most common indications for offering PGx testing that physicians mentioned were for medi­cations used in psychiatry, cardiology, oncology and for pain management |
| Informed decision making  Lemke et al 2017 | *I think it can help both physician and patient make informed decisions together, based on likelihood of responding poorly to medications -based on the genetic profile.”* | Some primary care physicians indicated that they had a number of patients who are highly motivated to learn more about their health in general, and that these individuals would likely be interested in testing. One physician mentioned pre-emptive testing and how PGx testing could be offered during an annual exam. Another primary care physician (P01) articulated how through PGx testing, a mutual benefit of informed decision-making can occur for both physician and patient |
| Efficient decision making  Lemke et al 2017 | One pri­mary care doctor (P08) elucidated: *“A lot of times we try a medicine and they’re only on it for two weeks, and they paid for a whole month. They’re only on it for two weeks and they had horrible side effects. Let’s toss that and move onto something else. That’s a lot of money, and time, and side effects that they don’t necessarily need to suffer from if we knew ahead of time that they weren’t going to react well to it.”* | Participants discussed the medi­cation odyssey that some patients embark on before they have a successful outcome and that this process can cause suffering, harm and increased costs to the patient. Physicians mentioned how PGx testing could make this process of medication decision-making for some patients much more efficient and save them from having to suffer and incur additional costs. |
| Follow-up  Van Der Wouden et al, 2020 | “I feel the follow-up should be a shared responsibility between pharmacist and GP. If the pharmacotherapy has changed as a result of PGx, then both GP and pharmacist should be monitoring how things are going.” (P3:10) | Pharmacists also felt that they had the capable leadership skills required for implementing PGx; being confident in their knowledge and ability to perform all tasks in the implementation chain. Interestingly, one pharmacist reported that they had been influenced by  another pharmacist, who had taken the initiative to test all patients for CYP2C19 initiating clopidogrel in his practice. This influenced this particular pharmacist to initiate a similar initiative, not only in his practice but within all pharmacies in a formal regional collaboration. |
| Increased patient autonomy  Lemke et al 2017 | One provider (P09) stated: “ *…the patients, if they’re interested, they can just go ahead and initiate it themselves [after physician places the order, patients do the test kit when and where convenient] and that just opens up doors and decreases the barriers.*” | Another value of PGx testing described was specific positive outcomes for patients. For example, some of the physicians discussed how using PGx direct access testing can foster increased patient autonomy and sat­isfaction. |
| Less fear and anxiety about trying a new medication  Lemke et al 2017 | “*The reassurance to me is key and there’s a psychological benefit. If I knew that drug A would be better for me than drug B, there’s a psychological component to saying, ‘Okay, my doctor knows that drug A is going to be effective for me or that it’s not going to be harmful for me.’ Both for the patient’s reassurance and certainly for mine.*” | Another positive outcome mentioned by some of the primary care providers was psychological benefit to patients. A few physicians discussed how findings from PGx testing can offer reassurance that the medication plan should either stay the same or be changed. Test findings were described as having important explana­tory benefits for patients, who were searching for rea­sons of why medications worked or did not work so well. One physician (P13) brought up how PGx find­ings allowed the patient to have less fear and anxiety about trying a new medication: |
| Valuable tool in the future  Lemke et al 2017 | “*For the general population, who is not going to be on pain meds or any of the antidepressants, anti-anxiety agents, I’m not sure how beneficial it’s going to be.*”  However, one provider (P12) speculated that its future utility may increase: *“But in the future, maybe every patient, it could be offered to them.”* | Although the majority of participants described value and utility of PGx testing in positive terms, a few providers mentioned that they did not think PGx test­ing was useful in their patient population and/or that PGx testing may not be useful now but will be more valuable in the future. For example, one practitioner (P13) commented: |

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| **Social influences**  **Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours.** | | | |
| Employment discrimination | Genetic information not shared with employers (pt. view)  Haddy et al, 2010 | There is a stigma with mental health; therefore, I may be worried about letting out information to others as it may influence attitudes. With diabetes, it doesn't matter, in fact there's an advantage. (Group A 18-36 years)  If it was important for your health or public health then the employer may need to know—it would have to be on a “need to know” basis…. I wouldn't want to have to disclose things at an interview as it may alter if you get a job. (Group D 36-60 years) | Participants' attitudes toward family and friends knowing medical and genetic information depended on the illness; for example, mental illnesses were reported to be discussed only with very close friends and family, if at all. Other conditions, such as diabetes and asthma, were reported to be discussed freely. Sharing genetic information to help prevent disease was acceptable, for example, genetic testing for cystic fibrosis, haemophilia, and Huntington's Disease. Group C held concerns regarding pressures placed on relationships from testing for genetic predisposition to disease, especially if symptoms may only become evident in later life.  The extent of information shared with schools and employers was also conditional on the illness. Diseases such as asthma and diabetes were more openly shared to ensure the safety of the patient. Participants were very reticent regarding the sharing of mental illness information with an employer, as they perceived there was a negative stigma attached to this condition.  A majority felt that access would depend on the medical condition- some conditions were more sensitive than others, for example, mental health issues versus asthma. |
| Employment discrimination | Genetic information not shared  Haddy et al | There are huge issues with insurance; for example, if you can determine if you will get Huntington's or whatever, there are huge ramifications. It could mean that the “perfect people” could get insured but everyone else couldn't. I would want my healthcare professionals to know [about my genetic information] but I wouldn't want it on some central database. That would be highly dangerous. It may even affect government strategies—what they give money to or not. It's a very big issue. (Group D 36-60 years) | There was a strong negative response to insurance companies having access to any genetic information. Concerns included the obligation to disclose medical information leading to lack of insurance cover and risk of exploitation by associated corporations. |
| Employment discrimination | Insurance, employment discrimination  De Marco 2010. | ‘M: Can you see any disadvantages?  R: To me just the cost like she said.  R: I think it gonna depend on, again, public or private insurance.  M: If insurance covers it?  R: Mmm, insurance, yeah.’ (FG5)  ‘I think there would still be a trust issue though with the medical community. I think that’s the, that’s the problem that we get into when we start talking about personalized medicine.’ (FG5) | White focus group members also agreed that insurance companies might not pay for a procedure to determine the best medication because of high costs. In addition, white groups, confounding genetic testing to determine drug compatibility and genetic testing to assess disease vulnerability, worried about possible insurance and employment discrimination due to discovery of a genetic predisposition for a specific disease or from simply being tested. White groups also expressed concerns about receiving clinically important information. |
| Employment discrimination | Genetic discrimination and confidentiality  Park et al 2006 | Would the government-sponsored halfway houses for drug addicts—would they require you to take this test if they find that you are genetically inclined to drug use would they go ahead and spend their resources to treat you realizing that your relapse rate is so much higher?  I would do the test and give the patient the information and throw it out.  I think with labeling and insurance companies, this is like hitting (African Americans) with a smoking gun.  No matter what we do, it’s not going to make a difference because there’s a predisposition so they’ll remove services from certain areas …  When does it become racial profiling …? | Physicians expressed elevated concerns about confidentiality and the potential for genetic discrimination. They anticipated insurance struggles for patients who tested positive for genotypes associated with increased risk of addiction. Physicians felt that the test might limit patients’ rights and worried about employers possibly requiring testing of prospective employees. The effect of genetic status on policy decisions regarding who was a ‘‘good bet’’ to treat also emerged as a concern.  Physicians echoed their previously expressed concerns regarding the potential for genetic discrimination with the addition of information about allele frequencies across racial groups.  Physicians were also very worried that racial differences in risk alleles would affect African Americans as a group, resulting in higher insurance premiums based on race.  Some physicians felt that information about racial differences in the frequency of particular alleles associated with addiction was socially explosive information, with one participant saying it raised the specter of eugenics and social engineering. Physicians also worried that information about group differences in the prevalence of alleles associated with addiction might affect policy decisions regarding which social services are provided to different racial/ethnic groups, with the possibility that some might misinterpret this information. |
| Health insurance, employment discrimination, and stigma | Health insurance, employment discrimination, and stigma  Park et al 2006 | "Her insurance could say, ‘‘Oh, here’s a smoker who’s got a genetic predisposition, and she’s failed treatment, so raise her rates, or drop her.’"  "It is the beginning of genetic profiling. We talk about racial profiling. This is a very, very serious issue.  The cigarette industry can get real cruel at times … Could they use and get a hold of this information to look at trends and patterns and then market and target [based on genotype]?" | Physicians were very apprehensive that patients who tested positive for the genetic test might have difficulty obtaining health insurance, face employment discrimination, and experience stigma. Physicians feared that health insurance companies would mandate that patients take the test and then raise premiums, deny or create obstacles to coverage, or terminate coverage for those patients identified as having a genotype associated with increased risk of addiction  Physicians were very apprehensive about telemarketers or cigarette companies exploiting the information to identify consumers who might be more vulnerable to cigarette marketing.  General impact of genetic testing   * Difficulty obtaining health insurance * Employment discrimination * Exploitation of information by commercial industry |
| Confidentiality/privacy of data | Information stored in a confidential manner  Haddy et al 2010 | What is secure? There is no such thing as secure anymore. Bury it! (Group D 36-60 years)  Is it necessary to be stored? (Group A 18-35 years) Maybe it shouldn't be stored—use it, then destroy it. Recollect it on an as-needs basis. (Group D 36-60 years)  I don't now think twice about blood test results being stored—wouldn't be any different. I trust doctors. (Group A 18-35 years)  I could keep it myself—Doctor could have on request. (Group D 36-60 years) | Participants strongly expressed a desire for medical information, both general and genetic, to be stored in a confidential manner. There was scepticism regarding the ability of information to be held securely in our current system.  Two participants in separate groups discussed whether genetic information needed to be kept at all;  Various genetic information storage options were discussed, including storage by the doctor or patient. |
| Confidentiality/privacy of data | Confidentiality of results  Frigon et al 2019 | “We don’t want everybody to know about it [results of the test], but we want professionals to know about it,” (Patient, group 2). | A large majority of patients were mainly concerned about the conﬁdentiality of the results: |
| Confidentiality/privacy of data | Storage and future use of information  Barr et al 2008 | B: Another concern is well where all this genetic results get held, do they get held in a mainframe computer somewhere (multiple voices)  A: I couldn’t give tuppence, I couldn’t give tuppence where they’re held, stored my (multiple voices)  B: Or what they used it for?  A: Or what they used it for. If it’s going to beneﬁt me and my family in the long run, then I’m all for it. I mean I would hope you know, my granddaughters are going to be tested to show that they’ve not got the gene that I may well have passed on to them. And if there’s any medication they can take when they get to a certain age that would prevent them from probably getting the same disease, I’d be really happy. I’m only sorry that I didn’t know about it sooner (English Public Group 2). | This exchange is useful, for it highlights the interactional contextual of how people react to being asked for a pharmacogenomic test. ‘A’ is forced to defend his support of pharmacogenomics by a participant who raises her concerns about the **storage and future use of test results**. Whereas he first expressed his desire to have a test to be ‘treated properly’ (with the hesitation, ‘or, is it’, which implies he may not have been absolutely certain as to the aim of the test), ‘A’ then seems to respond to the possibility of these concerns by conflating susceptibility and treatability and by saying that he would want his granddaughters tested to make sure they were not carriers of a gene that would pre-dispose them to his same  disease. We highlight this exchange to bring attention to the point that medical treatment is not a two-person exchange system. Pill taking is invariably a social act (Karp 2004) and it is through a network of significant others that a patient will come to question the wisdom of medicating themselves or the effects of a test on their family and friends. |
| Confidentiality/privacy of data | Disclosure, privacy, and confidentiality.  Issa et al 2009 | ‘The privacy issue’s gonna be a major priority, major priority.’ (FG 1)  ‘Who uses that information? I doubt the HIPAA act will prevent who gets it?’ (FG 3)  ‘And if they share this kind of stuff with your life insurance company, and they raise your rates on that too. I just took a test to get some life insurance, how crazy is this? And it’s a policy where you pay a hundred dollars a month and you invest the money, but you still have a 150,000 dollar life insurance, but because I come back with high cholesterol and high blood pressure, it’s affecting how much interest I get off the money now. So when I’m 55 years old, if I was in perfect health, then I get 60,000 dollars. I’m 37 now, now that I have this, I only get 27,000 dollars. I made 5,000 off my investments instead of 30,000–40,000 because of my cholesterol.’ (FG 1) | There was a considerable degree of discussion about issues surrounding disclosure, privacy, and confidentiality. |
| Confidentiality/privacy of data | Data and privacy concerns  Lemke et al 2017 | “I think people get concerned when they’re sending their cheek cells off that their DNA is getting sent in the mail and they don’t know what’s actually truly happening to it, and people think that maybe they’re getting cloned or finding out genetic information that’s going to come back and hurt them in the future in some ‘Brave New World’ situation where the government is tracking our genetic codes and that can harm them in some way. I think that’s nonsense, but I know that’s how some people think.”  “But they may bring that up and say, ‘Is this going to be available to insurance companies? And am I going to be rated higher because I have a certain profile?’” | A number of physicians described how concern with data and privacy could be a challenge for patient uptake of PGx testing. One provider (P11) commented on concerns patients may have about protection of their genetic information from the government.  Another practitioner (P14) mentioned patient privacy concerns and insurance company access to their test information: |
| Confidentiality/privacy of data | Privacy and personal pharmacogenomic information (pt. view)  Lee et al 2017 | The information should be secure but readily available.  “We’re giving away extensive information and we don’t know what it means. Right now I do this in an environment of a sense of trust.” (PGx)  “I don’t want my DNA floating everywhere.” (TC)  “I would think that any doctor who’s treating me should be able to have access to my full information.” (PGx)  “The privacy part shouldn’t matter. If that saves your life…someone else being nosy can save my life, I would really appreciate that.” (PGx)  I would like control over who has access. “I would like to be asked about it…I would just want to know, and just be able to get an OK with that.” (PGx)  “How you personally choose to share your DNA information with anybody else should be your call.” (TC)  We have no privacy. Hackers can access anything. “There is no sense of privacy; it’s all shared between insurances and other kinds of care facilities. I don’t think we have a measure of privacy, no matter what that HIPAA thing says.” (PGx) | The majority of both groups agreed genetic information was sensitive and should be stored securely, but participants in both groups diverged in their views over who could access their pharmacogenomic results.  Some participants felt any physician should have access as long as it was relevant to their practice, as exemplified in this comment:  Conversely, within both groups, some participants wanted to control who could access their information, as in this comment: |
| Confidentiality/privacy of data | Data ownership responsibility and liability  Unertl et al, 2015 | Does that information [the full range of PREDICT results] remain undiscovered if I don't actively push it to the primary care physician or can it automatically get to them so that they can use that information for the 48 other drugs that I'm not going to be prescribing?” | Providers discussed how the persistent nature of pharmacogenomics data presents new challenges related to long-term data ownership, responsibility, and liability. |
| Abuse of test results | Test information not used in a harmful manner to patients  Park et al | What does this mean for us [as physicians]? … And it has to do not only with linking behaviors or diseases with genes, or as you said, what is the penetrance of these? How many of them get expressed, is there any way to predict which patients will express this particular gene? And if they do, what are … how do we manage it? What are the drugs, what are the strategies we use to tackle this? And ethically speaking, do we really want to know?  To me, [the identification of a genotype associated with addiction] is very inflammatory whether you’re Caucasian or not, African American or not. | The additional associations with risk of addiction and race exacerbated many physicians’ concerns about their responsibility to ensure that any information generated by a test they recommended for their patients would not be used in a harmful manner to patients.  Other physicians did not feel that a 10% difference in the prevalence of genotypes between racial groups posed a particular problem; rather, the association with addiction was the most powerful barrier to integrating pharmacogenetic treatment for smoking into clinical practice. |
|  | Use of information over time  Dressler et al 2019 | ”How to stay ‘on top’ of this?” (P2)  ”Where it is standard of care, how it changes from best practice to standard of care” (P1) |  |
| Social inequalities | No social inequalities  Frigon et al 2019 | “We would not accept a medicine for the rich and one for the poor for the DNA test,” (Patient, group 2). They advocated for the tests to be accessible to everyone, like most of the public healthcare in Quebec. | When addressing the question of the cost of PGx testing, patients agreed on the fact that there should be no social inequalities with the venue of those tests: |