A close up of a sign

Description automatically generated

**Justification for the guidance and evidence review**

Appendix E

FEBRUARY 2020

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**Professional Record Standards Body**

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Community Interest Company No 8540834

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**NHS England**

NHS England oversees the budget, planning, delivery and day-to-day operation of the commissioning side of the NHS in England as set out in the Health and Social Care Act 2012. It holds the contracts for GPs and NHS dentists. The Secretary of State publishes, annually, a document known as the mandate which specifies the objectives which the board should seek to achieve. National Health Service (Mandate Requirements) Regulations are published each year to give legal force to the mandate.

**The Professional Record Standards Body (PRSB)**

The PRSB (www.theprsb.org) is the UK wide organisation that develops consensus-based care record standards in collaboration with professional and patient organisations, the healthcare IT community and relevant government departments (e.g. NHS Digital). The standards are intended for widespread use in digital health and social care records. PRSB was established in 2013 as a “not for profit” Community Interest Company.

**Document Management**

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Planned Review Date and Route for User Feedback

The next maintenance of this guidance is planned for [UNKNOWN DATE], subject to agreement with NHS England as the commissioning body.

Please direct any comments or enquiries related to the project report and implementation of the guidance to **support@theprsb.org.**

Glossary of Terms

|  |  |
| --- | --- |
| Term / Abbreviation | What it stands for |
| ABD | Advisory Board Discussion |
| ACMG | American College of Medical Genetics |
| ADASS | National Association of Directors of Adult Services Standards |
| Adverse Drug Reaction | An unintended, unwanted or harmful reaction (physiological or otherwise) to a drug or combination of drugs (known or suspected); that has occurred following situations including (but not limited to) routine clinical administration, use off-label, poisoning and medication errors. |
| AHP | Allied Health Professions Scotland |
| AHRQ | Agency for Healthcare Research and Quality |
| Allele | A variant of a gene that occurs at the same specific position (locus) on a chromosome but exists in alternative forms due to changes in DNA sequence. An individual most commonly has two alleles at each locus, one inherited from each parent. An individual with two identical alleles is homozygous for that gene (heterozygous if the alleles are different). |
| Alert | A type of notification that conveys a warning of important, time-sensitive, and/or safety information. |
| Alert fatigue | A desensitisation phenomenon that can emerge when electronic alerts are used in live clinical settings. This is thought to occur due to the sheer volume of daily electronic alerts and notifications seen by prescribers that are of limited clinical utility. An unintended consequence is that the end-user may ignore or override the alerts without consideration of the content, with significant safety implications. |
| API | Application Programming Interface |
| BAM | A binary format used for storing genomic sequence data and associated meta data |
| BHF | British Heart Foundation |
| BNF | British National Formulary |
| CDS | Clinical Decision Support |
| Clinical decision support systems (CDSS) | Computer programs that use rules and guidelines to filter, organise or otherwise process a patient’s raw clinical data into actionable evidence-based information and recommendations; delivered to the end-user at appropriate points in the clinical workflow, in order to aid decision making at the point-of-care. |
| CMIO | Chief Medical Information Officer |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| CPRD | Clinical Practice Research Datalink |
| DDI | Drug-drug interaction |
| Drug-gene association (DGA) | A pharmacogenomic relationship where the presence of specific genetic variants affects the pharmacokinetics or pharmacodynamics of a drug or class of drugs. For certain genotypes a DGA may increase the risk of serious ADRs. |
| Dispensing and verification stage | The point in the lifecycle of a prescription where the authorised preparation and supply of medicines to a named individual (usually a patient) occurs, in line with the requirements of the prescription. The role is most often performed in a pharmacy. This stage involves the correct interpretation of the intentions of the prescriber and may involve verification of this as part of the pharmacist’s legal duty. |
| DPWG | Dutch Pharmacogenetics Working Group |
| Electronic health record (EHR) | A secure and longitudinally maintained digital version of a patient’s paper medical record that is intended (insofar as is possible) as a complete repository of the key clinical and administrative data required for a patient’s care; including (but not limited to) that relating to a patient’s problems, encounters, past medical history, diagnoses, investigations, treatments, medications and workflow tasks (handover). Furthermore, the EHR may include certain functionalities so that the end-user can directly order laboratory tests and prescription medications. |
| EMA | European Medicines Agency |
| FASTQ | A text file containing a specific type of genetic sequence data |
| FDA | U.S Food and Drug Administration |
| FGR | Focus Group Report |
| FG1 | Focus Group 1 |
| FG2 | Focus Group 2 |
| FHIR | Fast Healthcare Interoperability Resources |
| GACS | Genomic Archiving and Communication System |
| Gene | A DNA sequence (contiguous or not) that comprises the basic functional unit of inheritance. The expression of a gene influences an individual’s phenotype. Every person has two copies of each gene; one inherited from each parent. |
| Genetic variant | A difference in the DNA base sequence of an individual conferring a particular allele - at a specific nucleotide position, gene, or locus - that is less common than the most frequently encountered allele in the general population. The term does not automatically imply disease and different variants have characteristics that may be pathogenic, protective, predisposing, benign or otherwise. |
| Genome | The complete set of an individual’s DNA including all of their genes. |
| Genotype | Can refer to the overall combination of genes held by an individual in their genome or the two inherited alleles for a particular gene. |
| Genotyping | An umbrella term for techniques used to determine the genotype of an individual that utilise assays to compare the individual’s DNA sequence to a predetermined reference sequence. These methods require prior identification of the genetic variants that are looked for. |
| GIM | General Internal Medicine |
| GP | General Practitioner |
| Interoperability standard | A document established by consensus and approved by a recognised body that provides guidance and rules governing the ability of multiple systems to exchange and use information. |
| Hard stop | An active alert that either completely blocks the intended action of an end-user or prevents progression in the workflow without the intervention of a third-party. |
| ID | Identification |
| IT | Information Technology |
| JGPITC | Joint General Practice Information Technology Committee |
| LUMC | Leiden University Medical Center |
| NHS | National Health Service |
| NICE | The National Institute for Health and Care Excellence |
| Point of order entry | American terminology for the point a prescription is written in electronic prescribing systems |
| Notification | A one-way communication used to convey information to an end-user. The term does not automatically imply a level of urgency. |
| PACS | Picture Archiving and Communication System |
| PRCC | Patient Representative Consultation Call |
| Pharmacogenomics | The study of how the genome influences the body’s response to drugs. |
| Phenotype | The physically observable expressed characteristics of a gene or a combination of genes at the level of the organism. For example, eye colour, height, muscle density, biochemical properties, personality traits etc. Phenotype is determined by the interaction of the genotype expressed and the physical environment. |
| PID | Project Initiation Document |
| PREDICT | Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment |
| Prescribing | The recorded authorisation (written or otherwise) for the use of a medicine or treatment by a health professional with prescribing authority. |
| Problem | Any condition experienced by a patient (such as a symptom or diagnosis) that the clinician feels is important enough to be recorded in the healthcare record. |
| Problem list | A current list of a patient’s problems or health issues, ideally with dates and stating which are active and inactive, which is intended to give clinicians a quick and accurate summary in future encounters. |
| PRSB | Professional Record Standards Body for health and social care |
| QA | Quality Assurance |
| RCGP | Royal College of General Practitioners |
| RCPCH | Royal College of Paediatrics and Child Health |
| RCPsych | Royal College of Psychiatrists |
| RCSE | Royal College of Surgeons of England |
| RCT | Randomised Controlled Trial |
| RPS | Royal Pharmaceutical Society |
| Sequence | The order of nucleotide base pairs in a specific length of DNA. |
| Sequencing | An umbrella term for the various techniques that can be used to determine the exact sequence of a particular length of DNA. |
| SJS/TEN | Steven-Johnson Syndrome / Toxic Epidermal Necrolysis |
| Soft stop | An active alert that allows progression in the workflow only when a reason for the override is provided. |
| *TPMT* | Thiopurine-S-Methyltransferase |
| UAE | United Arab Emirates |
| UCLH | University College London Hospital |
| VCF | Variant Call Format – a file for storing gene sequence variations |

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# **Introduction**

This document provides illustrative quotes from the consultation process, along with evidence from the literature to justify the guidance. The quotes have been labelled as following to indicate where they originated:

FG1 – Focus group one

FG2 – Focus group two

Country – consultation call with international comparator from that county

PRCC – patient representative consultation call

ABD – Advisory Board discussion

SR – Specialist review

# **Justification for guidance and evidence review**

|  |  |
| --- | --- |
| **Justification for guidance and evidence review** | |
| Alerts **should**be used: | |
| 1. In the main as part of a **dual alerting strategy**: at the **point a prescription is written** **AND** at the **point of verification and dispensing** by the pharmacist, irrespective of which other health professionals are alerted. | |
| Quotes: “…when you’re the prescriber you might park a decision to one side. Someone down the line will pick it up – usually a pharmacist. These alerts might have to appear at multiple points to ensure safety.” (FG1)  “…having the community pharmacist aware of alerts is an extra layer preventing prescribing errors and it does contribute significantly to patient safety because I do know that sometimes you know when I'm prescribing however many hundreds of things a day that sometimes the community pharmacist will come back to me and say did you really mean this? A lot of the time I do but sometimes it’s an error and in terms of patient safety that is an issue that needs to be considered alongside the very valid point about burden on patients as well.” (FG2)  “It should be considered that if the system flagged a pre-test alert at the pharmacy, the supplying pharmacist would be obliged to check whether the test had been ordered by the prescriber before prescribing the medicine.” (FG2)  “…don’t design your system so that it only fires for the prescriber and not the pharmacist. We actually have a dual firing, so the pharmacist gets the same alert as the prescriber [for safety netting] but also if the dose is decreased by 70 percent the last thing you want is for the pharmacist to then call because they don’t know why…” (USA)  “The pharmacist shares the legal responsibility for safe supply of medicines with the prescriber - so the community pharmacist should be advised of a pharmacogenomic alert.” (FG2) | “Alerts are triggered at prescribing order entry and dispensing of the pharmacist.” (USA)  “At LUMC….in the outpatient setting…the physician sees a popup message and the pharmacist, if he has the genetic test results of the patient, sees the same popup message again. However, to make sure that the pharmacy has the genetic information of the patient it has been incorporated in the Dutch health care law that a [community] pharmacist is allowed access to… pharmacogenomic test results.” (Holland)  “Pharmacists need to receive the same alerts so that a) they can explain the situation to the patient if necessary, b) they can make other medicines recommendations (e.g. Over-the-counter medicines) and c) so that they know about it if the patient asks them, which it would be reasonable for a patient to do if they had unanswered questions after a conversation with the GP.” (SR)  Evidence: Most alerts in electronic CDS systems are shown at order entry (the time a prescription is written). [1] In a 2014 study of pre-test alerts in secondary care in the USA the majority of alerts were shown to attending physicians, nurse practitioners and pharmacists. [2] These were presented “during prescribing or to pharmacists when the orders were processed for dispensing.”  A majority of stakeholders in both focus groups and the consultation calls endorsed the view that pharmacists should be alerted in the community, but it is not yet clear how this would be implemented in practice. |
| 1. In the main when a drug is prescribed that has a known **actionable drug-gene association**, which would **change the prescriber’s choice** of action. | |
| Quotes: “…alerts…are generated when providers put in medications. Every time a prescription is ordered the system checks to see if there is a relevant phenotype that's available and if there is it will show an interruptive alert.” (USA)  ”[Different services] are very different in their risk aversion so [in the case of azathioprine] our hospital treats GI patients with Crohn’s…transplant patients and…oncology patients…if you’re someone who is an oncologist…you actually expect neutropoenia from all the other drugs [the patient is] on [so the alert may not change the prescriber’s choice of action, but] if you’re a GI doctor who is treating Crohn’s and this is your third line drug the last thing you want is your patient hospitalised because you gave them neutropoenia… So, you’re tailoring of the message regarding the extent of dose reduction in the context of the same genotype is dependent on the service ordering it.” (USA) | Evidence: A drug-gene association (DGA) is considered to be actionable if awareness of it will likely lead to a prescriber choosing a different drug or alternative dose.[3] More specifically, for research purposes, DGAs are considered to be actionable if three evidence criteria are met: i) analytical validity (where the test assay is accurate) ii) clinical validity (where the test identifies at-risk patients) iii) clinical utility (where pre-emptive pharmacogenomic testing is superior to the conventional trial-and-error of prescribing).[4]  A recent editorial[5] justified the need for actionability in genomics, emphasising that:   * Clinician buy-in to genomic testing requires a certain ‘threshold of actionability’ in order to occur. * Perceived actionability is desirable but sometimes ‘subjective’ and ‘situation-dependent.’ * A ‘fundamental’ medical principle is that tests should only be ordered ‘whose results will guide clinical management |
| 1. In the main where a particular **drug therapy is being initiated for the first time** in an individual. | |
| Quotes: “[For pharmacogenomics guidelines] …. most of the recommendations are primarily only relevant, not at the time of order entry, but more specifically only…the first time you initiate a drug…[otherwise] the patient may never be prescribed this drug so who cares or they may already be on this drug…[so for example] the first time address is ordered on a patient we actually look at the medication history and we decide whether or not to trigger an alert…[if it’s when a drug is] first initiated that you’re going to be popping up an alert.” USA  “There's a couple of exceptions [to alerting at the time a drug is first initiated]. One big exception is clopidogrel…[and] the reason that was an exception is that you can be on that drug for a long time and we don't really have any biomarkers to tell you whether or not the drug is inhibiting the platelets or not. So, if you’ve been on that drug for a year and all of a sudden, I find out that you have a variant that interferes with your clopidogrel metabolism… I probably still would want to know about [the relevant pharmacogenomics]. There's a handful of drugs…[where] even if the patient’s been on the drug for a long time, we probably would want to find the variant and inform the clinician…. Apparently, alendronate would also fall into that same category, but we haven’t implemented that one yet.” (USA) | “A patient may be on a drug and not currently suffering any ill effect or reduced efficacy. That's not to say that couldn't happen in the future. Obviously, that would not be the case in an acute allergic reaction to a drug with a particular genetic susceptibility, [but] for example if you believe in clopidogrel and CYP2C9 there is an ongoing risk of increased efficacy or increased bleeding risk depending on the genotype. In which case it may still be reasonable to conduct a pharmacogenetic test for a patient who is on the treatment if a test hasn't been done before.” (FG2)  Evidence: Two recent studies in the Netherlands on pharmacogenomic drug exposure in patients [6, 7] estimated approximately 25% of all drugs prescribed in primary care ([6]: seven year evaluation period, n ≅ 9.7 million patients; [7]: n = 856 002 new prescriptions / year ) had pharmacogenomic exposure with 5.4% of new prescriptions in one study anticipated to result in a change of drug or dose due to an actionable DGA[7]. Also, retrospective analysis in the USA of elderly hospitalised inpatients (n = 20) who were part of a cohort of pre-emptively genotyped outpatients (n = 867) found the 20 hospitalised patients were exposed to 108 newly prescribed drugs, approximately one third of which were ‘pharmacogenomic drugs’.[8] The studies focused primarily on prescriptions where drugs were given to patients for the first time; with the underlying assumption that serious ADRs are less likely following the first exposure of a drug, but this is not the case from all DGAs. |
| 1. Where the results of a **pre-emptive pharmacogenomic test are available** (post-test alerts) | |
| Quotes: “We also have alerts that are associated with actionable genotypes and that are generated when providers put in medications. Every time a prescription is ordered the system checks to see if there is a relevant phenotype that's available and if there is it will show an interruptive alert that includes information about the genomics concerned and also alternative medications and so we spend a lot of time developing the knowledge base for that …We put into place a testing system where we had a small panel of pharmacogenes…We have about 15 – 16,000 people tested within our health system and it is driven by recording of pharmacogenomic results in our EHR.” (USA)  “When the problem list entry exists [containing patient pharmacogenomic data], and the relevant drug is prescribed those are the 2 conditions that come together to trigger the alert.” (USA) | “So I think what is very good about the system is that it really delivers the information at point of care so as soon as you record in your system that someone is a CYP2D6 poor metabolizer… and you start prescribing a drug for which we have a CYP2D6 recommendation then immediately during prescribing you get this [alert] on your screen.” (Holland)  Evidence: Worldwide, there are no examples of national programmes for pre-emptive pharmacogenomic testing (multigene panel testing in anticipation of a possible later prescription).[9] However, the majority of pharmacogenomics alerts, where systems are in place, are ‘post-test’ (occur where the results of pre-emptive panel testing are available)[1] |
| 1. Where the **results of a pre-emptive pharmacogenomic test are not available**, which should prompt the prescriber to order a pharmacogenomic test if clinically appropriate (pre-test alerts). | |
| Evidence: Several of the international organisations consulted during the project utilise pre-test alerts in their pharmacogenomic clinical decision support, although they are less commonly implemented than post-test alerts.[1] | |
| 1. Always **where pharmacogenomic testing is mandated** for a drug by existing professional guidance standards | |
| Quotes: “…some of the pharmacogenomics are more mature than others. Testing is mandated with some pairs – there are red lights that need to be flagged…” (FG1) | Evidence: Pharmacogenomic testing is not routinely used in the NHS and is provided in the UK in a limited number of specialist centres. Current UK prescribing guidelines only mandate pre-emptive pharmacogenomic testing for abacavir and carbamazepine in certain patient populations.[3] |
| 1. At the point where the results of a **pharmacogenomic test first become available**, showing the individual has a known actionable drug-gene association, **which should prompt of a review** of the individual’s current medications (post-test alerts). | |
| Quotes: “When a result is made available somebody should be actioning that – to see implications of that result on a patient’s care – a meds review at the very least…” (FG1)  “[The pharmacogenomic test] result should come in as any other abnormal result, not necessarily at time of prescribing.” (FG2)  “[The] simple way of looking at this is to treat this genomic information as we would with any other result that we get coming into [the GP] clinic and into the record. So we have an alert when we get any abnormal results, we get a list of normal results; they go into the record and then when you access the patient's record the information will be there and an alert may well come up at that time just as you're about to prescribe…” (FG2) | Evidence: 92% of respondents to a survey (of n = 84 clinicians) conducted at Vanderbilt University Medical Centre preferred ‘immediate, active notification’ as soon as a significant actionable DGA was reported and available in the EHR; as opposed to the alternative options of i) at the next appointment ii) at the point of a relevant prescription order entry iii) no alert or notification required.[10]  The notification of pharmacogenomic test results to prescribers, as they become available has been commonly implemented in other countries, for example, in one CDS system in the USA where ‘…emails are sent to each affected patient’s primary physician and nurse practitioner when high-risk phenotypes are added to the problem list [automatically following a lab test result].’[2] |
| Alerts **should not**be used: | |
| 1. Where the pharmacogenomic **test result does not imply an actionable variant**. | |
| Triggering of alerts in circumstances where there is no actionable pharmacogenomic information may contribute to unwanted and unintended consequences such as alert fatigue - a desensitisation phenomenon that occurs when CDS systems are utilised in live clinical settings.[11] | |
| 1. Where other factors clearly **supersede** an individual’spharmacogenomics. | |
| Quotes: “…at some point clinical knowledge needs to be used to override or needs to be taken into account. Alerts are there to help and guide but there's so many other factors.” (USA)  “In paediatrics…developmental pharmacology is super important [for e.g.]…in a neonatal population you don’t have to worry about…fir[ing] all the time for every patient if they have a gain of function or loss of function in [*CYP2C19*] for voriconazole…[because] when you’re three days old you don’t have any [*CYP2C19* enzyme], so it is irrelevant…we tailor these alerts to be suppressed if it’s not appropriate [based] on [for example] developmental pharmacology.” (USA) | “…in an effect called phenoconversion…you have DDIs that then increase or decrease the enzyme [of that DGA], you’ve changed what your phenotype is…pharmacogenomics is irrelevant in some cases…[e.g.] if other [genetic] pathways are compensating…if there’s phenoconversion [due to] DDIs and the renal function [is poor]…it doesn’t matter [about the pharmacogenomics]…We’ve built our whole service on looking at the patient as a whole and not in isolation as a genotype.” (USA)  Evidence: A 2019 review emphasised a key principle that pharmacogenomics ‘is a powerful tool but does not override the need for clinical assessment and judgement.’[12] |
| Alerts **should**share: | |
| 1. Recommendations that are **evidence based**; utilising **up-to-date consensus-based guidance** from approved professional bodies, where practicable. | |
| Quotes: “There’s no point in alerting a prescriber or dispenser if they can’t do anything about it. [Alerts should happen] where a clear intervention could take place and there is clear guidance on what should be done. [For example, for] some drugs the guidance says to reduce the dose but does not say by how much – clear guidance for prescribers is necessary.” (FG1)  “[We should understand that] … there are different levels of evidence and some drug-gene pairs are more established than some others…that have clinical equipoise…there is more granularity in those relationships.” (FG1)  “…most important…is having clear guidance so [for example] we have CPIC guidelines…ultimately I would like to see in the U. S. professional societies start to come out with those guidelines because that's where physicians turn to now…” (USA)  “When we originally started, we did everything ourselves - the evidence reviews, we pulled out of the original literature and now we just follow CPIC …” (USA)  “In the Netherlands we have a quite long-standing track record of implementing pharmacogenomics and it all started in 2005 when the DPWG was initiated. [In] the DPWG we did a systematic review of the literature for each of the gene-drug pairs that we identified and then…provide a written recommendation for the pharmacy. So, these were to be clear cut concise recommendations…and I think today we have… written actionable guidelines for…47 [DGAs that are available].” (Holland)  “We have a common health system of course in Italy but it is very heterogenous…so in each region we have a kind of a specific health system with light differences in the application of the test…so we have that shared guidelines but then they are specifically applied in the different regions… [The EHR vendors have said] it's very important to include also some pharmacogenomic guidelines or at least some way to integrate pharmacogenomic information in their health clinical records and that was the beginning of our collaboration.” (Italy) | “For the recommendations [alerted] the approach that we have taken is to use already established guidelines…primarily from CPIC and FDA. So, we curate that information that is publicly available and established.” (Canada)  Evidence: The currently available consensus-based guidance regarding pharmacogenomic DGAs is heterogenous. A new study, conducted in Greece and the UAE, compared guidance by two major regulatory bodies, the FDA and EMA, and CPIC – a well-established consortium in pharmacogenomics.[4] Despite a single and universal evidence base only 25% (n = 56) of the total DGAs (n = 218) covered by the two major regulatory bodies have label inserts from both and 32% of those DGAs have discordant recommendations.[4] Of the 68% of concordant DGAs (n = 38) only 17 have the most safety critical tag of ‘testing required’, and of these 10 are medications used as substitutes for enzymes in specific in-born errors of metabolism. Of the other 30 ‘testing required’ tags provided by the FDA, 15 are not mentioned at all by the EMA. Only four out of the 65 DGAs with published CPIC recommendations are so far tagged as ‘testing required’, and 17 have not been characterised in FDA guidelines.[4]  When clinical guidance with a solid evidence base is prescriptive regarding testing (e.g. abacavir (*HLA-B\*5701*) and carbamazepine (HLA-B\*152) in order to avoid abacavir hypersensitivity syndrome in HIV positive patients and carbamazepine related Stevens-Johnson syndrome in South East Asians, respectively[13]; then rates of clinical adoption and prescriber ‘buy-in’ to the alert systems are optimised.[14] However, there is a paucity of high quality clinical evidence (RCTs) to demonstrate clear benefits of pharmacogenomics testing.[14] The majority of the most commonly clinically encountered DGAs have limited or absent FDA guidance.  There is a requirement for standardisation of guidance regarding DGAs in order for the safe implementation of pharmacogenomic alerts now and in the future as new evidence emerges.[4] |
| 1. Succinct information regarding the **pharmacogenomic variant** **and/or** the **phenotype**. i.e. **a straightforward summary**. | |
| Quotes: “I understand [certain terminology is] routinely used in a pharmacogenomic setting. We’re talking about asking [for example] GPs to discuss this…practitioners who don't usually use this terminology. I think it’s [important] how you present it to those [professionals], but I appreciate in the pharmacological world this sort of thing would be routine but it’s not routine in clinical practice.” (FG2)  “So, there is a very concise text for the popup that really tells you for example if you're CYP2D6 poor metabolizer…it allows you to handle pharmacogenomic information without having any pharmacogenomic knowledge as such…” (Holland)  “Really the word of the day is the providers don't want too much information; they are easily overloaded, many of them were not trained in genomics medicine at all although I would hope that's being corrected now in medical schools…but the provision of like star alleles…was almost too much, at least at the point of presentation…Providers in our studies preferred simpler information maybe phenotypic information, a poor metabolizer [or] an intermediate metabolizer [etc.] and a recommendation for what to prescribe or a dosing adjustment. So, phenotype and recommendations for alternatives I think is what [a] systems alert consists of.” (USA) | “We don't actually show the gene or star allele and so that is probably a decision you can go either way on for most alerts we're showing the drug name and the genetic phenotype like poor metabolizers… and then we have text around what that means and we try and keep it focused on the clinical implications… and then we have a select flexible list of alternative actions and…override reasons…” (USA)  What we've found is that given the option between seeing genotype or phenotype clinicians overwhelmingly preferred phenotype because they're not trained on genetics in general…they don't know what the gene names are they don't know what these star\* notation variants are…” (USA)  Evidence: A USA study involving an online simulation of pharmacogenomic alerts and related questionnaire delivered to physicians (n=52) was done.[15] Several participants reported a preference for conciseness of the text included in the alert but the majority, 79%, did not want the allele information of the patient included in the alert.[15] |
| 1. Clear, unambiguous and **specific actionable recommendations** for the end-user e.g. a calculated dose reduction. | |
| Quotes: “There are a lot of alerts in prescribing and having one which is clinically and specifically actionable is key.” (FG1)  “In the U.S. there is a range of how much information is provided [in an alert]. We've gone to the pretty concise end and tried to standardize our messaging and tried to be very actionable - “tell me how to change the dose or pick a different drug”. So, there is a choice to be made up how much information to present to the to the prescriber and dispenser.” (USA)  “[Alerts should share] …a recommendation for what to prescribe or a dosing adjustment…you prescribe a different drug; you adjusted the dose of your current drug or you literally can't prescribe this drug. I think those are the three that I think of...” (USA)  “…if you're CYP2D6 poor metabolizer and you’re prescribing nortriptyline and then it really tells you [in the alert] reduce the dose by 60 percent based on that CYP2D6 genotype.” (Holland)  “What we heard from [prescribers was] ‘these [alerts] need to be actionable. We only want to see it if we actually have to change care’…” (USA)  “…the biggest thing that we found is that the CPIC guidelines don't make it clear what alternatives the clinician should be using…so for example with clopidogrel there are clinicians that are very familiar with that medication but they're not as familiar with the alternatives like prasugrel or ticagrelor so if we're telling them to just consider alternatives but not telling what alternative to consider then they kind of get frustrated, they get a little confused, they are kind of like well what am I supposed to do here because there's not a black and white alternative. it's a big hurdle right now to figure out if we're going to tell people not to use the medication that they’re used to using - what do you happen to do instead?...I think you guys with the NHS have an opportunity to…decide all right in the case of these genomic interactions: X, Y and Z. are going to be our recommended alternatives. [If you do this] I think you have a strong chance to get [clinician] buy in.” (USA)  “…the biggest barrier [to our implementation] was physicians being able to take actions on the result and it’s not because we didn’t find something actionable its mostly because clinician’s lacked specific knowledge and understanding of how to utilise pharmacogenomic insights in practice…Even if you integrate pharmacogenomic insights into electronic or other medical records physicians are not ready…because they often don’t understand the level of certainty and what actions they can take with the alerts.” (Canada) | Evidence: A 2006 review of drug safety alerts (n = 17 studies) recommended several factors for ‘appropriate and useful’ alerting, which included that alert information content ‘must be clear and unambiguous’, in order that the end-user can evaluate the importance of the alert ‘at a glance’.[16]  A study investigating the reasons given by end-users for overriding DDI safety alerts emphasised the requirement for specific actionable recommendations.[17] Actionable in this context is taken to mean that not only is it possible and practicable to undertake the recommended course of action in the specific setting concerned; it also considers that an actionable precaution should ideally be enacted from within the CDS system itself because when ‘users must separately order the precaution [this] increas[es] the time required and the likelihood of omitting the precaution.’[17] In cases where the alert must be actioned separately there is also an additional burden on the end-user due to the fact that a reason for overriding the alert or cancelling the order must still be provided.[17]  There are several drugs with robust data for gene-based drug dosing optimisation in both adults and children.[18] Despite this, the implementation of pharmacogenomic drug dosing guidelines into clinical practice is currently poor, even in cases where, for example, CPIC dosing guidelines are available.[19] In Italy the FARMAPRICE prototype pharmacogenetic CDS system is an example where once a drug has been selected at the time of prescription order entry a dosing recommendation is provided based upon a patient’s stored genetic profile or where appropriate an alternative drug and dose recommendation.[19] However, as with several other potentially promising prototype pharmacogenomic CDS systems (see for example [20]) the system is yet to be thoroughly tested by clinicians in routine clinical practice.[19]  The implementation of pharmacogenomics into clinical practice is largely in its infancy – a recent review has provided a useful overview of many of the current initiatives and institutions involved worldwide (see [21]). |
| 1. An **external link** to more detailed **background information** **and/or** further guidance. | |
| Quotes: “… it's two-step alerts…the first very succinct message… and then maybe click here for more information…about the description of the gene-drug interaction or the literature background…” (Italy)  “One of the decisions that needs to be made [in] alerting for pharmacogenomics [is] the information you put on the actual page versus how much you provide for example in an info button where the provider needs to go out and look at the rest of the information if they're so interested. So, that's a dimension I think that hasn't yet been settled.” (USA)  “If you want you can click on [a link within the alert] and then you…are referred to a second page that tells you a little bit about the pharmacokinetics…different metabolizer phenotypes and all that sort of information…there's even a third level where…you will get the full report that we have written that actually includes the evaluation of the individual papers on which the recommendation is based.” (Holland)  “…every single one of our alerts has directed information if they want to know more… from a website that we've created…[so] that they can see in much more detail what the implications of a specific pharmacogenetics lab test means.” (USA) | Evidence: In the implementation of pharmacogenomics electronic CDS in other countries alerts often provide external links to more detailed guidance or background, for the end-user.[2, 14] This standard practice is generally desired by prescribers, with a USA study involving an online simulation of pharmacogenomic alerts and related questionnaire found that 80% of physicians (n=52) participating found such links useful.[15]  A survey conducted by the Mayo clinic, following implementation of pharmacogenomic alerts into an EPS for primary care found that 53 % of end-users who recalled interacting with an alert found that it was difficult to find additional background information to clarify what was felt to be confusing and frustrating alert content; which suggests that this was an inadequately fulfilled need for the prescribers at the point-of-care.[22]  The content and format of additional background information and further guidance supplementary to pharmacogenomic alerts appears to vary across different systems and settings and it is not yet apparent that any particular implementation is superior. Future work may help to resolve this. |
| 1. Information that is readily **explainable to individuals receiving care**. | |
| Quotes: “The guidance might also include the production of patient guidance leaflets. Guidance to patients in a printed form is desirable at some point. Especially if the alert is out of the blue.” (PRCC)  “As a motivated patient I would want to be notified of my pharmacogenomic information and when the evidence base changes. A message to read, but only if it’s relevant to me. You don’t want the patient equivalent of alert fatigue if it’s not relevant information. Perhaps a courtesy alert if its relevant but not necessarily urgent and I could discuss it with my consultant on my routine appointment.” (PRCC)  “As a patient I would always want to be consulted [about my pharmacogenomic information, where it will lead to a change of medication]. It can be cumbersome for the patient but it’s important from a safety perspective and also needs to be clinically relevant. For example, I’d like to discuss it with a health professional and understand the research in the context of what the actual toxicity [ADR] is, such as hair loss or limb loss…In the past I have had a genetic counsellor drop me a line [to discuss genetic information], but I also am happy with communication by email or letters, it depends on the individual. It’s important that patients are not flooded with new information.” (PRCC)  “[As a patient] I just don’t know how personalised medicine is going to work without patients having more access to their genetic information and be allowed to be a bit more empowered in the decision making process so what I would like to see ideally would be to also have these alerts also be shared with patients and also that we’re being updated on new evidence because I never get updated on anything…That’s a theme that I would like to stress perhaps in terms of recommendations for the future.” (FG2)  “…as a patient…I think [that with the disclosure of pharmacogenomic information] you could frighten some patients enormously. Others will be fascinated by it and want to know more. So, I think…a nuanced approach to [communication with patients is needed] as well.” (FG2)  “…one of the advantages that that the availability of genomic alerts gives us is that it does give us some choice about therapeutic options and so the pharmacists do have an important role in talking patients through that.” (FG2) | Evidence: A recent meta-analysis (n = 31 studies) looked at patient and healthcare provider ‘needs and preferences’ relating to pharmacogenomic testing.[23] The study curated several recommendations from the literature regarding the sharing of pharmacogenomic information with patients, including: i) delivery of results in person via a healthcare professional, for purposes of clarification, interpretation and emotional support ii) adjunctive handouts for the purposes of later recall and sharing of pharmacogenomic data with other prescribers; including information such as gene name, genotype and interpretation / phenotype iii) prioritising the use of layman’s terms and avoidance of medical / scientific jargon in verbal and written communications iv) providing information targeted and relevant to the patient with limited use of numbers, utilising vignettes and media such as videos and pictures where appropriate v) including information regarding metaboliser status, in an easy to understand format - patients were motivated by a desire to have the best treatment option informed by their pharmacogenomics and were concerned in particular with the accuracy of testing.[23] These findings are generally supported by a 2018 study that used semi-structured interviews with patients and clinicians to investigate how pharmacogenomic results should be communicated.[24] In addition, patients wanted access to a summary of their pharmacogenomic data in future.  An established body of evidence demonstrates that patients often do not correctly recall information and advice given to them by health care professionals during consultations (about half the time)[25], with significant safety implications relating to disease management.[26] However, a recent study has shown that communicating pharmacogenomic information to patients at the point of prescribing meant patients were able to recall medication changes more often - in 86% of visits versus 67% in controls.[26] Further work is required to develop the optimum strategies for communicating pharmacogenomic information to patients, in order to maximise safety and efficacy benefits. |
| 1. **Justification of the action taken** by a prescriber to be seen by health professionals downstream in the prescription cycle, such as the pharmacist. e.g. why a particular dose reduction occurred, or an alert was overridden. | |
| Quotes: “Information explaining why a dose reduction has occurred may be useful for other professionals such as the pharmacist and / or nurse.” (FG1)  “Any healthcare professional that has a responsibility and duty to patient, they need to see that information even if the GP has chosen to override that [alert].” (FG1)  “… perhaps the next person in line like the pharmacist ought to know what action is being done if the initial prescriber has altered a dose or letting them know that they’ve overridden; where prescribing now it’s the prescription that gets transmitted not the action done or any comments. How are we going to get around that?” (FG2)  “If a healthcare professional has overridden an alert, I think there should be a justification of this and this needs to follow down the [prescribing] chain.” (ABD) | “So, if an alert gets overridden then the prescriber at the time that they are overriding the alert actually get a second screen that pops up asking them for a reason why they're overriding the alert and they provide a reason why it's being overridden… We don’t allow much [to be overridden], we don't really like it…” (USA)  Evidence: A study investigating the reasons given by end-users for overriding DDI safety alerts in CDS concluded that the ideal alert would:   * “Allow the user to document… a coded override reason, a free-text comment, or both…made available to other [healthcare] providers…”[17] * An option to “defer to pharmacist / primary physician” with a requirement that the prescriber “select [and] require [a] responsible party to review and approve the [prescription] order.” |
| Alerts **should**be presented to: | |
| 1. **Any health professional** with **prescribing or dispensing authority** involved in an individual’s care. | |
| Quotes: “…different people might need to see different things and talk to the different professionals involved at different stages….” (FG1)  “…it's important that it's the people who prescribe the drugs [who are alerted], independent of whether or not they’re a physician or not…” (Holland)  “The people who see the alert are anyone at the institution who has prescribing authority or medication dispensing authority. Any pharmacist who is going to process the prescription as well as any physician, fellow, nurse practitioner, physician’s assistant… who has prescribing authority. Anyone who can prescribe a medication can be alerted.” (USA) | |
| 1. Health professionals in **multiple clinical settings;** including those in primary care, and secondary care including community pharmacies. | |
| Quotes: “Our whole alerting system and EHR encompasses both [primary and secondary care]. [For every] single alert we're creating we have versions that differ based on whether you’re in that outpatient or inpatient setting." (USA) | |
| Alerts **should**be reviewed: | |
| 1. In cases where retrospective evaluation shows **robust evidence that the alert does not promote a favourable change to prescribing behaviour** | |
| Quote: “We had [the CPIC guidance for Proton Pump Inhibitors] implemented for over a year and every single person bypassed it…The overwhelming message we got from our [healthcare] providers was [for this particular DGA] we don’t care and we’re not changing our practice.” (USA) | Evidence: Generally, information on the effectiveness of alerts in a local setting is only available retrospectively after an appropriate period of evaluation (see [27-30]). Despite strong evidence for alerting a particular DGA in the literature, sometimes there is likely to be scenarios where, for reasons that may not be immediately apparent, the alert is continually ineffective or overridden by prescribers. There does not appear to be examples in the literature where such a scenario has been evaluated or described for pharmacogenomic CDS. Nevertheless, in such cases the alert should be reviewed and modified or discontinued as necessary. |
| The implementation of clinical decision support for alerts **should**: | |
| 1. Include active steps to **mitigate potential unintended consequences** with implications for safety, **such as alert fatigue**. | |
| Quotes: “The challenge of alert fatigue is [in part] because people haven’t gone through this process – establishing the principles that we are trying to…Making the alert relevant to the prescriber makes the fatigue go away.” (FG1)  “We thought a lot about alert fatigue and we always think about that and minimizing that.” (USA)  “[T]here are different levels of mitigation [of alert fatigue]…[for example] excluding [situations where] you don’t need it; say I want to put pharmacogenomic alerting for the drug tacrolimus…and any time the ingredient tacrolimus arrives you’ll get all the creams that have tacrolimus in it, and no one necessarily wants to have the pharmacogenomic alert for tacrolimus cream!” (USA)  “Our current approach [to overcome alert fatigue] has been carefully gauge the prevalence so we're deliberately… [ensuring] that no more than 10 percent of the population will have alerts … our hypothesis going in is that if we tailor the recommendation [in the alert with]…very specific wording… based on analytic validity and clinical validity… if it's crystal clear [to the prescriber]…we will minimize fatigue and then of course we always tier the recommendations.” (USA)  “…we were looking at the alert fatigue problem in quite a lot of depth and one of the irritations with electronic prescribing systems at the moment is that you put in your penicillin V and it says, after you’ve picked it, they are allergic now put in the reason why you’re going to change your mind where if at the point of drug choice the penicillin V…was treated in such a way that it was less desirable…in that allergy state [but preserving]… clinical freedom…and if that was at the point of picking [your choice of drug] you avoid having to get through a series of alerts which are not actually necessary.” (FG2)  “There is a professional obligation to do something with the alerts [by the health professional that views them]. Lots of colleagues cancel these [alerts] as a reflex action. [In such cases] colleagues [should] retrigger the alert and do what it says.” (ABD) | Evidence: Strategies to mitigate unintended consequences of alerts are commonly discussed in the literature, e.g. alert fatigue is a desensitisation phenomenon that occurs when CDS systems are utilised in live clinical settings.[11] As the majority of alerts seen by a prescriber are of limited clinical consequence the sheer number of daily notifications results in users ignoring or overriding the alert.[11] A new retrospective study in the USA has demonstrated clearly the detrimental impact of alert fatigue on alert effectiveness and safety.[30] It analysed prescriber-patient interactions where a CDS system alerted co-prescription of opioids (211,000 visits) and benzodiazepines (85,000 visits).[30] Data was collected over one year (six months pre-intervention, six months active intervention). Despite the high frequency of alerts regarding a life-threatening DDI the alerts had a minimal effect on prescribing behaviour, probably due to alert fatigue.  There is increasing interest in the development and adoption of features to minimise alert fatigue. A 2009 retrospective study in the USA attempted to validate one strategy for mitigating alert fatigue caused by drug-drug interaction (DDI) alerts.[31] The authors compared a priority ‘tiering’ method (39,474 alerts) with a control (31,876 alerts), conducted at different sites. Under the tiering strategy, only identified high-risk DDIs were actively alerted - low-risk DDIs were alerted passively. They found that the number of severe alerts overridden at the tiered site (0%) was far less than the non-tiered site (66%). This suggests a significant reduction in alert fatigue for clinically important safety alerts due to the strategy.  Given the important safety implications of alert fatigue, further work is needed in order to make recommendations, both for alerts in general and specific to pharmacogenomics. |
| 1. Be overseen by a **multi-disciplinary oversight committee** that includes representatives from relevant stakeholders. | |
| Quotes: “The first thing we [implemented] before we even built our first alert or decided on our first drug-gene pair was an oversight committee…that is multi-disciplinary [with] stakeholders including prescribers…scientists and genetic counsellors. We have [wide] representation on that multi-disciplinary committee. We think about what…we want to prioritize because you have limited…resources.” (USA)  “So we have an oversight committee... that meets quarterly and…we talk about…[things such as the] tailoring [of] the alerts…[for example] to prevent over alerting and alert fatigue…at one point…we went to the oversight committee and asked them [about a] proposed plan to decrease the number of alerts that fire for thiopurines agents and the physicians there said no please don't do that.” (USA) | Evidence: St Jude Children’s Research Hospital introduced a multidisciplinary oversight committee into its pharmacogenomics service in 2011[2], as a form of formal governance. Subsequently, Boston Children’s Hospital introduced similar.[29] Stakeholders include clinicians of various specialties, pharmacists, informaticians, geneticists, and others with relevant expertise. In both, the committee is ultimately responsible for approving which DGAs are incorporated into the EHR for the firing of electronic alerts (basing decision making on curated primary evidence and guidelines e.g. CPIC), and for the wording of recommendations shared in alerts.[2, 29] Vanderbilt University Medical Center initiated a pharmacogenetics service in 2010, where the oversight is provided by the local Pharmacy and Therapeutics Committee; who would ordinarily be responsible for deciding which drugs are on the entity’s formulary but in this case also decide which actionable DGAs should be stored in the EHR.[10] |
| 1. Consider the provision of **expert support for prescribers** in a pharmacogenomics context, including the return and disclosure of results, to prescribers and the individuals they are treating, where necessary | |
| Quotes: “…given that the knowledge around [pharmacogenomics] is doubling every 72 days the rules are going to change in a well-ordered system quite regularly and if the rules change, when are they going to be rerun? Are they going to be re-run offline…and if so, who's on the hook for the new alerts?” (FG2)  ““[Regarding] clinical responsibility, whoever ordered the test the results should come into that person's inbox to manage it. I think it could just go with flow of normal information... and then, at least you have clinical responsibility because the person who orders the test is the person who will receive the results - usually that's what happens in practice.” (FG2)  “…[A] perennial issue with any multiplex panel is that it crosses disease risk and pharmacogenomics scenarios…we just finished an experiment around disease risk with eMerge and the frontline providers want someone else to handle [the long term follow up of pharmacogenomic results] … I think they're more willing to take on responsibility for the drugs they prescribe but they do get concerned about the drugs they don't prescribe and so one of the things we're doing here is we're opening up a pharmacogenomic clinic to offer that help if they have a multiplex panel and a patient with maybe a complex medical list or drug list and they want to get some help basically figuring out how the results interdigitate with the actual drug exposures.” (USA)  “If you look at successful implementations…[for sharing pharmacogenomic information have been] pharmacy led…clinical pharmacists have that understanding of pharmacogenetics and knowledge and they are able to educate physicians and engage them and provide a review for every patient…[and deal with] complicated case to give specific recommendations for the physicians.” (Canada) | Evidence: In 2016, a team from Vanderbilt University published a survey of clinician’s attitudes who had participated in the institution’s pharmacogenetics CDS programme, PREDICT, since 2010.[10]  Attitudes of prescribers regarding who should be notified and who was responsible for actioning the results of a pharmacogenomic test were heterogenous. Respondents assigned responsibility for acting on a test result to various health professionals including the primary care provider (12.5%), provider who ordered the pharmacogenomic test (54.0%), provider who previously prescribed a drug affected by the DGA and the specialist treating the medical condition affected by the DGA (77.5%).[10] In the USA clinicians are receiving an increasing number of ‘unsolicited genomic results’ (those that they did not order).[32] A 2019 study using semi-structured interviews also found a lack of clarity regarding who was responsible for actioning these results.  These results suggest that the clinical responsibility for the actioning of results from multiplex pharmacogenomic panels is not easy to establish and that the tradition of responsibility belonging to the health professional who originally ordered the test may not be appropriate. Further, work is necessary to establish clinical responsibility. In the interim, additional expert support in pharmacogenomics has been implemented in some USA centres and could be beneficial in other systems and settings. |
| 1. Include dynamic methods to **monitor the performance of alerts**, and how prescribers use them, for data collection, educational and quality improvement purposes. | |
| Quotes: “…alert evaluations [can be] very simplistic [and] not really meaningful… [we want to see] what the clinician did with that alert, did they change the dose? Did they check or select a different drug?” (USA)  “We have found that for a lot of clinical decision support it's helpful to get in place an electronic surveillance system…up front…[Monitoring] how often alerts are firing… how people are responding [etc.] gives you a better idea about how well it's working…and…helps acceptance overall.” (USA)  “[There is a focus] now on ‘learning health systems’, which is basically quality improvement and using your own data to improve your quality of your processes…” (USA)  “…at the time that a specific alert fires [the clinical pharmacogenetics coordinator is] notified so [they] can follow up with the clinician and educate them if there’s a need to do so.” (USA) | Evidence: Suboptimal deployment of computerised CDS interventions, such as when alerts fire to the wrong patient or health professional and/or at the wrong time in the workflow or too frequently, can harm patient safety.[33] A 2018 analysis of CDS monitoring in the USA described a monitoring framework including a two week pre-activation phase (no active users), a two week post-activation phase followed by continuous automated (real time) and as required (e.g. when an end-user reports a problem) monitoring of alerts. The authors concluded that active monitoring of alerts should be part of the part of all CDS systems; providing an additional safety benefit notwithstanding careful design and robust testing.[33] Indeed, malfunctions still commonly occur even in the most comprehensively tested alerting systems[33] and unintended consequences such as alert fatigue were not originally anticipated at the development stage; only emerging after CDS systems were used in live clinical settings[11]. |
| 1. Include careful consideration of how the individual’s pharmacogenomic data used to trigger an electronic alert should be stored. | |
| Quotes: **“**The data should be stored in a way that can be iteratively analysed.” (FG1)  “The other big challenge has been to revise old results to be consistent with updated interpretations… [the] reinterpretation problem…[If] it’s pharmacogenomic data we have usually looked at it in terms of the overall risk of what is the end result of the change. So, if it's going from a non-actionable to an actionable, we have paired that that with an active mode of communicating that information to the original [prescriber]. If it's going the other direction, it’s …passive…we update the EHR and then the next time [no active alert will fire].” (USA)  “I would be cautious of trying to shoehorn this in the problems or allergies list.” (FG1)  “We [used the problem list] for several reasons, one is practical [as] we had experience building problem list entry active alerts and two there was some thought that if a patient were to arrive with pharmacogenomic results that we thought were valid then we could put that actionable result on the problem list….When the problem list entry exists and the relevant drug is prescribed those are the two conditions that come together to trigger the alert.” (USA)  “… [the research asked prescribers] would you want [pharmacogenomic data] in the allergies list...in the problem list... [or in a] separate genetic information screen? [(unique repository)] …[prescribers] generally liked the idea of having it in a problem list but [these] are not well maintained...They were interested in the idea of a [separate] genetic information screen…in the future…” (USA)  “Analogous to] a PACS system we have a GACS system…with BAM files and VCF files and then we serve them up on demand...at the time of [prescription] order entry…you send that drug over to your decision support engine and then …[via] a FHIR based interface…if you say to the GAC server the patient ID, the chromosome number and the range…[of] the region that [you’re] interested in... the GACS server…uses a GA4GH htsget protocol to quickly extract those variants from the VCF file and extract meta data from the BAM file as well and then it does an on-demand translation of those variants in to FHIR, a FHIR message comes back to the decision support engine and within the decision support engines we might do for instance variant to genotype conversion - determine the pharmacogenomic star alleles and from that decide whether or not we need to say anything back to the clinician at the time order entry. You know either change the dose or change to a different drug, or in some cases you know recommend that they order a genetic test before they prescribe the drug…we're now doing a variant reanalysis service…, a problem annotation service and [following recommendations by the] ACMG we look at 60 genes for any incidental findings and report them as well.” (USA) | “We keep [our system] up to date and our reports are very dynamic in the sense that when new recommendations become available in real time we update the reports that individuals have so at any one time if an individual logs in to see their data they will see the most up to date recommendations. [When]integrating with the [EHR] it has been a crucial piece that information exchange is not…a one-time event…so our approach has been to push for a system where whatever information is requested from the [EHR] end it interacts with API to our system to pull up the most up to date information [for that individual/patient]. (Canada)  Evidence: With adequate storage capacity pharmacogenomic testing should only need to be done “once in a lifetime.”[14] However, “updates [of the evidence / guidance or the CDS system software] might sometimes require the pre-processing and analysis workflow to be rerun iteratively for optimal alerting; for instance previously unknown and clinically relevant genetic variants may become defined and characterised over time.”[34] Furthermore, it may be that because certain pharmacogenomic tests results cannot yet be definitely interpreted; that providers of such services incur a duty to reinterpret the data when it becomes feasible to do so.[35] In order to meet that ethical duty a patient’s pharmacogenomic data would have to be stored in a way that is secure, accessible, enduring and in a format that facilitates reanalysis. This would require the storage of raw (FASTQ, BAM) and intermediate (VCF) pharmacogenomic data files, which are too large to be stored in the EHR.  As such early attempts to integrate pharmacogenomics into the EHR have stored pharmacogenomic data (as a phenotype) either in the allergy or problem lists, rather than a unique repository within the EHR.[14] For example, guidelines in the USA state that the DGA of abacavir (*HLA-B\*5701*) should “be recorded as an abacavir allergy in the patient’s medical record.”[36] This was originally done in order to integrate pharmacogenomics with existing system supplier produced EHR systems and it has been argued that other solutions e.g. “ancillary [systems] that interface with the [EHR] will be required [in future].”[36]  A working prototype using a GACS server to store pharmacogenomic information in parallel to the EHR has now been described[20]. The system requires both genetic (not phenotypic) information, in the form of BAM and VCF files, retrieved from the GACS via a FHIR enabled API, and a prescription order entry in order to trigger an alert. A new paper from the Mayo Clinic has demonstrated the use of a unique repository of pharmacogenomic data within the EHR in order to trigger alerts.[37] The authors contend that the method has several advantages over using the allergy or problem list.  Specific recommendations about the storage of pharmacogenomic information are beyond the scope of this guidance, especially as there remains much to be resolved within the literature. Developing a common standard for the storage of pharmacogenomic data is an important implementation challenge where further work needs to be done. |
| 1. Consider and meet requirements for **equitable access** to medicines, **regardless of self-reported ethnicity.** | |
| Quotes: “We don't [trigger alerts based on self-reported ethnicity] and the reason we don't is because we think the pharmacogenetic result trumps the patient’s ethnicity so for carbamazepine for example it doesn't matter if you are white or Asian, we're still going to test you.” (USA)  “…we have chosen not to ever have ethnicity as a driver [for triggering alerts]…as most people don’t even know what they ‘truly are’…we can’t rely on say…only testing the Asian population for HLA…when we build a rule [for triggering alerts] it is not ethnically constrained.” (USA)  “We touched on ethnicity. The predictive utility of pharmacogenomic tests (and any other type of predictive genetic test- e.g. polygenic risk scores) is critically dependent on ancestry since tests evaluated in one ancestral group may not be transferable to another. Most pharmacogenomic tests have been evaluated in European ancestry individuals yet a huge proportion of NHS contacts are with non-European patients.” (FG2)  “What we emphasize here in Canada is a panel that is suitable for a diverse population - we have a very wide mix of ethnicities here in Canada and if for example we have focused the most common markers that are primarily derived from studies in a Caucasian population. It would not have been a suitable panel for a large fraction of individuals that live here in Canada.” (Canada) | Evidence: A 2018 review asked whether incorporating self-reported ethnicity was of benefit to genotype based prescribing decisions.[38] A notable example of an ADR with an actionable DGA that varies markedly with ethnicity is carbamazepine-induced SJS / TEN and *HLA-B\*15:02* that occurs in approximately 8% of Han-Chinese but less than 1% of Caucasians. Furthermore, the inadequate performance of pharmacogenetic dosing algorithms for warfarin, which are derived from European populations, in certain ethnic groups has implications for when alerting in settings with ethnically diverse populations. The authors concluded that in such settings self-reported ethnicity may not be a reliable proxy for underlying genotype but that its use may be justified in some circumstances e.g. when considering access and affordability of healthcare.  This is an area of pharmacogenomics with wide ranging implications for patient care and warrants detailed further consideration. |
| The implementation of clinical decision support for alerts **should not**: | |
| 1. Place an **undue burden** on prescribers or individuals receiving care. | |
| Quotes: “[We don’t want prescribers saying] …’I put all this work into [selecting] the drug and finding the dose and inputting the frequency and sending it to the right pharmacy electronically and *now* you tell me I shouldn’t do this!’…you don’t want to frustrate them.” (USA)  “The alert really should come at the beginning before the clinician does all the work to be told to do something else when all the information to trigger was available at the start.” (FG2) | Evidence: A 2017 article adapted the AHRQ’s five ‘rights’ of CDS for pharmacogenomics. The authors emphasised the principle that alerts should deliver information at the ‘right time in the workflow’ at a logical point ‘precisely when it will have the best impact on decision making’.[39] Furthermore, the burden of “too many warnings” on prescribers results in the phenomenon of alert fatigue with demonstrable safety implications for patients in real life clinical settings.[11] |
| 1. Provide pharmacogenomic information in alerts **without access to the formal pharmacogenomic test result**. | |
| Quotes: “The alert is not designed to take place of formal result however it should still be linked to that detail.” (FG1) | Evidence: Pharmacogenomic reports generally “consist of raw unstandardized, narrative interpretations…as pdf documents…” that are necessarily separate from the CDS rule-engine as they are “difficult to compute.” [40] In one USA study 52% of physicians (n=52) participating in an online simulation and questionnaire responded that pharmacogenomic alerts should provide “a link to the patient’s genetic lab report.” [15] |

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