Professional Record Standards Body

Better records for better care

Guidance for using pharmacogenomic information in clinical practice

FINAL REPORT

November 2020

Professional Record Standards Body

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London, SE1 4YR.

www.theprsb.org

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Acknowledgements

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

The final report is the main deliverable of the project. It has been produced by the project team and will be:

- assured by the PRSB Assurance Committee
- presented to the Project Board.

The purpose of the final report is to:

- describe the approach to developing the guidance
- provide guidance that is fit for purpose and has buy-in and support from the professions and people who will use it
- provide justification of the guidance, via the findings of the evidence review and consultation process
- provide recommendations for future work, in particular work required to perform an effective rollout of the guidance

Reviewers

This document must be reviewed by the following people:

Reviewer name	Title / Responsibility
Assurance Committee	PRSB Assurance Committee
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Approved by

This document must be approved by the following people:

Name	Signature	Title	Date	Version
Project Board		Project Board		
Assurance Committee		Assurance Committee		

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

Contents

1. Introduction

1.1. Executive summary

PRSB was commissioned by NHS England to investigate and issue guidance on how genetic information that could affect prescribing decisions can be communicated effectively to healthcare professionals and shared with patients to agree treatment decisions throughout the lifecycle of a prescribed medicine with the aim to action this information where appropriate.

This field of medicine is known as pharmacogenomics. Recent UK based initiatives have made genetic information available within the health record. This includes information on how medicines are handled by the body. Variations in such genes could increase the likelihood of individuals experiencing adverse drug reactions (ADR), which could be avoidable for example through alteration of dose or prescribing an alternative medicine. The challenge now is first ensuring that pharmacogenomic information is available to clinical teams and shared with patients, and second that processes and systems to enable information exchange, notification of actionable variants and ultimately taking action given this information, are in place to support uptake nationally.

This report sets out a common set of principles; a summary of the guidance; and recommended actions to support widespread implementation of pharmacogenomic information in the NHS. These are summarised below:

Principles:

1. The availability of up-to-date and curated genomic information within the health care record is required to facilitate the implementation of pharmacogenomics.

2. Notification and/or information exchange mechanisms agnostic to the electronic (or other non-automatic) system should be in place to inform prescribing or facilitate a change in prescribing for the benefit of the patient. Supporting information must be evidence based, up-to-date, standardised and accessible at any time during an individual's care.

3. Implementation should be in line with, and complementary to, existing clinical practices therefore not placing a significant additional burden to the workflow of patient care.

This guidance aims to enable the safe provision of pharmacogenomic information. It could be implemented in several ways dependent on local factors. Aside from the requirement to have the genomic and pharmacogenomic information available in the

health care record, this work looks at how this information could be alerted or flagged at appropriate points in the clinical pathway to inform prescribing. We are unaware of a robust clinical safety case demonstrating a clear preference for any particular form of electronic alert and both active and passive alerts may induce alert fatigue[a] if clinically irrelevant.[1] Further peer-reviewed research is required in this area. Resource poor settings may benefit in particular from patient held alerts such as cards or bracelets.[2] To date, the majority of implementations in other countries with access to sophisticated IT systems use active (interruptive) alerts[b].[3, 4] Introduced gradually, where there is a high degree of risk of significant harm to the patient well designed interruptive alerts may be appropriate as a safety net mechanism.[5] Depending on circumstances, passive alerts and 'hard stops'[6] may also be appropriate additions or alternatives.

Summary of the guidance

Pharmacogenomic information should be used at the prescribing and dispensing stages where there are actionable drug-gene associations based on pharmacogenomic test results. Or where pharmacogenomic test results are not available prompting a test to be ordered. Alerts should not be used where there is no actionable drug-gene variant.

Communications should share best practice information based on current evidence including specific actionable recommendations that are easily explainable to patients in order that decisions about medications are shared between clinicians and patients and that signposting to further information is provided as needed. The alerts should be available to any health professional in any clinical setting with prescribing or dispensing authority who is involved in a patient's care.

Alert fatigue is a widely recognised unintended consequence of any system of electronic alerts and the risks associated with it should be minimised by ensuring alerts are focussed on actionable drug-gene associations, that systems are well designed and active curation of alerts is carried out locally by multi-disciplinary committees (alerts should be regularly monitored for effectiveness).

Clinicians should have access to the formal test results and access to expert support in pharmacogenomics when making prescribing decisions in consultation with patients.

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[a] In this document **alert fatigue** is defined as a desensitisation phenomenon that is thought to occur due to the sheer volume of daily electronic alerts and notifications seen by prescribers that are of limited clinical utility; resulting in the end-user ignoring or overriding the alerts without consideration of the content.

[b] In this document **active** and **passive** alerts in electronic Clinical Decision Support systems are outlined in section 3.1**.** The term '**hard stop**' refers to 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. '**Soft stop'** is a term sometimes used to refer to an active alert that allows progression only when a reason for the override is provided.

Recommendations

PRSB's recommendations for the implementation of alerts in clinical decision support systems are based on consultation with international and UK stakeholders:

- Pharmacogenomic information should be available to clinicians independent of alerts, which are a failsafe mechanism and pharmacogenomic alerts should not replace test results or clinical judgement.
- Patients should be supported to share decision making and should not be denied medications from which they would derive benefit on the basis of pharmacogenomic alerts.
- Pharmacogenomic alerts should share information that is actionable, evidence-based, accurate, concise, timely, and unambiguous with a prescriptive recommended action (e.g. a change of drug must include a viable alternative, a change of dose must include the dose to be administered, a prompt to request a test must explain which test etc.).
- In the main, alerts should be triggered when a prescription is written or earlier and at the verification and dispensing stage (post-test alerts), when new test results are received or when prescribing but a mandated pharmacogenomic test has not taken place (pre-test alerts).
- In the case of pre-test alerts, clear and specific guidance should be made available to the prescriber outlining what action to take in the interim, pending the pharmacogenomic test result. Furthermore, there should be easy access to fulfil alternative actions recommended in an alert (e.g. the medication must be available as part of a local formulary; it must be possible to order the test) otherwise it may not be actioned.

To support the implementation of pharmacogenomic information in the UK NHS England should:

- pilot use of pharmacogenomic alerts to test the guidance developed by the PRSB with a set of focussed alerts and develop a strategy for informing individuals and clinicians as new evidence emerges. The pilot should evaluate the effectiveness of different types of alerts including passive alerts (and context sensitive information) as well as active alerts at the point of prescribing. Research for peer review in this area should be encouraged.
- address the key limitations identified including where responsibility lies for test results and prescribing decisions; curation of drug-gene associations as new evidence emerges including clear actions for prescribers (accounting for local formularies).

- work with NICE to incorporate the national guidance for prescribers into NICE guidelines.
- consider the impact on equitable access with Genomics England's Disparity Group.
- work with the medical colleges, and other professional bodies, and Health Education England to help prescribers understand the value of alerts (and decision support) and identify any broader training needs related to pharmacogenomic information.
- co-produce guidance and materials to help patients to understand the results and what they mean in terms of medications so they can be involved in decisions about their medications and treatment.
- produce a rating scale on drug-gene interactions for local use and interpretation.
- work with clinical systems suppliers to design out alert fatigue.
- establish the information governance and medico-legal requirements surrounding sharing pharmacogenomic information.
- work with clinicians, other professionals, citizens, system suppliers, NHS Digital and the UK Terminology Centre to develop information and technical standards that support pharmacogenomic (and genomic) information sharing, its storage, coding and interaction with medications databases.
- ensure local multi-disciplinary oversight committees are established (where they do not already exist) to develop local guidance for prescribers based on national guidance, interpret the national evidence to support local populations and commissioning arrangements in the context of existing alerts and review their effectiveness and adjust them as required.

In summary, whilst there is evidence for the use of alerts for pharmacogenomic information, implementation is in its infancy internationally and there are a number of system wide actions that need to be taken to enable effective implementation in clinical systems. Therefore, we recommend a small-scale pilot of alerts for a small number of drug-gene pairs that will deliver clinical safety benefits alongside a work to address some of the challenges before a wider rollout with a major focus on developing strategies for mitigating alert fatigue.

Alerts are only one tool for ensuring pharmacogenomic information supports safe prescribing. Other means should be explored that can be actioned currently in systems including changing the colour and font so that clinicians are alerted to pharmacogenomic information. As digital systems mature and pharmacogenomic information becomes more widely available in the NHS, it will be possible to employ a more nuanced approach to sharing information about drug-gene variants. Tools

such as clinical decision support will play an increasingly important role in informing clinicians early in the treatment pathway about a patient's drug-gene variants with accompanying evidence to support safe and effective prescribing decisions

1.2. Purpose of this document

This document is a summary report of the guidance for using pharmacogenomic information in clinical practice. It presents:

- Guidance for the alerting of pharmacogenomic information that is agnostic of systems and settings (See section 4 of this report for the guidance) developed following a literature review and consultation.
- The methodology adopted to develop the guidance (See section 2 of this report).
- Findings from the consultation and recommendations (See section 3 of this report).

This project has been led by Dr Reecha Sofat, Associate Professor at the Institute of Health Informatics, University College London and Consultant in Clinical Pharmacology, General Internal Medicine and Stroke at the UCLH Foundation Trust.

1.3. Background

1.3.1. Project summary

The purpose of this project is to improve the safety of prescribing choices by facilitating the use of actionable pharmacogenomic information at the point of care, agnostic of systems and settings; making the information available to prescribers and other health professionals so individuals may derive benefit from their pharmacogenomic information.

It is recognised that pharmacogenomic information may need to be actioned in different healthcare settings with different levels of resources. This may or may not include access to electronic prescribing systems and health care records; the implementation of which is often heterogenous with poor interoperability. For example, in the NHS such systems are currently more advanced in primary care; with limited use in secondary care. Although the implementation of electronic sharing of pharmacogenomic information will not be possible without electronic systems, the key recommendations in this guidance i.e. what information is needed and when it is needed, by whom still apply to resource poor environments. The guidance is intended to be suitable for and adopted by both primary and secondary care and, where appropriate, in other domains such as social care.

It is acknowledged that this is an emerging field at an early stage of development; there is a need for a wider programme of work on the system-wide implementation challenges of sharing pharmacogenomic information beyond this project. This report identifies the further work needed (see section 3).

1.3.2. Project context

The emerging field of pharmacogenomics[c], defined here as the study of variability in drug response due to heritable changes in the human genome[7, 8], holds promise for targeted therapeutics. Pharmacogenomics has the potential to facilitate precision in drug dosing, improved targeting of therapies for diseases, and reduced incidence of adverse drug reactions (ADRs).[8] However, integration into clinical practice has been limited by multiple system-wide challenges and barriers that have been compounded by gaps in the evidence base; both locally in the NHS and internationally.[8, 9]

The interpretation of pharmacogenomic information is a specialised skillset that, at least as things stand today, is beyond the formal training of most health professionals.[10] Therefore there is a need for the translation of an individual's pharmacogenomic data from the laboratory into a form that is easily understood by health professionals and clinically actionable at the point-of-care.[11] The two main vectors for this lab-to-clinic communication are generally computerised and include:

1. Formal Clinical Genomics Reports where domain experts in pharmacogenomics provide a written interpretation of a pharmacogenomic test result for the clinician[10]
2. Clinical Decision Support (CDS) where computerised rules-based systems trigger notifications and alerts that communicate specific recommendations and warnings to clinicians, regarding an individual's pharmacogenomics[10]

Medicines use is by and large evidence based, where national and local guidelines are in place to support such decisions.[12] However, it is also well known from both NHS and international data that despite an evidence base, individuals experience ADRs [13-17] ADRs have been associated with

- admission to hospital in approximately 6.5% of UK adult inpatients[13] and 2.8% of UK paediatric inpatients[14]
- adverse events during hospital inpatient stay in approximately 14.7% of UK adult inpatients[15] and approximately between 9.5% (international data)[16] to 17.7% (UK data)[18] of paediatric inpatients.

An individual's pharmacogenomics can potentially contribute to predictable life-threatening ADRs, for example type IV hypersensitivity reactions. This occurs where a drug is prescribed and an adverse reaction could have been predicted, given the genetic variation in that individual and knowledge of how that drug is handled. This is

[c] In this document the broader term pharmacogenomics, which generally refers to all the genes in the genome influencing drug response, is used *interchangeably* with narrower term pharmacogenetics, which more often refers to the relationship between a single gene and single drug. The distinction between the two terms is generally considered arbitrary by leaders in the field.[1]

commonly referred to as an actionable drug-gene association (DGA). For example prescription of the anti-retroviral drug abacavir can cause a life threatening hypersensitivity syndrome in individuals with the *HLA-B*5701* allele; [19] carbamazepine can cause life-threatening Stevens-Johnson syndrome in individuals with the HLA-B*152 allele. Currently, abacavir and carbamazepine are the only two drugs where British prescribing guidelines mandate pharmacogenetic testing before commencing treatment, and only in certain populations.[8]

However, pharmacogenomic testing is not yet routinely used in the NHS and is provided in the UK in a limited number of specialist centres. Worldwide, there are no examples of national programmes for pre-emptive pharmacogenomic testing that is where information from multigene panel testing is available in anticipation of a possible later prescription.[8] However, the majority of pharmacogenomics alerts, where systems are in place, are 'post-test' that is they occur where the results of pre-emptive panel testing are available.[4]

It is well known that the majority of individuals carry actionable pharmacogenomic variants[20] and may have a chance of being prescribed a drug with an associated actionable DGA in their interaction with healthcare:

- Primary care: a retrospective analysis of the NHS medical records of ~ 7 % of English primary care patients aged 50 - 99 years (n = 648,141) found that eight out of ten individuals were exposed to at least one 'pharmacogenomic drug' (actionable DGA) over a 20 year evaluation period; with the exposures representing 16% of all drugs prescribed.[21]

- Secondary care: a retrospective analysis in the USA of elderly hospitalised inpatients (n = 20) who were part of a cohort of pre-emptively genotyped outpatients (n = 867) was done. In total the 20 hospitalised patients were exposed to 108 newly prescribed drugs, approximately one third of which were 'pharmacogenomic drugs'.[22]

As a caveat it should be recognised that some individuals will never come into contact in their lifetime with a specific drug and its particular associated genetic variant.

The overall purpose of the developed guidance (see section 4) is to improve the safety of prescribing choices by facilitating the use of understandable and actionable pharmacogenomic information at the point of care. This is agnostic of particular systems and settings, but with a focus on computerised alerting. **The aim was to develop systemwide guidance for the alerting of pharmacogenomic information to prescribers and other health professionals in order that individuals may derive benefit from their pharmacogenomic information**.

The Professional Records Standards Body (PRSB) was commissioned by NHS England to undertake a consultation and validation exercise in order to develop the guidance for 'alerting' pharmacogenomic information to prescribers at the point-of-care and to help understand if pharmacogenomic alerts represent a safe and workable implementation of pharmacogenomics into clinical practice.

1.3.3. Project objectives, scope and governance

The objectives, scope and governance are described in appendix A (separate document). Project board membership is summarised in appendix B (separate document).

2. Methodology and methods used to develop guidance

2.1. Methodology

This section summarises the overall methodological approach used to develop the guidance. Appendix D has further details of the consultation approach, as well the specific methods involved.

2.1.1. Project approach

The overall approach to the development of the guidance was phased.

The **first phase** was the scoping phase which consisted of:

1. an evidence review and synthesis
2. a focus group meeting with a small number of key UK stakeholders (including primary and secondary care clinicians, pharmacists and geneticists).
3. interviews with national and international stakeholders (including country comparator opinion leaders).

The **second phase** was the development of guidance that consisted of:

1. further meetings with domain specific stakeholders and the use of existing PRSB networks and meetings to test the guidance; including the PRSB Advisory Board meeting

2. a second wider multi-disciplinary and patient focus group meeting to test and refine the guidance.

The **third phase** was the finalisation of the project deliverables. This included:

1. final review of the guidance and final report, including specialists in pharmacy and genomic medicine.
2. a final project team review to reflect, revise and finalise findings of the report and refine the guidance.

Selected output from the consultations and evidence review used to inform the draft guidance can be found in appendix E (separate document).

2.2. Phase one methods – defining project scope

2.2.1. Evidence review

The scope of the literature review for the evidence synthesis was necessarily limited; by time and budget constraints but also by the fact that the literature on pharmacogenomic alerts in healthcare is at a relatively early stage (~10 years of pilot or prototype systems). The key findings from the literature review were based around 4 themes that would later be discussed in the first focus group (see 2.2.2, further details can be found in appendix D (separate document)).

The evidence review:

- informed a preliminary draft set of discussion points to form a basis for consultation at the first focus group meeting, on the project scope

And later:

- allowed identification of research groups working on pharmacogenomic alerting systems for further consultation
- provided peer-reviewed evidence for the recommendations made in the draft guidance.

2.2.2. Focus group one

The evidence review was followed by a focus group (attendees are listed in appendix B (separate document). The aim of this focus group was to explore the scope of pharmacogenomic alerts guidance should be to improve safety and care of individuals. Discussion was facilitated by illustrating the common themes from the

evidence synthesis. The key themes discussed were those resulting from the evidence review:

1. What information is being 'alerted'?
2. How is the information presented?
3. How is the information available dynamically through the lifecycle of a prescription?
4. How is this going to iteratively evolve?

A report on the findings from focus group one can be found in appendix F (separate document). Selected output from the first focus group consultation, in the form of quotes used to inform the guidance, can be found in appendix E (separate document).

2.2.3. Consultation calls

To gain an insight into the current implementation of pharmacogenomic alerts and clinical decision support in different systems and settings, semi-structured interviews were conducted with international experts who are already implementing pharmacogenomics alerting systems in healthcare and research settings. In addition, consultation calls were held with patient representatives and UK-based professionals. All consultation calls held can be found in appendix B (separate document). The output from the consultation calls was used to inform the draft guidance. Quotes from the consultations can be found in appendix E (separate document) as justification for the guidance.

2.3. Phase two methods – developing the guidance

2.3.1. PRSB advisory board

A consultation session was held at the PRSB Advisory Board meeting representing a broad range of professional expertise including several experts in health informatics as well as patient groups. The discussion in the meeting included feedback on the preliminary findings of the consultation to help inform development of the draft guidance. Selected output from the Advisory Board meeting, in the form of quotes, can be found in appendix E (separate document) as justification for the guidance.

A consultation survey was sent to Advisory Board members following the meeting resulting in 24 responses. Details of the participants and outputs can be found in appendix D (separate document). The responses were used to inform the guidance.

2.3.2. Twitter Chat with Patient Representatives

In order to gather additional patient perspectives, the PRSB organised a twitter chat with patient representatives, entitled ‘What does your clinician need to know about your genes?’ The five questions asked to spark discussion, and responses can be found in full using the PRSB’s twitter handle @ProfRecordSB.

2.3.3. Development of the initial draft

The outcome data of the consultation process was used to develop a first draft of the guidance. This was then followed by consultation with a second focus group and with the project board for review and update purposes; additional feedback was also sought from key stakeholders via phone and email.

2.3.4. Focus group two

The second focus group was held with patient representatives, healthcare professionals, PRSB representatives and members of the project team (attendees are listed in appendix B (separate document)). The purpose was for stakeholders to review and contribute to the draft guidance to ensure that the guidance was practicable, understandable and fit for purpose. A copy of the draft guidance used for the consultation can be found in appendix G (separate document).

Views were sought on the draft guidance recommendations and implementation challenges; as well as several clinical scenarios (appendix C (separate document). The implementation challenges for discussion included:

1. Alert fatigue
2. Clinician and pharmacist buy-in to pharmacogenomic alerts
3. The influence of other clinical factors e.g. polypharmacy and co-morbidities
4. Ensuring the consistent interpretation of guidance in different settings
5. The need for education and training in pharmacogenomics
6. The development of guidance relating to actionable drug-gene associations
7. Challenges related to the current capabilities of clinical systems

Selected output from the second focus group, in the form of quotes, can be found in appendix E (separate document) as justification for the guidance.

2.4. Phase three methods – finalising the project deliverables

A further, final, review of the guidance and final report was conducted, which included discussion and feedback by specialists in pharmacy and genomic medicine (See appendix B (separate document) for participants). Following this a final project team review was conducted to reflect, revise and finalise findings of the report and refine the guidance.

2.4.1. Final project deliverables

The draft guidance was updated following the consultation. The final guidance can be found in section 4 of this report; with key findings from the consultation and recommendations for implementation and further work in section 3 below.

3. Key findings and recommendations

3.1. Introduction to pharmacogenomic alerts

Electronic alerts are classified based on the status of pharmacogenomic test results.

- **Post-test alerts:** These alerts are triggered where an individual has pharmacogenetic test results recorded within the EHR.
- **Pre-test alerts:** These alerts are triggered in where the individual's pharmacogenetic test results are not recorded within the EHR, but the choice of drug might trigger the prescriber to request a pharmacogenomic test.

Electronic alerts can be further subcategorised as 'active' or 'passive' (figure.1)

- **Active alerts:** These alerts are interruptive and should be actioned in order for the end-user to progress further in the workflow.
- **Passive alerts:** These notifications are informational and appear in the workflow but are optional to view or respond to. There may also be 'passive' links to internally curated guidance or external sources of information.

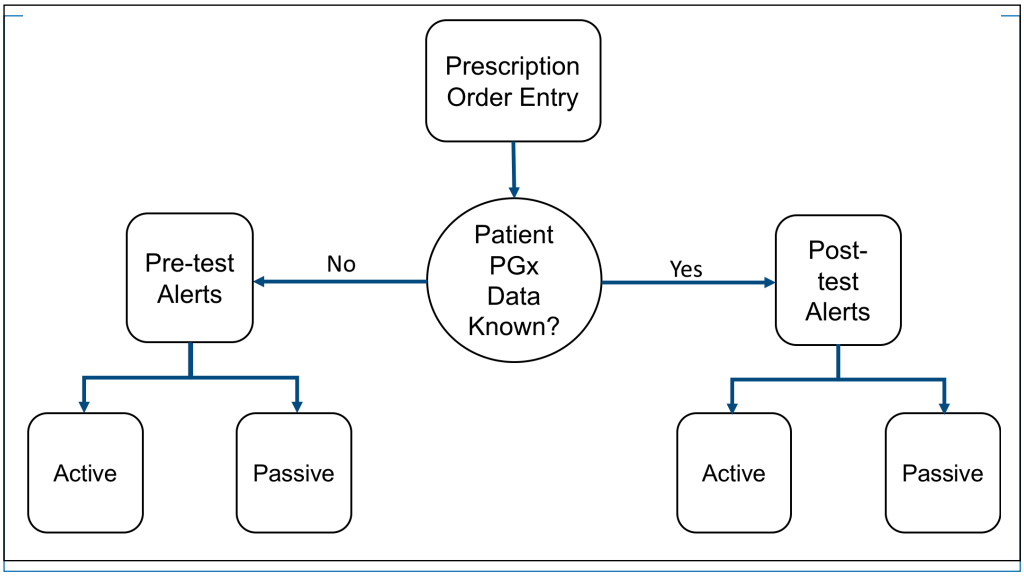

Figure 1: Flow diagram showing the classification of alerts

In the examples we have explored, pharmacogenomic alerts are generally, but not always, electronic popups within an EHR and use static text to convey information such as:

- the reason for the alert
- the relative importance of the alert
- a summary of the relevant DGA / phenotype
- a recommended course of action and options (via radio buttons)
- a link to further resources

Electronic alerts are generally triggered at the time a new prescription is written within an electronic prescribing system.

Physical alert cards have been described for use in resource poor settings[2] and as part of the European U-PGx project, which included a QR code linked to a website providing customised prescribing recommendations for settings with limited or no in-house electronic CDS.[3]

Key findings from the literature review and the consultation with international colleagues and UK stakeholders and recommendations for implementation and further work are set out below.

3.2. Current status of implementation of pharmacogenomics alert systems

Key findings:

- There is much interest in, and work taking place on, the use of pharmacogenomic alerts in other healthcare systems to improve the patient safety and effectiveness of prescribed drugs. International collaborators have been keen to share their findings and we should learn from their experiences albeit applied to the NHS where possible.
- Much of the international work is pilot/prototype work using clinical decision support in secondary care; where the majority of pharmacogenomics alerts implemented are 'post-test' (occur where the results of pre-emptive panel testing are available)[4] However, worldwide, there are currently no examples of national programmes for pre-emptive pharmacogenomic testing.[8]

Recommendations:

I. NHS England should pilot the implementation of pharmacogenomic alerts, on a small scale initially, to develop mitigations for the risks and unintended consequences and to test the guidance developed by the PRSB.

II. NHS England should address the systemwide recommendations identified in this section in parallel with the pilot.

3.3. Establishing clinical responsibility and oversight in pharmacogenomics

Key findings:

- A 2019 review emphasised a key principle that pharmacogenomics 'is a powerful tool but does not override the need for clinical assessment and judgement, this should not be forgotten.'[23]
- During the consultation stakeholders have emphasised the need to avoid using alerts where other clinical factors clearly supersede a patient's pharmacogenomics e.g. developmental pharmacology in paediatrics (section 2.9, appendix E).
- The incorporation of additional clinical factors into electronic alerts, such as end-organ dysfunction, is technically challenging and to our knowledge has not been implemented in pilot/prototyping work.

- 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.[21] Most prescribers have had limited exposure to pharmacogenomics during their training. They may not feel comfortable handling genetic information unrelated to their specialty or prescribing unfamiliar drugs due to contraindicated genetic variants or polypharmacy.

- Clinicians are receiving an increasing number of 'unsolicited genomic test results' (from tests that they did not order)[24] and prescribers can also be unsure of where clinical accountability lies in terms of who should be notified, interpret, disclose and take action when pharmacogenomic test results are returned. Stakeholders in our consultation process were unable to form a consensus on this matter. This is reflected in the literature where a survey of clinician's attitudes, who had participated in the PREDICT pharmacogenetics CDS programme, found that respondents assigned responsibility for acting on a test result to variously to health professionals including the primary care provider (12.5%), the provider who ordered the pharmacogenomic test (54.0%) and provider who previously prescribed a drug affected by the DGA and the specialist treating the medical condition affected by the DGA (77.5%).[25]

- Several international stakeholders have introduced a multidisciplinary oversight committee into their pharmacogenomics services[25-27] as a form of formal governance; with primary roles that include:
    - Ultimate responsibility for approving which DGAs are incorporated into the EHR for the triggering of electronic alerts (in electronic systems) basing decision making on curated primary evidence and guidelines)
    - Deciding the precise wording of recommendations shared in alerts.

- In some cases, the oversight committee has been created as a novel entity and in others the role may be delegated to the local Pharmacy and Therapeutics Committee; who would ordinarily be responsible for deciding which drugs are on the entity's formulary. Our consultation with stakeholders in primary care suggests that such oversight in the NHS should be compatible with and conducted by existing committees and governance structures.

- Currently, different clinical systems use different ratings systems to highlight the relative importance of the alerts based on local clinical prioritisation and some stakeholders would prefer that pharmacogenomic alerts fit into existing alert systems where they are already in place.

Recommendations:

III. The pilot should start with relatively focussed alerts for pharmacogenomic information rather than trying to incorporate other parameters e.g. renal or hepatic impairment. This should bring pharmacogenomic information into focus and not complicate it with other factors. As clinical systems and evidence develop consideration should be given to how to combine different factors into a single alert with a recommended action. Clinical judgement should be exercised when evaluating the relevance of pharmacogenomic alerts in various clinical contexts, seeking expert help where there is uncertainty.

IV. The responsibility for pharmacogenetic test results and any required subsequent actions must be clearly delineated for prescribers and built into education and training.

V. Local guidance and recommendations should be determined and supported by local oversight and advisory committees to ensure that prescribers act appropriately on wider implications of pharmacogenetic test results. Oversight committees should have input from a multi-disciplinary team of health professionals; particularly those with prescribing or dispensing authority or with expertise in pharmacogenomics or clinical decision support. Its responsibilities should include but not be limited to reviewing alerts on a regular basis and take an active interest in prescriber education. It is important that there can be local interpretation of pharmacogenomic alerts in relation to other medication alerts to support local populations and local commissioning arrangements but equally variability should be reduced by ensuring that ratings are based on national principles and categorisation.

3.4. Selection of drug-gene pairs and guidance development for prescribers

Key findings:

- There is a requirement for standardisation of the guidance regarding DGAs in order for the safe implementation of pharmacogenomic alerts now and in the future as new evidence emerges. [28] This finding emerged from the literature and consultation process, both of which highlighted the limitations of guidelines produced by regulatory bodies (FDA and EMA) and consortia (CPIC), in this respect (see appendix E sections 2.10 – 2.12).
- There is a currently a paucity of high-quality clinical evidence (RCTs) to demonstrate clear benefits of pharmacogenomics testing.[29] There are examples in the literature of commonly prescribed medications with spurious

pharmacogenomic associations that should not be alerted; for instance, statin therapy remains in the therapeutic range “irrespective of the KIF6 genotype”.[30]

- Issues relating to equitable access to medicines emerged from the literature review and consultation process (see appendix E section 2.24). For instance, it is unclear whether incorporating self-reported ethnicity is of benefit to genotype based prescribing decisions, as it may not be a reliable proxy for underlying genotype but its use may be justified in some circumstances such as when considering access and affordability of healthcare; e.g. as a prompt for running a point of care test for at risk individuals where pre-emptive testing is unavailable.[31] Furthermore, the fact that the majority of DGAs have been evaluated in individuals of European ancestry has implications for when alerting in settings with ethnically diverse populations e.g. the inadequate performance of pharmacogenetic dosing algorithms for warfarin in non-Caucasian individuals.[31] This is an area of pharmacogenomics with wide ranging implications for patient care and warrants detailed further consideration.

Recommendations:

VI. There must be evidence-based curation of drug-gene associations at a national level which may be subject to local implementation depending on requirements. This must include a clear action for prescribers to take, which can be executed at a local level (i.e. taking into account local formularies etc.). Consideration will need to be given to iteration and update of the evidence-base for drug-gene associations to ensure that recommendations remain valid and current for individuals and clinicians as new evidence emerges.

VII. Since there is currently a move to harmonise medication recommendations, NICE is producing the national-level guidance and all new medications have to go through a NICE Technology Assessment (TA) before they can be used: NHSE should work with NICE to determine how and where pharmacogenomic drug-gene recommendations can be incorporated into the NICE guidance. This could include cost-benefit / safety-benefit analyses to establish which initial drug-gene associations to pilot and subsequently roll-out. Consideration needs to be given to how the guidance is stored so that it can be accessed by the clinical decision support systems and used in alerts.

VIII. In determining the drug-gene pairs for implementation, the national Pharmacogenomics Working Group should consider the impact on equitable access and link with Genomics England’s Disparity Group as there is a risk that rolling out alerts could exacerbate disparities with the burden greatest in the under-served populations.

3.5. Pharmacogenomic alerts - principles

Key findings:

- Prescriber buy-in and rates of clinical adoption are optimised where there are simple recommendations that are prescriptive.[29]
- A review of drug safety alerts (n = 17 studies) has 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'.[32] Other studies have also emphasised the requirement for specific actionable recommendations.[33] These findings were supported by a strong consensus during the consultation process (section 2.11 – 2.12, appendix E).
- Consultation with international experts implementing pharmacogenomic alerting systems shows that alerts are generally triggered at the time prescription is written but may occur at other times[4] For example, in a 2014 study of pre-test alerts in secondary care in the USA the majority of alerts that were shown to attending physicians, nurse practitioners and pharmacists, were presented "during prescribing or to pharmacists when the orders were processed for dispensing." [26] During the consultation stakeholders emphasised that dispensing pharmacists will require access to alerts in addition to prescribers to enable them to check for prescribing errors.
- Stakeholders with prescribing authority have expressed concerns about what action to take in the interim period following a pre-test alert, when a pharmacogenomic test result in pending.
- Both local and international stakeholders emphasised that alerts should be presented to any health professional with prescribing or dispensing authority with responsibility for the patient, at an appropriate time and in multiple clinical settings as required (section 2.16, appendix E). This will enable them to advise the patient accordingly and may assist them in other medicines recommendations (for example, over-the-counter medicines).
- 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. One suggestion was that it could be an extension of the existing NHS Digital transfer of information programme for pharmacist interventions.
- Generally, information on the effectiveness of alerts in a local setting is only available retrospectively after an appropriate period of evaluation ((see references [27, 34-36]). International implementors have described to us

scenarios where, despite strong evidence for alerting a particular DGA in the literature and for reasons that may not be immediately apparent, the alert is continually ineffective or overridden by prescribers (section 2.18, appendix E).

- There is to our knowledge currently no robust evidence (e.g. randomised trial or systematic reviews) demonstrating clear safety advantages of particular types of alert (e.g. active / passive, hard / soft stops, electronic / physical) over another. Although various benefits and limitations for each have been widely discussed, (particularly outside of pharmacogenomics) and the majority of implementations in settings with mature IT infrastructure have focused so far on interruptive (active) electronic alerts[3, 4] (including the international stakeholders we consulted); we have not made any firm recommendations in this regard.

Recommendations related to implementation of alerts for sharing pharmacogenomic information are set out in the guidance in section 4.

3.6. Alert fatigue

Key findings:

- Alert fatigue is a desensitisation phenomenon that occurs when electronic CDS systems are utilised in live clinical settings, where the sheer number of daily alerts and notifications (many of which have limited clinical consequence) results in users ignoring or overriding the alert.[37] It is a potential barrier or risk to implementation.
- A new retrospective analysis of over 296,000 prescriber-patient interactions where a CDS system alerted co-prescription of opioids and benzodiazepines has demonstrated a significant detrimental impact of alert fatigue on alert effectiveness and safety.[36]
- Whilst designed to be helpful and supportive within clinical systems, there are major consequences to workflow that have been identified. Moreover, alert fatigue could result in patient safety issues. Alert fatigue already exists in most electronic prescribing systems.
- Alert fatigue might be more of a problem in different clinical settings and clinical specialties. It was expressed as a major concern by primary care clinicians particularly for common disease drugs and high-volume drugs although in certain settings e.g. cancer it might be less of an issue.
- Additional findings included a number of potential mitigation approaches including:
    - Sharing specific actionable recommendations within the alert itself
    - Only triggering interruptive alerts for the highest risk drug gene associations

- Suppression of low priority alerts through:
  - Tiering / risk stratification
    - Comparison of a priority 'tiering' method with a control, in drug-drug interaction (DDI) alerts in two separate sites found that the number of severe alerts overridden at the tiered site (0%) was far less than the non-tiered site (66%).[38]
  - Undertaking audits of alert utilisation and effectiveness and disable alerts that are not effective (if safe).
- Ensuring the alerts are appropriate to the role. For example, pharmacists may see a different subset of alerts from a hospital doctor.
- Effective design of the alert / ergonomics so that it presents the information in the order that it is needed, it clearly illustrates the importance of the alert and it provides easy access to information about alternative actions.
- Making the pharmacogenomic information available earlier in the workflow so that prescribing decisions can be made before the prescription is written.

Recommendations:

IX. Nationally, the likely consequence and degree of certainty of drug-gene interactions should be categorised into a scale, insofar as is possible, that can then be interpreted locally for implementation. This will support suppression of low priority alerts and reduce variation in interpretation of the information.

X. Work with the system suppliers on developing principles for effective alert design as part of a wider programme of work on alert fatigue considering other types of alerts e.g. national safety alerts.

XI. When piloting alerts, test the use of passive alerts (and context sensitive information) earlier in the clinical workflow in addition to active alerts to definitively establish the relative effectiveness of these approaches, including hard-stops and related methods. Research for peer-review in this area should be encouraged. Consider the best approaches for implementing alerts into different clinical settings and the type of drug and its use.

3.7. Clinical systems, data and the need for iterative analysis

Key findings:

- Given the permanence of an individual's genome a pharmacogenomic test should in theory only need to be conducted "once in a lifetime".[29] However, the evidence base is constantly evolving.
- Analysis done by experts in medical ethics has concluded that there is an ethical duty requiring iterative analysis of an individual's genomic information as the evidence base changes[39]; test results must be available at the point of care and updated in line with changes to the evidence base e.g. when a genetic variant is later found to be associated with a new or different phenotype than was understood at the time of the test.
- This requires an individual's pharmacogenomic data to be stored in a way that is secure, accessible, enduring and in a format that facilitates reanalysis. Currently this means the use of raw (FASTQ, BAM) and intermediate (VCF) pharmacogenomic data files, which are too large to be stored in the electronic health record.
- Open questions remain in the literature on where pharmacogenomic (and genomic) data should be stored. Early attempts to integrate pharmacogenomics into the EHR have stored pharmacogenomic data (as a phenotype) either in the allergy or problem lists, rather than in a unique repository within the EHR;[29] however, a working prototype using a GACS server to store pharmacogenomic information in parallel to the EHR has now been described[40]. It is currently unclear which storage strategy is most advantageous in electronic CDS systems.
- Implementation of pharmacogenomics alerts in electronic clinical decision support systems will depend on local digital maturity and capability. For alerts to be integrated into these systems electronic health record systems must be able to receive and process structured, coded pharmacogenomic information. Clinical systems must have capability to support alerts and notifications.
- Pharmacogenomic results of a test need to be stored or issued in such a way that they can be computed by receiving systems. They should be coded and structured and consistent with prevailing messaging standards e.g. FHIR.

Recommendations:

XII. National information and technical standards should be developed to support the sharing of pharmacogenomic (and genomic) information. Early discussions should take place with clinical systems suppliers about integrating pharmacogenomic information and implementing alerts.

XIII. Pharmacogenomic test results must be coded in such a way that enables the clinical systems and especially their medication knowledge databases to interact with them. Consideration needs to be given as to how much information needs to go in the coded clinical concept and how much

should be stored in the knowledge database. (terminology v information models).

XIV. Modifications may need to be made to the structure and standardisation of current medication modules to allow pharmacogenomic information to be correctly processed. This is a significant piece of work that needs to take place with NHS Digital and the UK Terminology Centre, and it is vital that information flows and consequent coding requirements across the whole process are considered to understand how to best support sharing and use of this information. There is a significant danger of over alerting if care is not taken in determining how medications and pharmacogenomic results should be coded.

XV. Regardless of how alerts are implemented and triggered in electronic systems; an individual's pharmacogenomic data should be available in a format suitable for iterative analysis.

3.8. Education and training

Key findings:

- Health care professionals want to help their patients understand the result of a test and what it means in terms of clinical outcomes.
- Most prescribers have had limited exposure to pharmacogenomics during their training. They may not feel comfortable handling genetic information unrelated to their specialty or prescribing unfamiliar drugs due to contraindicated genetic variants or polypharmacy. Alerts can be used as important "just in time" guidance and the importance of alerts in this should be built into education.
- The importance of role appropriate education and training was highlighted in our discussions. Some health care professionals would need to understand the evidence-base for drug gene pairs in detail if, for example, they are involved in determining the relative importance of medication alerts for a local system. For instance, GPs may have different education requirements from pharmacists; as the latter cover pharmacogenomics at undergraduate and postgraduate levels. Health Education England (HEE) has a genomics education programme with a large amount of curated guidance and materials already available. HEE does not currently provide guidance relating to pharmacogenomics testing and is currently developing their strategy for pharmacogenomics education and training.

Recommendation:

XVI. Work with the medical colleges and (other professional bodies) and HEE to help prescribers understand the value of alerts (and decision support) as a means of learning and 'just in time' guidance, in addition to any

general education or training on pharmacogenomics as part of the medical training curriculum or Continuing Professional Development.

3.9. Patient considerations

Key findings:

- Patients have told us that they want to know how their identified gene variants effect how they will react to certain medications.
- Patients and clinicians need to be kept informed about relevant changes to the evidence base regarding their pharmacogenomic data and that they would like easy access to this data e.g. via patient portals.
- A recent meta-analysis (n = 31 studies) looked at patient and healthcare provider 'needs and preferences' relating to pharmacogenomic testing.[41] 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.[41] These literature findings are consistent with the views expressed by patient representatives during the consultation process.
- During the consultation process a consensus was found amongst prescribers that pharmacogenetic variants should be considered to be like and viewed in the same way as any other clinical data – "another tool to optimise medicines"; and that consideration of an individual's pharmacogenomics as being more complex or emotive shouldn't be encouraged several agreeing with the statement "we need to break down misconceptions around the ethics of pharmacogenomics versus the other types of genetic testing." This belief was echoed by some patient representatives but not all.

Recommendations:

XVII. A communication strategy for informing individuals and their clinicians when new evidence comes to light regarding drug-gene associations should be considered and developed during piloting.

XVIII. Work should take place with patient groups, prescribers and pharmacists to develop guidance and materials to support helping patients to understand the results and what they mean in terms of medications so they can share in decision making about their medications.

3.10. Medico-legal considerations

Key findings:

- Concerns over the medico-legal implications of introducing pharmacogenomics into healthcare systems, including in resource poor settings[42], and integrating pharmacogenomics into the EHR[43] have been raised for some time. However, the significance of various legal issues raised by our stakeholders such as the privacy and liability for and responding to the data shared in alerts remain unclear.[44]

Recommendation:

XIX. Work should be done to more fully establish the medico-legal issues surrounding alerts; aiming to achieve clarity on when various stakeholders are liable and their legal responsibilities e.g. prescriber, pharmacist, system supplier, other.

4. Guidance for pharmacogenomic alerts

4.1. General Principles

The implementation of pharmacogenomic information into clinical practice has the potential to improve use of medicines by reducing the number of ADRs either through using alternatives or alteration of drug doses. The information can and should be shared at different points in the clinical workflow using clinical decision support but from our evidence review and discussions with those that have implemented pharmacogenomic information into clinical practice, interruptive alerts have been used as the failsafe mechanism when a prescription is likely to result in significant harm to the patient.

This guidance sets out what information should be made available to professionals and when and is based on analysis of the evidence and consultation. Care should be taken to ensure that the implementation does not compromise established principles of prescribing such as the 'rights' of medicine administration e.g. the right individual, the right drug, the right dose, the right frequency, the right route, right time for administration, the right allergy status and the right to refuse treatment. Alerts can be considered a clinical decision support aid for ensuring an additional principle – the right pharmacogenomic status.[45]

4.1.1. General principles

- The integration pharmacogenomics information into decision support is extremely challenging and in its infancy. Clinical judgement should be exercised when evaluating the relevance of pharmacogenomic information in various clinical contexts, seeking expert help where there is uncertainty.
- Pharmacogenomic alerts should share information that is actionable, evidence-based, accurate, concise, timely, and unambiguous with links provided to relevant information.
- Pharmacogenomic information should be available to clinicians independent of alerts. Alerts should not take place of a formal pharmacogenomic result or clinical judgement and are ultimately an additional failsafe mechanism for the prescriber.
- Alerts should be used at the time a prescription is written and at the verification and dispensing stage when new test results are received or when prescribing but a mandated pharmacogenomic test has not taken place.
- Alerts should be presented to any health professional with prescribing or dispensing authority (with responsibility for the individual), at an appropriate time and in multiple clinical settings as required. It is also important for

pharmacists to have information on what action the prescriber took in response to the alert and why.

- The alerts should include a prescriptive (with little uncertainty) recommended action (e.g. a change of drug must include a viable alternative, a change of dose must include the dose to be administered, a prompt to request a test must explain which test etc.).
- There should be easy access to the means of fulfilling alternative actions recommended in an alert (e.g. the medication must be available as part of a local formulary; it must be possible to order the test) otherwise it may not be actioned.
- In the case of pre-test alerts, clear and specific guidance should be made available to the prescriber outlining what action to take in the interim, pending the pharmacogenomic test result.

4.1.2. General principles of implementation

- The implementation should start with basic pharmacogenomic alerts with clear guidance (polypharmacy, co-morbidities and other clinical factors should be considered later as clinical systems advance and the evidence evolves. Currently these considerations will fall into clinical judgement).
- Consideration should be given to minimising alert fatigue in electronic systems, reducing the burden on prescribers and mitigating unintended consequences for individuals, insofar as is possible by careful design and integration in the clinical workflow (passive and interruptive alerts should be considered).
- The implementation of pharmacogenomic alerts within any healthcare setting should have input from a multi-disciplinary team of health professionals; particularly those with prescribing or dispensing authority or with expertise in pharmacogenomics or clinical decision support.
- The results of pharmacogenomic tests are intended to be valid throughout an individual's lifetime; test results must be available at the point of care and updated in line with changes to the evidence base e.g. when a genetic variant is later found to be associated with a new or different phenotype than was understood at the time of the test.
- Individuals should not be denied medications, from which they would derive benefit, on the basis of spurious pharmacogenomic effects. Alert recommendations must be justified by high quality evidence and supported by up-to-date guidelines wherever available.
- Clear and specific guidance should be made available to the prescriber outlining what action to take in the interim, pending the pharmacogenomic test result.

- If, after an appropriate period of evaluation, there is good evidence that a particular alert is ineffective, give consideration to the fact that the alert may also therefore be unsafe and as well as an unnecessary burden to prescribers. Suppression of the alert may be warranted after seeking close consultation with prescribers who have interacted with the alerts over the evaluated period.

It is the intention of this guidance to be systems and settings agnostic. Pharmacogenomic information may be shared in different health care settings with different levels of resources. This may or may not include access to electronic prescribing systems and health care records. The actionable status of an individual's pharmacogenomic information and subsequent prescribing options are independent of systems and settings. Where electronic systems are used, these may be bought externally from system suppliers or custom designed and built internally by healthcare providers; each approach brings differing implementation challenges. Where electronic prescribing systems are unavailable this guidance may be adapted to existing systems and infrastructures.

Ideally, these recommendations assume that the implementation of this guidance will eventually and best take place in health settings where:

1. the use of an electronic health record / electronic prescribing system is already in place or planned
2. there is a clinical decision support system that can utilise information about structured and coded pharmacogenomic results
3. there is access to a structured knowledge base of drug-gene pair interactions and guidance for specific actions to take; and
4. ordering and obtaining the results of an appropriate pharmacogenomic test is practicable.

Where these conditions cannot be met it is recommended that, at a minimum, clinicians have access to genetic test results that have prescribing implications e.g. through visibility of the test results report and are notified of these new results. This information could then be recorded in the individual's record. The sharing of pharmacogenomic information must be compliant with existing information governance requirements and adhere to NHS England's Information Governance Framework.

4.2. Summary of guidance

See section 4.3 for full guidance (with explanatory notes). Further justification of the guidance is provided in appendix E (separate document).

We have used the term alerts in the guidance to mean the provision of information. This could be implemented as active (interruptive) or passive alerts, built into clinical

decision support systems. Implementations in other countries, in the main, used interruptive alerts and the majority of the evidence in the literature refers to the use of interruptive alerts. We recognise the challenges in implementing interruptive alerts in the NHS, in particular the unintended consequence of alert fatigue that has been raised throughout the consultation however we would recommend that where there is a high degree of risk of significant harm to the patient that interruptive alerts are used. We have also provided recommendations for minimising alert fatigue based on findings from this work.

In what conditions should an alert be used?

Alerts **should** be used in the main:

- Using a **dual alerting strategy**: at the **prescribing** **AND** **dispensing** stages
- Only for **actionable drug-gene associations**
- Generally, when:

  I. Where pharmacogenomic **test results are available** (post-test); either when a test result **first becomes available** or when **prescribing** a new drug
  II. Where pharmacogenomic **test results are NOT available** (pre-test); as a prompt to order a pharmacogenomic test, particularly where this is **mandated** by existing standards

Alerts **should NOT** be used, in the main:

- Where the pharmacogenomic **test result does not imply an actionable variant**
- Where other factors clearly **supersede** an individual's pharmacogenomics e.g. developmental pharmacology

What information should be shared in an alert?

Alerts **should** share:

- Best practice recommendations based on up-to-date **evidence**
- Clear, unambiguous and **specific actionable recommendations** for the end-user with access to **further information** as required
- Information that is readily **explainable to patients**

'Who should alerts be presented to?

Alerts **should** be presented:

- In **multiple clinical settings**, to be seen by **any health professional** with **prescribing** or **dispensing authority** involved in the patient's care.

How should alerts be implemented?

The implementation of alerts **should**:

- Consider **unintended consequences**, e.g. **alert fatigue**.
- Be overseen by a **multi-disciplinary oversight committee**
- Consider provision of **expert support in pharmacogenomics**
- Monitor alerts for **quality improvement** purposes.
- Consider the need for equitable access to medicines, regardless of **self-reported ethnicity**.
- Ensure access to the **formal test result**.

The implementation of alerts **should NOT**:

- Place an **undue burden** on prescribers, pharmacists or individuals receiving care.

4.3. Guidance for pharmacogenomic alerts

This section expands on the summary guidance and incorporates some justification (more detailed justification can be found in appendix E (separate document). The guidance has been informed by the results of both the literature search as well as consultations with national and international colleagues who have implemented pilot or prototype systems as well as more specific NHS domain experts.

4.3.1. In what conditions should an alert be used?

- Points 1 – 3 are general principles that apply to all alerts; generally, just before or at the time of prescribing

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.

[*This recommendation ensures the pharmacist is able to perform their essential duty of checking for prescribing errors in the context of the additional pharmacogenomic information available to the prescriber. Furthermore, pharmacists, including those in the community, share the legal responsibility for the safe supply of medicines with*

the prescriber, and should be alerted to pharmacogenomic information relevant to a prescribing choice. Consideration should be given as to how to implement this recommendation, given the fact it was well supported in the consultation process. In addition, consideration should be given to the fact that community pharmacists supply an increasing variety of over-the-counter medications, some of which are associated with actionable pharmacogenetic variants and may need to be alerted independently of a prescription being made. In the majority of cases an electronic alert should be triggered at the beginning of the prescription order entry process i.e. before dose, frequency, route of administration etc have been selected, to minimise frustration for the end-user if a change of prescribing choice is necessitated. Patients carrying alert cards or other physical alerts should be encouraged to show the alert to both prescribers and the dispensing pharmacist, at every contact.]

AND

2. 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.

[*A drug-gene association (DGA) is generally considered to be actionable if awareness of it will likely lead to a prescriber to choose a different drug or an alternative dose based upon clinical judgement. (See appendix E (separate document, recommendation 2 evidence, for more precise criteria).*]

AND

3. In the main where a particular **drug therapy is being initiated for the first time** in an individual.

[*This is not always the case, as some adverse drug reactions or events may occur some considerable time after an individual first took a drug.*]

- Points 4 – 5 apply to active alerts; generally triggered at the time of prescribing as well as passive alerts

4. Where the results of a **pre-emptive pharmacogenomic test are available** (post-test alerts).

[*Alerts are classified based on the status of pharmacogenomic test results. If a test has been done and an actionable pharmacogenomic result is available, consequently triggered electronic alerts are defined as post-test. Physical alert cards should only contain information validated by a pharmacogenomic test result for that patient (post-test).*]

OR

5. 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).

[*If a pharmacogenomic test result is not available or is pending, consequently triggered electronic alerts are defined as pre-test. If a test has been ordered but the results are not yet available a prescriber should be notified at the point of prescribing.*]

- Point 6 generally applies to the two broad categories of pre-test (electronic) and post-test (electronic and physical) alerts

6. Always **where pharmacogenomic testing is mandated** for a drug by existing professional guidance standards

[*For example British prescribing guidelines mandate testing for HLA-B*5701 when prescribing abacavir due to the risk of abacavir hypersensitivity syndrome in individuals treated for HIV and also HLA-B*152 when prescribing carbamazepine due to the increased risk of Stevens-Johnson syndrome, particularly in individuals of Han-Chinese and Thai origin. There is a need for pharmacogenomic testing standards to be developed for use in UK settings for other drugs with actionable pharmacogenomics. This recommendation does not imply that alerts should only occur for mandated DGAs.]*

- Point 7 generally (not always) applies at times other than when a prescription is written and could be a passive or active electronic alert

7. 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).

[*The above recommendation may refer to situations where either a new drug treatment is to be initiated (but has been delayed pending the results of a pharmacogenomics test) or where a treatment was previously initiated that may need to be modified or terminated in the light of new pharmacogenomic information. Unlike recommendation 4 this type of post-test alert is triggered at the point a pharmacogenomic test result first becomes available and not at the point a prescription is written. The decision to stop a treatment already underway, on the basis of alerted pharmacogenomic information requires careful consideration of the risk profiles involved and help from relevant specialists should be sought as required.*]

Alerts **should not** be used:

8. Where the pharmacogenomic **test result does not imply an actionable variant**.

[*Triggering of electronic alerts in circumstances where there is no actionable pharmacogenomic information may contribute to unwanted and unintended consequences such as alert fatigue. However, the pharmacogenomic test result should still be accessible within the EHR. In addition, prescribers should be made aware where pharmacogenomic data cannot be retrieved by the system, in order to avoid clinical errors following where an electronic alert should have been triggered but was not. A reasonable exception to recommendation 10 is in circumstances where an individual has a DGA previously considered not to be actionable (negative) that has subsequently been reclassified as actionable, in the light of new evidence. In such circumstances the responsible health care professional should be alerted if the information is likely to have a material impact on decisions regarding the individual's care. Physical alert cards are not required for patients without actionable variants, even in those individuals from a 'high-risk' ethnic group.*]

9. Where other factors clearly **supersede** an individual's pharmacogenomics.

[*For example, in the context of developmental pharmacology where in a neonatal population, a gain or loss of function mutation in CYP2C19 is not clinically relevant because there is no significant CYP2C19 enzyme activity. Again, in such cases, give consideration to the fact that the alert will be ineffective and in electronic form and may contribute to alert fatigue, in which case it should be suppressed on safety grounds.*]

4.3.2. Further considerations on the use of electronic alerts

Alerts **could** be triggered:

a. In the form of a text message, email, or other suitable format to health care professionals and patients.

[*Other suitable formats might include push notifications within media such as the NHS app, where individual patients could be alerted to important pharmacogenomic data. In resource poor settings alerts might take the form of physical alert cards that could be carried by the individual patient.*]

b. In the event that a duplicate pharmacogenomic test has been ordered for the same individual.

c. Or suppressed as appropriate by additional parameters such as age, drug-drug interactions, renal function, hepatic function, developmental pharmacology, drug-indication, phenoconversion or other relevant considerations.

[The integration of such parameters into decision support alerts is extremely challenging and in its infancy. Clinical judgement should be exercised when evaluating the relevance of pharmacogenomic alerts in various clinical contexts, seeking expert help where there is uncertainty].

4.3.3. What information should be shared?

Alerts **should** share:

10. Recommendations that are **evidence based**; utilising **up-to-date consensus-based guidance** from approved professional bodies, where practicable.

11. Succinct information regarding the **pharmacogenomic variant and/or** the **phenotype**. i.e. **a straightforward summary**.

12. Clear, unambiguous and **specific actionable recommendations** for the end-user e.g. a calculated dose reduction.

[*The minimum standard for the information shared in a pharmacogenomic alert should be recommended actions that are prescriptive with low uncertainty. For instance, if a drug is contraindicated then a specific alternative should be provided including easily accessible dosing as well as relevant formulary information.*]

13. An **external link** to more detailed **background information and/or** further guidance.

[*This could be provided as a clickable link in an electronic interface or as a QR code or other scannable link in physical alert cards.[3]]*

14. Information that is readily **explainable to individuals receiving care**.

[*Individuals may want to know the implications of a genetic test in relation to what they can and cannot be prescribed as a 'fail safe' mechanism to avoid adverse drug reactions. Individual's queries should be answered comprehensively. This will mean the provision of plain language summaries for patients.*]

- Point 15 generally applies to active alerts triggered in electronic CDS systems (soft stops)

15. **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.

[*Health professionals with a duty of care, that receive an alert downstream in the prescription cycle, should have access to all the pertinent longitudinal information related to a prescription. Providing this information to them at the time they are first alerted may avert the unintended consequence of increased workload if they then need to query the original prescriber's course of action.*]

4.3.4. Further considerations on information sharing

Information **could** be shared:

a. Information regarding the relevant genetic phenotype in preference to genotype.

[*There is some evidence that most clinicians prefer alerts containing phenotypic information, due to a perceived lack of experience with genetics in general and an unfamiliarity with the genotypic star-allele nomenclature. Furthermore, clinical decision support implementation at the variant level is complex and highly technically challenging.*]

4.3.5. Who should alerts be presented to?

Alerts **should** be presented to:

16. **Any health professional** with **prescribing or dispensing authority** involved in an individual's care.

[*Patients carrying alert cards or other physical alerts should be encouraged to show the alert to all prescribers responsible for their care before a prescription is written and to the dispensing pharmacist, at every contact.*]

17. Health professionals in **multiple clinical settings;** including those in primary care, and secondary care including community pharmacies.

4.3.6. Further considerations on presenting alerts to health professionals

Alerts **could** be presented to:

a. allied health professionals with prescribing authority involved in an individual's care in other clinical settings such as care homes and nursing homes.

[*This was suggested in the consultation process but several barriers to implementation were identified. This included the unfamiliarity of care staff with pharmacogenomics prescribing issues and interoperability considerations.]*

4.3.7. How should alerts be implemented?

Alerts **should** be reviewed:

18. In cases where retrospective evaluation shows **robust evidence that the alert does not promote a favourable change to prescribing behaviour**

[*If after an appropriate period of evaluation there is good evidence that a particular alert is ineffective, give consideration to the fact that the alert may also be contributing to alert fatigue. A given alert may be found to be ineffective despite guidance suggesting an actionable DGA, and a reason for the poor performance of an alert may not be obvious. Suppression of the alert may be warranted on safety grounds after seeking close consultation with prescribers who have interacted with the alerts over the evaluated period. Consideration of unintended consequences must take place whenever a change is made*.]

The implementation of clinical decision support for alerts **should**:

19. Include active steps to **mitigate potential unintended consequences** with implications for an individual's safety, **such as alert fatigue**.

[*A major aim of this guidance is to provide suggestions of best practice such that unintended consequences like that of alert fatigue are minimised. Careful implementation should help to mitigate the effects of alert fatigue. Strategies that have been used elsewhere, include but are not limited to, sharing specific, relevant and actionable recommendations in alerts, only triggering interruptive alerts for the most high-risk drug-gene associations and tiering of alerts according to severity. Exercise caution in the process of tiering, taking into consideration the views of providers and recognise that an alert for a specific drug-gene association may be seen in differing clinical contexts, services and populations. For example, an oncologist and a gastroenterologist who both prescribe the same drug, azathioprine,*

in their different populations may have very different levels of risk aversion to an episode of drug-induced bone marrow suppression depending on the clinical context. Other potential strategies include providing pharmacogenomic information passively earlier in the workflow, such as at the point of diagnosis or as an entry on the problem list, that if the prescriber chooses to action, avoids the need for an active interruptive alert at the point the prescription is written. Furthermore, methods to reduce the desirability of prescribing options in a list (e.g. greying out) have been used to reduce alert fatigue, in situations where there is a relative or absolute contraindication to the prescription. If a contraindicated drug is not selected in the first place, then the need to trigger a safety alert is negated.]

20. Be overseen by a **multi-disciplinary oversight committee** that includes representatives from relevant stakeholders.

[*The primary role of the oversight committee is the ultimate responsibility for approving which DGAs are incorporated into the EHR for the triggering of electronic alerts (in electronic systems); basing decision making on curated primary evidence and guidelines), and for the wording of recommendations shared in alerts. Examples of relevant stakeholders include, but are not limited to, any healthcare professional with prescribing authority, persons with expertise in pharmacogenomics, bioinformatics or clinical decision support; as well as the individuals whose pharmacogenomics is being tested for. Pharmacist representation is considered to be imperative because of their broad range of expertise in pharmacology.*]

21. 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

[*Most prescribers have had limited exposure to pharmacogenomics during their training. They may not feel comfortable handling genetic information unrelated to their specialty or prescribing unfamiliar drugs due to contraindicated genetic variants or polypharmacy. Prescribers can also be unsure of where clinical accountability lies in terms of who should be notified, interpret, disclose and take action when pharmacogenomic test results are returned. These issues are challenging to resolve and may require the availability of additional expertise in genomics during CDSS implementation. For example, certain hospitals within the United States have started to implement dedicated pharmacogenomics clinics for individuals who have actionable drug-gene associations.*]

22. Include dynamic methods to **monitor the performance of alerts**, and how prescribers use them, for data collection, educational and quality improvement purposes.

[For example, *such a method might include an electronic notification triggered to a coordinating member of staff when there is an apparently inappropriate override of an alert; incorporated into a report so that the issue can be discussed by the oversight committee and a remedial action taken if required.*]

23. Include careful consideration of how the pharmacogenomic data, used to trigger an electronic alert, should be stored.

[*Specific recommendations about where and how the pharmacogenomic information used to trigger an electronic alert should be stored are beyond the scope of this guidance. It is however an important further consideration insofar as factors relating to data storage might impact the implementation of alerts.*]

24. Consider and meet requirements for **equitable access** to medicines, **regardless of self-reported ethnicity.**

[*Ethnicity may have an impact on the strength of certain drug gene associations; however, this is not well defined, and tests evaluated in one ancestral group may not be transferable to another. It* has been argued that *self-reported ethnicity may not be a reliable proxy for underlying genotype where pharmacogenomic data is available and therefore the clinical decision support rules for triggering alerts should not be constrained by this factor. This guidance advises that organisations carefully consider issues surrounding ethnicity, taking into account the views of individual's concerned wherever possible. Above all individuals receiving care must not be disadvantaged as a result of the implementation of pharmacogenomic alerts.*]

The implementation of clinical decision support for alerts **should not**:

25. Place an **undue burden** on prescribers or individuals.

[*To avoid unintended consequences such as this, careful consideration should be given to the implementation and potential unintended consequences of alerts in real-life clinical settings. For example, the careful consideration of timing such that an interruptive alert warning of an absolute contraindication is triggered earlier in the prescription 'order entry' process; after a drug has been selected but before other parameters such as dose, frequency or route of administration have been selected, would help to minimise frustration for the end user.*]

26. Provide an individual's pharmacogenomic information in alerts **without access to the formal pharmacogenomic test result**.

[*Access to the complete pharmacogenetic test result should be available in the EHR. Prescribers should seek out specialist advice where there is uncertainty regarding interpretation. Furthermore, pharmacogenomic information should be considered in the context of other factors that may influence the prescribing choice e.g. drug-drug interactions or co-morbidities. Where physical alerts are used a secure link (e.g. QR code to a password protected patient portal containing the pharmacogenomic test results could be considered as a potential option.*]

4.3.8. Further implementation considerations

The implementation of clinical decision support for alerts **could**:

a. Take into account the challenge of where to store an individual's pharmacogenomic data – for example, as an entry in the problem list, the allergies list, or in a unique repository for pharmacogenomic data within the EHR.

[*The question of where to store pharmacogenomic results / data for the purpose of triggering alerts is currently unresolved and will be dependent on the supplier of the clinical systems.*]

b. Ensure that an individual's pharmacogenomic data is stored in such a way that it can be iteratively analysed and reinterpreted.

[*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. In order to meet that duty an individual's pharmacogenomic data would have to be stored in a way that is secure, accessible, enduring and in a format that facilitates reanalysis. If such a duty exists, irrespective of whether a processed version of the data is stored within the EHR (e.g. a PDF file containing a formal report or an entry encoded in the problem list (or elsewhere) for the purpose of triggering alerts), a separate datafile suitable for iterative reanalysis would need to be stored somewhere else in parallel. Raw (FASTQ, BAM) and intermediate (VCF) pharmacogenomic data files are too large to be stored in the EHR. For any given pharmacogenomic result, a time-stamped copy of the result and the subsequent analysis / 'rules' / algorithm applied to it along with the outcome (i.e. was an alert generated; if so, what type of alert; etc?) need to be kept recorded as part of a genomic 'spine'.* is likely that over time an individual patient will acquire serial genomic data in their record, potentially utilising a variety of evolving

technologies. Consideration should be given in advance to the potential unintended consequences and operability issues that may arise in electronic systems.]

c. Ensure that pharmacogenomic information is translated into a standardised agreed terminology e.g. SNOMED CT (clinical terminology) and can be shared using an agreed interoperability standard e.g. Fast Healthcare Interoperability Resources (FHIR) (technical interoperability).

[*Using a clinical terminology standard would facilitate understanding and communication between prescribers that see pharmacogenomic information in alerts. The use of technical electronic interoperability standards such as FHIR would facilitate the sharing of pharmacogenomic data for alerts within CDS systems and with computerised systems in other settings, such as in systems within and between primary and secondary care. However, there is currently limited evidence for the utility of FHIR in pharmacogenomics decision support systems, beyond the prototype stage - more research is therefore warranted before any hard recommendations can be made.*]

d. Ensure that where a live retrieval system is used to query the pharmacogenomics variants in a patient, there is a robust system for ensuring that the correct genome data has been accessed.

[*It is critical that safeguards are in place to ensure that the patient and their pharmacogenomic data remain aligned.*]

5. Conclusion

As a consequence of the consultation process undertaken in this project an overview of the progress and challenges in the field of pharmacogenomic alerts has been gained. Many of the consensus findings from the consultation, involving health professionals, patient representatives and domain experts; are supported by findings in the literature. These together have been reported and formulated how pharmacogenomics alerts could be implemented within the NHS. However, it must be emphasised that this is a work of guidance (not a standard) covering a discipline with an underdeveloped evidence base in several areas and a considerable number of implementation challenges that still need to be resolved. Therefore, we recommend a small-scale pilot of alerts for a small number of drug-gene pairs that will deliver clinical safety benefits alongside a national piece of work to address some of the challenges before a wider rollout with a major focus on developing strategies for mitigating alert fatigue.

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7. Appendices

Appendix A – Project scope, objectives and governance

See appendix A (separate document)

Appendix B – Project stakeholders

See appendix B (separate document)

Appendix C – Example clinical scenarios presented at the second focus group

See appendix C (separate document)

Appendix D – Methodology and methods used to develop the guidance

See appendix D (separate document)

Appendix E – Justification of guidance

See appendix E (separate document)

Appendix F – Focus group one report

See appendix F (separate document)

Appendix G – Draft guidance used for focus group two

See appendix G (separate document)