

**Methodology and methods used to develop guidance**

Appendix D

FEBRUARY 2020

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**Professional Record Standards Body**

7 – 14 Great Dover Street,

London, SE1 4YR.

**www.theprsb.org**

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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**

This is Appendix D of the final report.

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Reviewers

This document must be reviewed by the following people:

|  |  |
| --- | --- |
| Reviewer name | Title / Responsibility |
| Assurance Committee | PRSB Assurance Committee |
| Dr Afzal Chaudhry | PRSB Vice Chair, CMIO Cambridge University Hospitals NHS FT |
| Dr Reecha Sofat | Clinical Lead, Associate Professor Institute of Health Informatics, University College LondonConsultant Clinical Pharmacology, GIM and Stroke UCLH Foundation Trust |
| Lorraine Foley | PRSB CEO |
| Martin Orton | PRSB, Director of Delivery & Development |
| Helene Feger | PRSB, Director of Strategy, Communications and Engagement |
| Project Board | Project Board |

Approved by

This document must be approved by the following people:

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

Planned Review Date and Route for User Feedback

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

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

Glossary of Terms

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

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# **Introduction**

This section summarises the overall methodological approach used to develop the guidance, as well the specific methods involved.

# **Methodology**

## 2.1 Project Initiation

A Project Initiation Document was developed defining the overall project objectives and formed the ‘contract’ between the project team and the project board. Project board membership is summarised in appendix B (separate document).

### 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
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

Table 1. Webinar (focus group) attendance

|  |  |  |  |
| --- | --- | --- | --- |
| Webinar | Purpose | Date | No. of attendees |
| Focus group 1 | To develop project scope | 19th September 2019 | 14 |
| Focus Group 2 | To review project guidance | 21st November 2019 | 32 |

## Phase one methods – Defining project scope

### 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). A systematic and pragmatic approach was therefore used. 10 well-known articles were initially identified by key stakeholders at the PRSB as relevant to the subject; these key studies as the starting point for the evidence review. Key references within these papers were identified to supplement information and key words were identified to use in a limited search for relevant evidence in a single bibliographic database (Medline). This search was performed on PubMed and incorporated MeSH terms and key words. The search strategy was as follows:

 (("Pharmacogenomic Variants"[Mesh] OR "Pharmacogenomic Testing"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Precision Medicine"[Mesh] OR pharmacogen\*) AND ("Decision Support Systems, Clinical"[Mesh] OR "Medical Order Entry Systems"[Mesh] OR notification\* OR “Computerised Physician Order Entry”[All Fields] OR alert\*[All Fields])

The 293 articles identified were then excluded/included by title and abstract. Included articles were those relevant to pharmacogenomic alerting systems and clinical decision support; particularly examples of current practice and standards. Additional articles were identified from further stakeholder recommendations and specific queries to the Google search engine. Some of these articles were not specific to pharmacogenomics but were relevant in other ways e.g. for general alerting principles. Some of the evidence curated was used to justify the recommendations made, see final report and appendix E (separate documents).

The core project team conducted the evidence review which initially:

* 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.

### Focus group consultation one

The first focus group meeting took place on the 19th September 2019 with healthcare professionals, PRSB representatives and members of the project team (attendees are listed in appendix B (separate document). The aim of this focus group meeting, conducted in a webinar format, was to begin to explore what the scope of pharmacogenomic alerts guidance should be to improve safety and care of individuals. In this session facilitators sought the opinions of participants in relation to one of four key themes relating to pharmacogenomic alerts. Discussion was facilitated by illustrating some common themes from the evidence synthesis, interspersed with a series of ‘prompt’ questions as a starting point. 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?

The proceedings were recorded, and the outputs analysed in order to refine and revise the scope in the light of the focus group meeting. A Focus Group Report (FGR) was produced that presented the themes emergent from the multi-disciplinary focus group meeting and early evidence synthesis, see 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), labelled as ‘FG1’ in parentheses.

### 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. These contacts were selected based on the fact they had published peer-reviewed articles in the field and had first-hand experience with implementing and evaluating pharmacogenomic alerting systems, in real clinical settings. The calls with international comparators were transcribed and then analysed using thematic analysis. In addition, consultation calls took place in the UK, both with healthcare professionals with a special interest in health informatics and with patient representatives. Furthermore, two freeform face-to-face consultations were conducted with community pharmacists in the UK, to gain an insight into the potential role of alerts in the prescribing process. Selected output from the consultation calls, in the form of quotes used to inform the guidance, can be found in appendix E (separate document), labelled by country or as ‘PRCC’ (patient consultation) in parentheses.

The output from the consultation calls was used to inform the draft guidance recommendations.

Table 2. Countries involved in consultation calls

|  |  |
| --- | --- |
| Country | No. of calls |
| USA | 6 |
| Canada | 1 |
| Holland | 1 |
| Italy | 1 |
| UK | 4 |
| **Total** | 13 |

Selected output from the consultation calls, in the form of the quotes used to inform the guidance, can be found in appendix E (separate document). Call attendees are listed in appendix B (separate document).

## Phase two methods – Developing the guidance

### PRSB advisory board

A consultation session was held at the PRSB Advisory Board meeting on the 24th October 2019. The advisory board represents a broad range of professional expertise and includes 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), labelled as ‘ABD’ in parentheses.

### Consultation survey

A consultation survey was sent to Advisory Board members following the meeting. It was conducted in the format of a question and answer questionnaire, via an online survey platform (SurveyMonkey**®**); see output below. Data was collected between the 6th – 25th November 2019. The survey consisted of example scenarios involving a clinical vignette with an example of a pharmacogenomic alert; followed by six questions for prescribers and a different set of five questions for non-prescribers. Qualitative responses were given as free-form text.

The number of completed responses to the survey was limited, but a diverse range of professions was represented (Table 4), with a balance of prescribers and non-prescribers (Table 3). 19 of the respondents were based in either England (n=5), Scotland (n=14) or Wales (n=1) and 6 were unknown; there were no recorded representatives from Northern Ireland.

Table 3. Number of people who accessed and reviewed the survey

|  |  |  |
| --- | --- | --- |
|  | n | % |
| Prescribers | 11 | 46% |
| Non-prescribers | 13 | 54% |
| **Total** | 24 |  |

Table 4. Survey responses by role

|  |  |
| --- | --- |
| Role | n |
| Pharmacist | 2 |
| Physiotherapist | 6 |
| Podiatrist | 2 |
| GP | 2 |
| Nurse | 2 |
| Occupational therapist or assistant | 2 |
| Midwife | 1 |
| Dietician | 1 |
| Patient | 1 |
| Unknown | 5 |
| **Total** | 24 |

Notable responses from healthcare professionals to the survey are outlined below.

On when it would be useful for professionals to be alerted to pharmacogenomic information:

Responses included: ‘At all times’, ‘[at the time of] prescribing’, ‘on initial planning of medication’, ‘it would need to be integrated into existing prescribing decision support [which itself] needs root branch and review’, and ‘[when there is] increased patient risks’ or ‘prescribing risks’ or ‘[when treatment is likely to be ineffective [due to pharmacogenomics]’.

On who should be alerted to pharmacogenomic information:

Responses included: ‘Relevant staff’ including ‘[the] prescriber’ or ‘prescribing clinician’, ‘the patient’ and ‘the patient’s GP’, ‘[the] pharmacy regulatory body for the trust’, and ‘[t]he prescriber, the pharmacist and the acknowledgement of the alert should be visible to the person administering the medication’.

On what key information should be alerted:

Responses included: ‘[information on] the potential risk to the patient’ or ‘whether harm may be expected and how much’, ‘[phenotypic information such as] slow/rapid metaboliser, ‘[a] recommendation on another course of action’ and possible inclusion of information such as ‘whether this was a necessary drug or symptom relief only drug’. One respondent commented on the difficulty of answering the question and emphasised that ‘[pharmacogenomics] is not a ‘green field’ domain and there are many complex aspects to be taken into account, some more fully worked out than others’.

On what would help the communication of pharmacogenomic information to individuals:

Responses included: ‘[it] will depend on the individual patient/scenario’, but may include ‘leaflets’ and/or ‘videos’ that are ‘individually tailored’ with ‘short statements to read aloud’; ‘following a realistic medicine conversation initially’ and ‘[r]eferences to the evidence base (along with provenance) would be helpful in some cases’.

On the challenges of alerting pharmacogenomic information and possible solutions:

Responses included: ‘[Concerns over] increased [use of the prescriber’s] time [and] access to [pharmacogenomic] testing, particularly in rural areas’, and several responses relating to patients such as ‘[how to gain] patient consent for [pharmacogenomic] information being shared’, ‘patients may feel this is intrusive testing / information’, ‘[possible unforeseen implications] for patients with a certain genotype…Does this put them at risk and would they rather not know?...Will people require counselling [before testing]?’ Several respondents alluded to the potential for negative experiences and unintended scenarios related to alerts for the prescriber with one emphasising of the importance of the evidence-based literature on ‘the need to avoid ‘alert fatigue’.

Patient responses to the survey:

There was only one representative of a patient organisation that responded to the survey but they stated a preference for pharmacogenomic information in the alerts, and the actioned response, to be communicated to them by ‘text or email’, that they would want their doctor to be informed of an alert; interestingly they also communicated a concern over the possible unintended consequence of ‘false alerts’.

Selected output from the consultation survey was used to inform the draft guidance.

### 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?’, which took place on Monday the 18th November 2019 at 7pm. The five questions asked to spark discussion, and responses can be found in full using the PRSB’s twitter handle @ProfRecordSB.

### Development of the Initial Draft

The core project team used the outcome data of the consultation process at this stage to inform the first draft of the guidance. This was then followed by a consultation process where guidance was discussed with stakeholders attending the 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.

### Focus group consultation two

The second (larger) focus group meeting took place on the 21st November 2019 with patient representatives, healthcare professionals, PRSB representatives and members of the project team (attendees are listed in appendix B (separate document).The purpose of this second focus group meeting, conducted as a webinar, was for stakeholders to review and contribute to the draft guidance to ensure that the recommendations were practicable, understandable and fit for purpose. A copy of the draft guidance used for the consultation can be found in appendix G (separate document).

In this session facilitators sought the opinions of participants in relation to the draft guidance recommendations and implementation challenges; as well as several clinical scenarios, each in the form of a clinical vignette describing situations involving the prescription of a drug with a relevant drug-gene association along with either pre- or post-test alerts presented in the form of an electronic popup (refer to 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

Due to time constraints limiting the discussion on implementation challenges, additional feedback was sought via email. The proceedings were recorded, and the outputs analysed in order to refine and revise the guidance in the light of the findings from the meeting. Selected output from the second focus group consultation, in the form of quotes, can be found in appendix E (separate document), labelled as ‘FG2’ in parentheses.

## 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.

### Final Project Deliverables

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