Using pharmacogenomics to improve patient outcomes

A report from the Royal College of Physicians and British Pharmacological Society joint working party
Royal College of Physicians

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British Pharmacological Society

The British Pharmacological Society (BPS) is a collaborative, global community at the heart of pharmacology. Founded in 1931, the BPS represents more than 4,000 members from over 60 countries. As a vibrant science that studies drug action, pharmacology lies at the heart of biomedical science, linking together chemistry, physiology and pathology. Pharmacologists, both clinical and non-clinical, work closely with a wide variety of other disciplines that make up modern biomedical science, including but not limited to clinical medicine, biochemistry, neuroscience, molecular and cell biology, genetics, immunology and cancer biology. Clinical pharmacology and therapeutics is a medical specialty recognised by the RCP.

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Stakeholder organisations

This report is endorsed by the following organisations:

- Association of Cancer Physicians
- British Society for Allergy and Clinical Immunology
- British Society for Genetic Medicine
- British Society for Haematology
- British Thoracic Society
- Clinical Genetics Society
- Genomics England
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of Psychiatrists
- Royal College of Radiologists
- Faculty of Clinical Oncology
- Royal Pharmaceutical Society
- UK Kidney Association

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This report is dedicated to the memory of Professor Donal O’Donoghue, who championed the creation of the working party and co-chaired it at its inception.

This report is also supported by the Royal College of Paediatrics and Child Health.
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*Prof Donal O’Donoghue was involved in the early stages of the working party and report development. Following his death in January 2021, Dr Peter Belfield took over as interim RCP registrar until May 2021 when Dr Cathryn Edwards was appointed.

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Part of the answer is revealed in this hugely important document. In simple terms, our understanding of human biology has been transformed by the sequencing of the human genome and our new-found knowledge of genetic variation. We have always known that we were different, now we know why. And we can use that knowledge to predict illness, diagnose illness and to treat illness on an individual, personalised basis. This will revolutionise medicine and, combined with a digitally driven population health approach, fundamentally change the traditional model of care.

But it will not change the fundamental value on which the NHS is based: equality. Genomic medicine, of which pharmacogenomics is an integral part, must be available to everyone. It must therefore be funded centrally; it is too important to risk a postcode lottery. It gives the NHS a chance to reduce health inequality – we must not risk the reverse. Implementation of pharmacogenomics into the NHS would be the first example in the world of integration into a whole healthcare system, again highlighting the leadership of the UK in genomics.

I remember a time some 5 years ago when Prof Munir Pirmohamed came to see me to talk about the obscure, unknown and overlooked subject of pharmacogenomics, a subject of which I and most others knew little. No longer. It is now mainstream, it is the future, it can now help us to deliver a new, modern personalised healthcare system fit for 2022, not 1948.

Lord David Prior
Chair of NHS England
Executive summary

We all vary in our responses to medicines. Some people respond very well, while others may not respond at all, and some may develop side effects from their medicines. At present, we cannot predict how an individual will respond to the first medicine they are prescribed. This variability in response to medicines can be due to many factors, including an individual’s genes.

There is increasing scientific evidence that natural variation in particular genes influences how well a medicine works for an individual, and whether they will experience side effects. The study of this area is called pharmacogenomics. Pharmacogenomic testing can be used to discover which variants of genes an individual carries, and whether they impact on the response to medicines they are given. This information can be used to guide the choice of medicine and dose, increasing the likelihood that each person receives the most effective medicine for them, at the best dose, the first time they are treated.

Pharmacogenomic testing is already benefiting NHS patients in some special cases. For example, in breast cancer and colorectal cancer it is used to understand whether someone can safely be prescribed the drug 5-fluorouracil. Implementing pharmacogenomic testing in daily practice in the NHS has the potential to benefit many more people and improve their care.

However, wider implementation of pharmacogenomic testing in the NHS has been hampered by:

- the need for more research to understand the scientific evidence for testing
- high costs of testing in the past
- poor availability of tests outside specialist settings
- the need to train healthcare professionals in recent advances in pharmacogenomics
- a lack of pharmacogenomic information in the tools used on a daily basis by healthcare professionals, such as electronic healthcare systems.

This guidance, produced by the Royal College of Physicians (RCP) and the British Pharmacological Society (BPS) joint working party, considers these barriers as well as the opportunities provided by increasing pharmacogenomic testing. It includes a set of recommendations encompassing steps along the pathway to embedding pharmacogenomics in the NHS. It covers understanding the evidence for each test, working with patients and the public to understand their needs and communicate potential benefits of testing, training healthcare professionals to exploit advances in pharmacogenomics, working with leaders to develop the NHS National Genomic Test Directory and commission testing through the relevant pathways in the four nations, and ensuring that testing is implemented effectively in practice. It is vital that any pharmacogenomics service is adequately funded in all four UK nations, and equally available across NHS regions within each devolved nation.

The ultimate goal is to make pharmacogenomic-based prescribing a reality for all in the UK NHS. This will empower healthcare professionals to deliver better, more personalised care, and in turn improve outcomes for patients and reduce costs to the NHS. Although we focus on the UK, many of the issues discussed in the report are also relevant to other global healthcare systems, and learning from each other will be important in optimising medicines use around the world.
Introduction

People are living longer today than ever before. But an ageing population means more and more of us are likely to live with long-term health conditions that require medication. This means the number of medicines we are taking is increasing.

Many currently available medicines are ‘one size fits all’. This means that people are prescribed a medicine for a particular health problem at a set dose. But medicines don’t always work in the same way for different people; some people might respond very well to treatment, some might not show any response at all, and for some their medication may also give them unwanted side effects. We cannot completely predict how someone will respond to the medicine they are prescribed, but there is now good evidence that their genetic information – the information stored in their DNA – plays a key part.

What is pharmacogenomics?

Everyone has different genetic information, stored in the genes they inherited from their parents. Pharmacogenomics is the study of how genes affect a person’s response to drugs. It brings together the science of drugs (pharmacology) and the study of genes and their functions (genomics) to develop and prescribe medications that are tailored to a person’s genetic makeup.

Scientists have learned a great deal about how inherited differences in your genes can affect your body’s response to medications. Pharmacogenomic testing can be used to discover which variants of genes you carry, and how they are likely to influence the way your body responds to medicines you might be given. Because your genes hardly change throughout your lifetime, a pharmacogenomic blood test needs to be done once. The test results could then be used throughout your life to guide the choice and the dose of medicine, making it more likely that you receive the most effective medicine for you the first time you are treated, and with the fewest potential side effects (see the graphic on page 10).

What do we know so far?

Using a person’s genetic makeup to guide treatment is already a reality for some. The UK is a world leader in mapping individual genomes (all of a person’s genetic information), and the expertise and technology needed to roll out this approach to treatment more broadly is already well established.

In fact, pharmacogenomic testing is already benefiting NHS patients in some cases. For example, in breast and colon cancer, pharmacogenomics is used to understand whether a person can safely be prescribed the chemotherapy drug 5-fluorouracil. Research has also shown that there are genetic differences in the way people respond to the painkiller codeine. Codeine works better for some people than others, while in some it can have more side effects, but we do not routinely test before prescribing codeine.

Using pharmacogenomic testing more widely has the potential to keep people healthier for longer, improving their NHS care and outcomes. Unwanted side effects from prescription drugs cost the NHS £530 million annually in hospital admissions. Getting it right the first time could help save the NHS money and resources.

Summary for patients and the public
Patient requiring medication

Standard approach

The patient is prescribed a medicine for their health problem often at a set dose – a one-size-fits-all approach

The patient’s genes affect how they respond to the medicine and whether they have side effects

The prescription is changed or adjusted to suit the person

Medication stopped  
Dose lowered  
Dose increased

The patient is given the right medicine at the right dose for them

Pharmacogenomic approach

The patient has a pharmacogenomic test – a blood test carried out once in a person’s lifetime

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What is the problem?

Making pharmacogenomics available to everyone is not straightforward. The tests are not widely available. There has also been a lack of training, and there is limited information on pharmacogenomics in the online systems and tools used by prescribers every day, which makes it difficult to roll out more broadly.

What are the next steps?

Together, the Royal College of Physicians and the British Pharmacological Society joint working party on pharmacogenomics have set out a plan to try to overcome these barriers.

The report brings together what healthcare professionals know about pharmacogenomics and makes recommendations for how we can combine research, education and resources to bring this technology to clinics across the UK.

The recommendations include working with patients and the public to understand their needs. They also include communicating about the potential benefits of testing, understanding the evidence for each test, training healthcare professionals to make the most of advances in pharmacogenomics, working with NHS leaders to commission testing, and ensuring that testing is implemented effectively and fairly in practice. Clearly, any genomic data collected by the NHS as part of clinical care must be securely stored and kept confidential in line with the UK General Data Protection Regulation (GDPR).

The ultimate goal is to make pharmacogenomic prescribing a reality for everyone within the NHS. This will empower healthcare professionals to deliver better, more personalised, care.
Recommendations

> Clinical implementation of pharmacogenomics should occur in both primary and secondary care settings, as well as in specialised centres across the four nations in keeping with the Genome UK commitment. This should be implemented in a manner that reduces health inequalities, upholds the principles of the NHS, and reflects the wide range of drugs that have actionable pharmacogenomic recommendations available. Implementation into the NHS is likely to be a gradual and iterative process, which should evolve, steer towards and converge onto a comprehensive service incorporating all the elements outlined in this report.

> Mainstreaming pharmacogenomic services in the NHS throughout the UK should be commissioned and funded through the relevant pathways in the four nations rather than locally driven to avoid a postcode lottery of care and thereby exacerbate inequalities. Services should include standards for test turnaround times, flexibility in the type of technology used depending on the gene–drug pair, and standards for reporting, storing and incorporating test results in the electronic healthcare record. The UK is also a leader in whole genome sequencing, and the number of people who have had their genomes sequenced is increasing all the time. Pharmacogenomic information contained within these genomes should not be forgotten, but used in a manner that benefits patients.

> Pharmacogenomic services will need to be agile and able to work at pace to include newly discovered gene–drug pairs into the NHS National Genomic Test Directory, but also refine the list or recommendations of existing gene–drug pairs based on evidence generated.

> The implementation of pharmacogenomics should be accompanied by a comprehensive education and training package aimed at all sectors of healthcare to improve the skills of the workforce and embed pharmacogenomics into curricula for training the future workforce. This should include the following:

- An audit to establish a baseline of where pharmacogenomics is present in pre-registration standards and post-registration curricula, and a gap analysis to identify the standards and curricula missing this information.

- The provision of a layered approach to learning so that healthcare professionals can access ‘just-in-time’ information, short courses or formal qualifications, depending on their professional requirements and personal interests.

> Support for clinicians should be provided as pharmacogenomic testing is rolled out. This should consist of:

- strategic planning of service delivery models to incorporate workforce planning from the outset to ensure that there are enough healthcare professionals to deliver the service. There should be consideration around expanding and clearly defining the roles of existing staff to incorporate pharmacogenomics and medicines optimisation

- a pharmacogenomics consult service should be developed within each integrated care system (ICS) led by a multidisciplinary team comprising clinical pharmacologists, pharmacists and other interested specialists, taking into account guidelines and prescribing information. Given that most of the prescribing occurs in primary care, it is important that GPs and pharmacists are considered an essential component of this multidisciplinary pharmacogenomics service
work towards developing clinical decision support systems that can be used in all healthcare settings, focused not only on pharmacogenomics, but also on other advances in medicine (including rare disease and tumour genomics, and artificial intelligence), to develop an end-to-end solution

- considering whether currently available resources such as the British National Formulary (BNF) should include information on pharmacogenomics.

Pharmacogenomic services should be subject to continuous and iterative evaluation – this should include audit and research, together with patient input, to develop a learning health system which allows continual improvement in the service offered to maximise patient benefits.

Funding for pharmacogenomic research should be made available, not only to identify new gene–drug pairs, but also to refine existing gene–drug pairs, assess the public health benefits of pharmacogenomic implementation, and undertake patient-related work to understand uptake, acceptance, feedback, equity of access, ethical, legal and social issues, and changing perceptions of pharmacogenomics. Pharmaceutical and diagnostic industries, together with the regulators, should be involved in defining the research agenda, and provide funding where appropriate.

Pharmacogenomics implementation should be accompanied by clear lines of communication with patient representative bodies, the public and the media. In addition, patients and the public should be actively involved in service design for the NHS to ensure that the service is patient centred.
Introduction

With increasing life expectancy and more people living with multiple long-term conditions, the use of medicines is growing. In England alone, the NHS dispensed well over 1 billion prescription drugs in 2015, 50% more than in 2005.1

There is significant variability in people’s responses to these drugs, and harm can arise from both adverse drug reactions (ADRs) and lack of efficacy. In addition to causing adverse patient events, avoidable ADRs are estimated to cost the NHS £530 million annually in hospital admissions.2

There is now evidence that the potential for both ADRs and lack of efficacy for many drugs can be predicted by genetic variation in someone’s genetic profile. This is also known as ‘polymorphism’, i.e. different genetic sequences at the same locus. This genetic variability can be related to both pharmacokinetic (how the body processes the drug) and pharmacodynamic (how the drug affects the body) properties. A pharmacogenomic approach, where genetic variation informs choice of drug and dose, can facilitate greater precision in prescribing and an increasingly personalised approach to drug therapy (Fig 1). It has the potential to improve patient outcomes by increasing the efficacy of medicines and decreasing ADRs. This is associated with reducing the number of preventable health conditions and deaths, as well as the costs to the NHS.

The UK is at the forefront of a genomic revolution, having first undertaken the 100,000 Genomes Project, which is now aiming to extend to 5 million genomes. In England, the NHS Genomic Medicine Service (formed in 2018) and NHS Genomic Medicine Service Alliances (formed in 2020) aim to integrate research, education and diagnostic resources to bring pharmacogenomics, as a branch of personalised genomic-targeted medicine, to the bedside (Fig 2). Similar schemes are also present in Scotland, Wales and Northern Ireland. Guided by the National Genomic Test Directory, pharmacogenomics-informed prescribing has the potential to be a daily prescribing reality across the UK, and therefore professional body leadership should issue guidance and recommendations to support bedside integration by clinicians.3 To that end, this joint RCP/BPS working party report looks at evidence presented by representatives of a number of physician specialist societies as well as representatives from other royal colleges and the Royal Pharmaceutical Society. It aims to summarise the current state and promise of pharmacogenomics within the NHS in the UK and to highlight opportunities for further development. Representatives were nominated by their respective societies to give evidence on behalf of their specialty body.
Clinically, it is clear that there is marked interindividual variability in the response to drugs that are taken, affecting their efficacy and toxicity. This variation is largely attributable to four key factors: demographic, health, exogenous drug and food interactions, and genomic variation.

**Fig 1. Interindividual drug response**

National level

Linked priorities with medicines value programmes
NHSE/I and HEE Workforce Steering Group
National Genomics Pharmacy Advisory Group
International collaboration and horizon scanning

Regional level

NHS Genomic Medicine Service Alliances

Local level

A network of genomics champions

**Fig 2. An example of how personalised medicine is being embedded in England**

*NHSE/I = NHS England and Improvement; HEE = Health Education England*
A brief background to pharmacogenomics

Pharmacogenomics refers to the interface between drugs and genomics, using a patient’s genetic information to improve therapeutic effect and decrease inadvertent harm by giving a drug and dose that are optimal. It may also inform more targeted therapeutic drug or clinical monitoring.

This is based on an understanding of how genetic variants affect drug absorption, metabolism, distribution and excretion (pharmacokinetics), as well as drug targets such as receptors, enzymes and ion channels (pharmacodynamics) (Fig 3). Cytochrome P450 enzymes (CYPs) commonly impact drug metabolism, and are coded by genes (sometimes called pharmacogenes) that vary in the population (Fig 4). Differential metabolism by such enzymes can lead to diverse metaboliser phenotypes, ranging from ultra-rapid (able to metabolise a drug at a much greater rate than the population mean) to poor (complete lack of metabolism or lower rate of metabolism than the population mean) metabolisers.

Humans have a germline (nuclear) and a mitochondrial genome present in most cells of the body. The nuclear genome is transmitted from both parents (germline DNA) and follows Mendelian inheritance, while the mitochondrial genome is exclusively maternally inherited. Sequence variations within these genomes can affect the pharmacokinetics and pharmacodynamics of drugs. The focus of this report is on germline and mitochondrial DNA variation. It does not cover somatic genetic mutations, which are alterations that occur after conception or arise in a clonal manner in a malignancy. In oncology, knowledge of somatic gene driver mutations is now successfully used in targeted therapies for cancer. Lastly, this report also does not cover (a) conditions due to ultra-rare genetic mutations that are amenable to bespoke pharmacological intervention; and (b) techniques which are used for drug discovery based on genomics data.

Pharmacogenomics is currently used for a small number of drugs which span multiple specialties. For example, human leukocyte antigen (HLA) testing is mandated before starting abacavir to treat HIV infection. Pharmacogenomic tests should also be used before starting thiopurines and fluoropyrimidines, as well as carbamazepine, particularly in people of Asian descent. In most cases, genetic testing is needed to identify genetic variation in an individual, but phenotypic testing can be also used for some of the genetic polymorphisms. For example, thiopurine S-methyltransferase (TMPT) testing in the UK is often phenotypic, measuring the enzyme activity in the blood, rather than using genetic data to assess metaboliser status. However, in some centres in the USA, both genotype and phenotype are tested prior to drug prescription.
Abacavir – HLA-B*57:01

A 33-year-old man with bilateral pneumonia is found to be HIV positive and agrees to commence antiretroviral therapy (ART). He undergoes genetic testing, which shows that he does not carry the HLA allele HLA-B*57:01, and is commenced on abacavir/lamivudine/dolutegravir, which he tolerates.

> Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that inhibits HIV replication.
> The HLA allele HLA-B*57:01 was found to be strongly associated with abacavir hypersensitivity syndrome (AHS) in 2002, and a pivotal randomised controlled trial demonstrated that immunologically confirmed AHS could be completely eliminated by avoiding abacavir in patients with the HLA-B*57:01 allele.5
> Abacavir is thus contraindicated in patients who carry the HLA-B*57:01 allele and so screening for HLA-B*57:01 prior to prescribing abacavir has been part of routine clinical care in the NHS and other healthcare systems for over a decade.
> Prior to introducing pre-prescription HLA-B*57:01 testing, AHS occurred in approximately 5–7% of patients receiving abacavir.4,7
> Genetic testing for HLA-B*57:01 has been shown to be cost-effective and to reduce the incidence of AHS in real-world clinical practice.8,10
> The abacavir–HLA-B*57:01 association is often considered as a paragon of pharmacogenomics in clinical practice.

Specialties impacted by drugs affected by pharmacogenomic variation span multiple disciplines, including allergy and immunology, cardiology, dermatology, endocrinology, gastroenterology, infectious diseases, nephrology, neurology, oncology, respiratory medicine and rheumatology. Cross-cutting specialties such as clinical pharmacology, working in collaboration with pharmacists, will be of the utmost importance in the future to provide therapeutic guidance across specialties. Pharmacogenomics is also relevant to paediatrics, psychiatry, anaesthetics and other specialties, and will impact in particular on primary care services, which oversee the long-term care of patients and undertake the majority of prescribing in the NHS.

Establishing an evidentiary threshold to implement further pharmacogenomic-guided prescribing in mainstream practice has not been straightforward, but international consortia have now provided brief guidance which supplements that provided by regulatory agencies in the summary of product characteristics (SmPC). The most widely recognised consortia are the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG).11,12 However, these guidelines often assume pre-existing availability of genetic data (ie they don’t provide testing eligibility criteria). PharmGKB, a curated database, compiles a comprehensive summary of data relating to each gene–drug pair, and is a highly useful source of information. If a pharmacogenetic test is commissioned, it will need to have been included in the National Genomic Test Directory, which will outline eligibility, testing scope and actionability within the whole of the UK NHS.

If a patient is tested for the purpose of pharmacogenomics, questions sometimes remain about the best approach (Table 1):

> Is it best to pre-emptively check a panel of pharmacogenes or only the variant of interest?
> Should testing take place before prescribing, after an adverse event occurs or where there is lack of efficacy?
> As whole exome or whole genome testing becomes more widespread, how can we efficiently extract pharmacogenomic information?
Fig 3. Pharmacokinetic and pharmacodynamic factors affecting drug response
Normal CYP

Abnormal CYP

Fig 4. Cytochrome P450 pharmacogenetic variation leading to changes in enzyme activity and thereby metaboliser status
Table 1. Comparison of different pharmacogenomic testing approaches

<table>
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<tr>
<th>Testing approach</th>
<th>PGx gene panel</th>
<th>Gene targeted</th>
<th>Gene targeted point of care</th>
<th>Large gene panels with secondary PGx targets</th>
<th>Whole genome sequencing</th>
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<tr>
<td>Turnaround time</td>
<td>3–7 days</td>
<td>24–72 hours</td>
<td>&lt;24 hours (can be 30 mins)</td>
<td>7–14 days</td>
<td>4–6 weeks</td>
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<td>Examples</td>
<td>Variant-targeted SNP panels (eg Sequenom) or sequencing (eg Nimagen)</td>
<td>Real-time PCR testing for TPMT/NUDT15 for immunosuppressants</td>
<td>m.1555A&gt;G variant with aminoglycosides</td>
<td>DPYD testing added to large cancer panels</td>
<td>100K Genomes Project return of PGx results (ongoing work)</td>
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<td></td>
<td>LAMP testing for DPYD</td>
<td>Algorithm to guide warfarin dosing</td>
<td>SLCO1B1 gene testing for statins added to FH panel</td>
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<td>Advantages</td>
<td>Simultaneous testing of multiple PGx targets to inform future prescribing</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Cost-effective</td>
<td>Easily incorporated into existing clinical pathways</td>
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<td>Targeted</td>
<td>Targeted</td>
<td>Inexpensive</td>
<td>Technology advances may lower costs</td>
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<td></td>
<td></td>
<td>Inexpensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Challenges</td>
<td>High cost</td>
<td>Multiplexing more challenging</td>
<td>Different pathway – requires training of clinical staff</td>
<td>Limited applications – may only be relevant for a subset of patients</td>
<td>Requires bioinformatics pipeline and interpretation</td>
</tr>
<tr>
<td></td>
<td>Implementation across all healthcare sectors</td>
<td></td>
<td></td>
<td></td>
<td>Implementation issues for PGx panel testing apply</td>
</tr>
<tr>
<td></td>
<td>Requires linked electronic healthcare records</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment algorithms may change as PGx evidence develops</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

SNP = single nucleotide polymorphism; TPMT = thiopurine methyltransferase; NUDT15 = nudix hydrolase 15; DPYD = dihydropyrimidine dehydrogenase; LAMP = loop-mediated isothermal amplification; POCT = point of care testing; FH = familial hypercholesterolaemia
3 Current clinical implementation

3.1 The current situation in the NHS

Despite the growing awareness and recognition of the potential benefits of pharmacogenomics to patients and healthcare providers through safer, more efficacious and likely more cost-effective prescribing, widespread implementation of pharmacogenomics into any healthcare system, including the NHS, has not yet occurred. Nevertheless, testing for HLA-B*57:01 before starting abacavir in patients with HIV became routine in the NHS from 2005.14 This testing is in line with the abacavir SmPC, which states that abacavir should not be used in patients carrying the HLA-B*57:01 allele to avoid abacavir hypersensitivity syndrome.15 On the other hand, routine screening for the HLA-B*15:02 allele is not available on the NHS, despite the carbamazepine SmPC recommending that individuals of Han Chinese or Thai ethnicity be screened for HLA-B*15:02 prior to initiating carbamazepine ‘whenever possible’.16 These examples highlight the non-uniform manner in which pharmacogenomics has been adopted by the NHS.

Carbamazepine – HLA

A 58-year-old woman of Han-Chinese descent goes to her GP with a 2-month history of paroxysms of severe, short-lasting stabbing pain around her left cheek. She is diagnosed with trigeminal neuralgia and prescribed carbamazepine. She tolerates carbamazepine well and her symptoms abate. However, after taking carbamazepine for 2 weeks, she develops Stevens–Johnson syndrome and ends up being hospitalised for 6 weeks.

- Carbamazepine is indicated in some forms of epilepsy, bipolar affective disorder and trigeminal neuralgia.
- Although generally tolerated, carbamazepine can rarely cause serious hypersensitivity reactions, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal.
- HLA-B*15:02 is highly prevalent in Southeast Asia and has been strongly associated with carbamazepine-induced SJS-TEN.17
- HLA-B*15:02 has also been linked to SJS-TEN in patients taking oxcarbazepine18 and phenytoin.19
- Prospective testing for HLA-B*15:02 can significantly reduce carbamazepine SJS-TEN.20 However, implementing HLA-B*15:02 screening into clinical practice requires clear prescribing recommendations to aid appropriate selection of alternative drug therapy.21
- HLA-A*31:01 is more prevalent in Northern European populations19 and is associated with a broader range of carbamazepine-induced hypersensitivity reactions (including common maculopapular rash) than HLA-B*15:02.22
- Pharmacogenomics guidance has now been developed for carbamazepine based on both HLA-A*31:01 and HLA-B*15:02.18
- In the above case, it is highly likely that the patient is HLA-B*15:02 positive and genotyping could have avoided this serious adverse reaction.
3.2 Pharmacogenomic testing in other countries

Internationally, particularly in the USA and European countries, pharmacogenomic testing has been mainly restricted to academic and other highly specialised centres. The drivers have often been clinical researchers championing pharmacogenomics, which in most cases has been embedded within clinical research, implementation science programmes and other quality improvement initiatives.

One example is the pan-European Ubiquitous Pharmacogenomics consortium, which implemented real-world pharmacogenomic testing within a prospective implementation research study, testing 44 variants across a 12-gene panel relevant to 42 drugs in approximately 7,000 patients.

Another is St Jude Children’s Research Hospital in the USA, an early adopter site that began offering pre-emptive pharmacogenomic testing in 2011. By 2019, actionable results for 11 genes relevant to 35 drugs had been implemented into the electronic healthcare records (EHRs) for nearly 5,100 patients. St Jude enrols patients onto its PG4KDS protocol, which uses a clinical trial framework primarily to obtain informed consent to both withhold results from the many interrogated genes that are not currently deemed clinically actionable, and to enable return of clinically relevant unexpected findings (eg Klinefelter syndrome).24

Similarly, the PREDICT programme in Vanderbilt University Medical Center was set up in 2010 to enable pre-emptive pharmacogenomic testing in 2011. By 2019, actionable results for 11 genes relevant to 35 drugs had been implemented into the electronic healthcare records (EHRs) for nearly 5,100 patients. St Jude enrols patients onto its PG4KDS protocol, which uses a clinical trial framework primarily to obtain informed consent to both withhold results from the many interrogated genes that are not currently deemed clinically actionable, and to enable return of clinically relevant unexpected findings (eg Klinefelter syndrome).24

3.3 Genomic research

The UK has been at the forefront of genomic research, with accomplishments ranging from development of sequencing technologies (eg Sanger sequencing) to large-scale, big data population-based cohort studies (eg UK Biobank). Of particular importance was the 100,000 Genomes Project, a pioneering national initiative to expedite translation of genomics into the clinic. This world-leading project was coordinated by Genomics England, a company set up in 2012 and wholly owned and funded by the Department of Health and Social Care. The project recruited c.85,000 NHS patients from Genomic Medicine Centres (GMCs) across England and the devolved nations with a focus on rare disease and cancer. It returned actionable genetic results to the NHS healthcare teams caring for the patients. In the first-pass analysis of patients generally recruited because earlier panel gene tests were negative, actionable findings were found in 20–25% of recruited patients with a rare disease, and further analyses are pending. Findings in approximately 50% of cancer cases contain the potential for a therapy or a clinical trial.27 Genomics England also began a pilot study in 2019 involving analysis of whole-genome sequencing (WGS) data from cancer patients to identify the four clinically relevant DPYD variants that affect the safety of fluoropyrimidine therapy. The results are then returned to the healthcare teams in the NHS Genomic Medicine Centres so treatment can be adjusted where necessary.28

3.4 Genomic medicine services

Building on the success of the 100,000 Genomes Project, NHS England launched the Genomic Medicine Service (GMS) in October 2018 to further embed genomics into the NHS (Fig 5). Prior to this, genomic testing facilities across England were reconfigured into seven regional genomic laboratory hubs (GLHs) to consolidate and enhance genomic testing capacity and capability.29 The GLHs provide a national testing network that underpin the GMS as it strives to meet its commitment to the NHS Long Term Plan to sequence 500,000 whole genomes from patients as part of their routine NHS care by 2023–24.30 Similar testing facilities have also been established in Scotland, Wales and Northern Ireland (Fig 5). There is a broader ambition of the UK government to sequence five million genomes in 5 years, as outlined by the secretary of state for health and social care in October 2018.31 The NHS currently offers whole-genome analysis to seriously ill children with a suspected genetic disorder, and to adult patients who have certain rare diseases or difficult-to-treat cancers.31
In December 2020, seven GMS Alliances were launched across England to further establish the infrastructure embedding genomics into mainstream clinical care and to accelerate delivery of precision medicine. The GMS Alliances bring together multidisciplinary teams including clinical, digital and operational expertise, the GLHs at the core of the GMS, clinical genetic services, primary and secondary healthcare provider organisations, researchers and academia, and patients and public representatives. The GMS Alliances operate across the 42 integrated care systems (ICSs), which are regional partnerships borne out of sustainability and transformation partnerships (STPs) to improve regional coordination of care and collaborative working practices between community-based services and hospitals, physical and mental health services, and between health and social care.

Germline pharmacogenomic test results remain constant across an individual’s lifespan. Thus, to maximise the potential utility of pharmacogenomic testing, pharmacogenomic test results need to be appropriately embedded into the cross-boundary, cross-disciplinary joined-up care mechanisms to enable test results to be available to physicians, pharmacists and other prescribers at the point of prescribing, irrespective of the particular community or hospital setting. This would go a long way to achieving the government’s objective: ‘To achieve, maintain and measure success over the next 10 years we will have a clear evidence-based position on whether and how pharmacogenomics should be implemented in the health service at scale’ as outlined in the Genome UK report.

NHS England created a pharmacogenomics working group (including representation from all four devolved nations), which has undertaken initial work defining the pharmacogenes and variants that should be included in the National Genomic Test Directory, as well as developing clinical pharmacogenomics guidance tailored to the UK NHS. An important milestone for implementing pharmacogenomics into the NHS was reached in 2020 when the NHS commissioned genomic testing for the four DPYD variants as a pre-treatment screening test prior to administering fluoropyrimidine-based therapies.

Germline pharmacogenomic test results remain constant across an individual’s lifespan. Thus, to maximise the potential utility of pharmacogenomic testing, pharmacogenomic test results need to be appropriately embedded into the cross-boundary, cross-disciplinary joined-up care mechanisms to enable test results to be available to physicians, pharmacists and other prescribers at the point of prescribing, irrespective of the particular community or hospital setting. This would go a long way to achieving the government’s objective: ‘To achieve, maintain and measure success over the next 10 years we will have a clear evidence-based position on whether and how pharmacogenomics should be implemented in the health service at scale’ as outlined in the Genome UK report.

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Fluoropyrimidines – DPYD

A 68-year-old man goes to his GP with altered bowel habits and is diagnosed with a left-sided colon adenocarcinoma. The oncologist undertakes DPYD genetic screening which reveals the patient carries a reduced-function DPYD genetic variant. He commences chemotherapy, which includes capecitabine at a 50% reduced starting dose. He tolerates this reduced dose and it is cautiously incremented to 75% of the standard dose over subsequent cycles.

> Fluoropyrimidines are antimetabolite chemotherapy drugs indicated in gastrointestinal, breast and head and neck cancer treatment. Fluoropyrimidines include parenterally administered 5-fluorouracil (5-FU) and its oral inactive forms (prodrugs) capecitabine and tegafur.
> Approximately 10–40% of patients who receive fluoropyrimidine therapy develop serious adverse reactions (eg myelosuppression, diarrhoea), and fatal toxicity occurs in ~1% of patients.
> Dihydropyrimidine dehydrogenase (DPD) is an enzyme that inactivates ~80% of 5-FU and is encoded by the gene DPYD. DPD activity varies between individuals.
> Genetic studies have so far established four DPYD genetic variants that encode DPD with reduced activity and increase the risk of 5-FU-related serious adverse reactions.
> Prospective DPYD-genotype-guided fluoropyrimidine prescribing has been shown to reduce the risk of fluoropyrimidine-related serious adverse reactions.
> NHS England and the relevant NHS organisations in Scotland, Wales and Northern Ireland commissioned DPYD genomic testing in October/November 2020, making routine testing for the four variants available.
Fig 5. NHS genomic medicine services in England (including genomic testing) are delivered via Genomic Medicine Service Alliances, with similar genomic testing services present in Scotland, Northern Ireland and Wales.
Education and training

Around 1.6 million people work for the NHS in the UK. Approximately half have a clinical role, either patient-facing or in laboratories or other clinical services. The working party agreed that all healthcare professionals (HCPs) should have an awareness of pharmacogenomics.

There was, however, recognition that not all HCPs will need the same level of competence. This means that there will be different levels of knowledge and skill needed by an HCP depending on their discipline, specialism (and subspecialism) and if they are prescribers or involved in other aspects of medicines management.

Ideally, pharmacogenomics will be integrated into relevant clinical pathways, and it is likely to expand beyond the existing pathways and specialisms that currently use pharmacogenomic tests. This aligns to patient preferences to have pharmacogenomics integrated within their clinical plan and means that pharmacogenomic education and training requirements are not confined to one specialism or professional group.

It is likely that, alongside an education and training workplan to upskill the workforce on knowledge of pharmacogenomic tests and implications for medicines management, there will also be a requirement for a parallel education and training workplan to support the integration of pharmacogenomic tests into the clinical workflow, covering topics such as interpretation and communication of results, data storage and access, to mention just a few. It is also likely that clinicians will need support and guidance on how to incorporate genomic information from direct-to-consumer tests into treatment plans for patients.

4.1 Pharmacogenomics in education and training frameworks

In March 2021, Health Education England’s Genomics Education Programme (GEP) conducted a desktop review of all curricula and proficiency standards from regulatory bodies aligned to the different points along the education continuum, a framework that can be used to consider the different education and training touchpoints throughout an HCP’s career (Fig 6). Content analysis was used to identify where and when pharmacogenomics (and associated search words) was mentioned within the documents.

As shown in Table 2, the presence of pharmacogenomics is not universal in pre-registration education documents, mentioned only in the General Medical Council’s standards and in a minority of the clinical scientists’ curricula. Similarly, for post-registration training (Table 3), there are limited mentions of pharmacogenomics in medical and healthcare science curricula, and, where it is mentioned, the statements are broad and knowledge-based, rather than defining specialty-specific applications. However, genomics, within the context of mode of action of pharmacokinetics, is mentioned within the Prescribing Competency Framework. This implies all organisations who use this framework to inform their education and training around prescribing will be covering aspects of pharmacogenomics. During the desktop review, no specific pharmacogenomic-related competency frameworks for different professions or clinical tasks or roles were identified, apart from the Prescribing Competency Framework.
4.2 Education and training resources: current and future considerations

Lifelong learning in pharmacogenomics should also be available to all HCPs. This learning should be relevant to the clinical role, up to date and easily accessible. The working party agreed that a layered approach to learning should be available so that HCPs can access ‘just-in-time’ information, short courses or formal qualifications, depending on their professional requirements and personal interests.

To scope out the current education and training offering, the GEP conducted a desktop review to identify education and training resources in pharmacogenomics (limited to resources accessible via online search engines). A summary of exemplar resources can be found in Table 4. Descriptive analysis of the resource attributes showed a wide range of education and training opportunities available, from formal qualifications through to bitesize learning. However, the content of most of the available resources covers fundamental concepts and is pitched at an introductory level, especially the resources developed in the UK. When mapping these against the Continuum of Education, the current offering of education and training is skewed to the needs of those at pre-registration level, suggesting a gap in provision of educational resources to support those in practice where individuals will be looking to access ‘just-in-time’ information aligned to their role-appropriate clinical competencies.

4.3 Workforce planning

When the number of pharmacogenomic tests available for use in the NHS increases, consideration will need to be given to the overall workforce structure and whether the current numbers and clinical roles are fit for purpose in delivering an expanded pharmacogenomics service. Because of this, when the strategic planning of service delivery models is carried out, workforce planning and development should be incorporated from the outset to ensure that there are enough HCPs to deliver the service. Consideration should also be made around expanding the roles of existing staff to incorporate pharmacogenomics and medicines optimisation.
Table 2. Pharmacogenomics in pre-registration curricula

<table>
<thead>
<tr>
<th>Governing body</th>
<th>Profession</th>
<th>Pharmacogenomics included?</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medical Council</td>
<td>Medicine</td>
<td>Yes: Outcome 22e</td>
</tr>
<tr>
<td>General Dental Council</td>
<td>Dentistry</td>
<td>No</td>
</tr>
<tr>
<td>General Pharmaceutical Council</td>
<td>Pharmacy</td>
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</tr>
<tr>
<td>Nursing and Midwifery Council</td>
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</tr>
<tr>
<td></td>
<td>Midwifery</td>
<td>No</td>
</tr>
<tr>
<td>Health and Care Professions Council</td>
<td>Art therapists</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Biomedical scientists</td>
<td>Yes: Standard 13.8</td>
</tr>
<tr>
<td></td>
<td>Chiropodists/podiatrists</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Clinical scientists*</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dietitians</td>
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</tr>
<tr>
<td></td>
<td>Hearing aid dispensers</td>
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</tr>
<tr>
<td></td>
<td>Occupational therapists</td>
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</tr>
<tr>
<td></td>
<td>Operating department practitioners</td>
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</tr>
<tr>
<td></td>
<td>Orthoptists</td>
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<tr>
<td></td>
<td>Paramedics</td>
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<tr>
<td></td>
<td>Physiotherapists</td>
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<td>Practitioner psychologists</td>
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<tr>
<td></td>
<td>Prosthetists/orthotists</td>
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</tr>
<tr>
<td></td>
<td>Radiographers</td>
<td>No</td>
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<tr>
<td></td>
<td>Speech and language therapists</td>
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</table>
Table 3. Pharmacogenomics in post-registration curricula or competency frameworks

<table>
<thead>
<tr>
<th>Responsible body</th>
<th>Number of curricula</th>
<th>Pharmacogenomics included (latest version of curricula)?</th>
</tr>
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<tr>
<td>The UK Foundation Programme Office</td>
<td>1</td>
<td>Tangentially, through reference of the Prescribing Safety Assessment which assesses against the General Medical Council Outcomes for Graduates, which mentions pharmacogenomics</td>
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<tr>
<td>Royal College of Physicians</td>
<td>35</td>
<td>Present in 7 curricula: audiovestibular medicine, clinical pharmacology and therapeutics, genitourinary medicine, medical oncology, palliative medicine, pharmaceutical medicine, rheumatology</td>
</tr>
<tr>
<td>Royal College of Anaesthetists</td>
<td>1, plus 5 annexes</td>
<td>Annex B</td>
</tr>
<tr>
<td>Faculty of Dental Surgery</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>Royal College of Emergency Medicine</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Royal College of General Practitioners</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Royal College of Obstetricians and Gynaecologists</td>
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<td>No</td>
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<tr>
<td>Faculty of Occupational Medicine</td>
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<tr>
<td>Royal College of Ophthalmologists</td>
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<td>Royal College of Paediatrics and Child Health</td>
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<td>Royal College of Pathologists</td>
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<td>Present in 1 curriculum: medical virology</td>
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<tr>
<td>Royal College of Psychiatrists</td>
<td>11</td>
<td>No</td>
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<tr>
<td>Faculty of Public Health</td>
<td>1</td>
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</tr>
<tr>
<td>Royal College of Radiologists</td>
<td>2</td>
<td>Present in 1 curriculum: clinical oncology</td>
</tr>
<tr>
<td>Faculty of Sexual and Reproductive Health</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Royal College of Surgeons of England</td>
<td>11</td>
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<tr>
<td>National School of Healthcare Science</td>
<td>35</td>
<td>Present in 27 curricula: clinical bioinformatics – genomics, clinical bioinformatics – health informatics, clinical bioinformatics – physical sciences, analytical toxicology, clinical and laboratory transfusion, clinical biochemistry, histocompatibility and immunogenetics, molecular pathology of acquired disease, molecular pathology of infection, clinical biomedical engineering, imaging physics, radiotherapy physics, reconstructive sciences, audiological sciences (adult), audiological sciences (paediatric), cardiac (adult), cardiac (congenital and paediatric), gastrointestinal physiology, neurophysiological science (EEG), neurophysiological science (EP), ophthalmic and vision sciences (electrophysiology), ophthalmic and vision sciences (imaging), ophthalmic and vision sciences (visual perception and psychophysics), respiratory and sleep science (adult), respiratory and sleep science (paediatric), urological science, vascular science</td>
</tr>
<tr>
<td>Royal Pharmaceutical Society</td>
<td>1 (Competency framework)</td>
<td>Yes: Competency 2.4</td>
</tr>
</tbody>
</table>

* Out of the 34 different curricula for clinical scientists, pharmacogenomics (or related search terms) was mentioned in the following 14 curricula: audiology, cancer genomics, cardiac science, clinical biochemistry, clinical bioinformatics (genomics), clinical microbiology, gastrointestinal physiology, genomic counselling, histocompatibility and immunogenetics, neurophysiology, ophthalmic and vision sciences, respiratory and sleep sciences, urodynamic science and vascular sciences. + Aspects of these training curricula are also produced by the Royal College of Pathologists.
<table>
<thead>
<tr>
<th>Resource title</th>
<th>Owner</th>
<th>Country/Region</th>
<th>Resource type</th>
<th>Access</th>
<th>Target audience</th>
<th>Content focus</th>
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<tbody>
<tr>
<td>Pharmacogenomics knowledge base: PharmGKB</td>
<td>Financially supported by NIH/NHGRI/NICHD and managed by Stanford University</td>
<td>USA</td>
<td>Web-based text</td>
<td>Free to access</td>
<td>Non-specific</td>
<td>Core concepts; medication and/or gene specific information; pharmacokinetics and/or pharmacodynamics schematics</td>
</tr>
<tr>
<td>Pharmacogenomics education programme: PharmGenEd</td>
<td>University of California San Diego</td>
<td>USA</td>
<td>Webinars and text-based information</td>
<td>Resources for HCPs: free Resources for teaching faculty: registration required</td>
<td>HCPs and teaching faculty</td>
<td>Core concepts; limited clinical applications; economic issues</td>
</tr>
<tr>
<td>U-PGx: ubiquitous pharmacogenomics</td>
<td>U-PGx consortium</td>
<td>Europe</td>
<td>Text based and webinars</td>
<td>Members only</td>
<td>Prescribing clinicians and pharmacists</td>
<td>Core concepts to clinical applications</td>
</tr>
<tr>
<td>Using personalised medicine and pharmacogenomics</td>
<td>FutureLearn (in partnership with University of East Anglia)*</td>
<td>UK</td>
<td>Massive Open Online Course (MOOC)</td>
<td>Free to access, with optional paid upgrade</td>
<td>Prescribing clinicians</td>
<td>Core concepts with exemplar clinical scenarios and ethical considerations</td>
</tr>
<tr>
<td>Explaining pharmacogenomics</td>
<td>Training Matters</td>
<td>UK</td>
<td>Online CPD module (15 mins)</td>
<td>Free to access</td>
<td>Pharmacy technicians</td>
<td>Core concepts</td>
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<tr>
<td>Introduction to genomics in pharmacy</td>
<td>Centre for Pharmacy Postgraduate Education (CPPE)</td>
<td>UK</td>
<td>Online CPD module (2 hrs)</td>
<td>Free to access for members of CPPE, fee for non-members</td>
<td>Pharmacy workforce</td>
<td>Core concepts</td>
</tr>
<tr>
<td>Pharmacogenomics and stratified medicine</td>
<td>HEE Genomics Education Programme</td>
<td>UK</td>
<td>Master’s module (15 credits)</td>
<td>HEE funding for NHS/PHE staff</td>
<td>NHS/PHE workforce</td>
<td>Core concepts (Level 7 learning outcomes) with exemplar drug–gene pairs</td>
</tr>
</tbody>
</table>

*Next run 2021/22 academic year.
Core PGx concepts
Threshold concepts: Clinical examples to illustrate relevance to patient care

Contextualising PGx concepts
Expand appropriate underlying concepts tailored for specialty/role

PGx in clinical practice
Competencies appropriate to role undertaken; ‘just-in-time’ information

- Requirement for additional education and training resources: ‘just-in-time’ information
- Availability of PGx education and training resources

Fig 6. Pharmacogenomics education and training requirements
Looking towards the future

5.1 Strategies for implementing pharmacogenomics across the NHS

Implementing the first nationwide pharmacogenomic testing service will mean overcoming a number of challenges, which are outlined in Table 5. Key areas to consider include:

> designing the pharmacogenomics clinical service
> standardising the consent process
> providing the supporting laboratory-based genotyping service
> storing and returning pharmacogenomic results in a user-friendly manner across the divergent healthcare record systems present in the NHS
> increasing the knowledge, education and confidence of healthcare prescribers in pharmacogenomics
> maintaining and building patient and public trust in the NHS Genomic Medicine Service
> funding the service.

In addition, clinical governance will be important to catalyse diffusion of best practice across NHS service providers. Moreover, continuous clinical research endeavours should be more closely intertwined with healthcare service delivery, so that new discoveries that are clinically and cost-effective can be more rapidly translated into clinical practice, leading to a cyclical process of incremental improvements to clinical practice. While the challenges are striking, each also represents an opportunity of equivalent magnitude, and so the overall opportunity to benefit patient care, if pharmacogenomics implementation is done effectively, is enormous. Each of these challenges is detailed below.

5.2 Funding

A national, equitable pharmacogenomics service that is a core part of the NHS and harnesses the available laboratory infrastructure requires funding nationally in each of the UK’s devolved nations. In the wake of the COVID-19 pandemic and stretched public finances, it will be more important than ever to focus initially on selected gene–drug pairs that are most likely to be clinically and cost-effective, to anticipate and measure testing volumes, and to follow up patients in the long term. This is because the overall cost-effectiveness of a single germline pharmacogenomic test will improve, the more prescribing decisions it influences over time per patient.

5.3 Clinical service design

The NHS introduced DPYD pharmacogenomic testing for fluoropyrimidine therapy in October/November 2020, and learning lessons from this (currently ongoing via the GMS Alliances in England) is important to enable wider pharmacogenomic test rollout. Considerations for selecting the next highest priority gene–drug pairs include the frequency and severity of the associated clinical outcome (ADR or reduced efficacy), the quality and consistency of the research evidence base, the effect size of the genomic variation on the clinical outcome, the clinical indication(s) for testing and feasibility of testing within existing patient pathways, and the anticipated number of patients who would become eligible for testing. Depending on the clinical scenario, different testing modalities may be required – for example, point-of-care genotyping tests have been evaluated for warfarin, clopidogrel and aminoglycosides.

To support the introduction of pharmacogenomics, specialist support should also become available to patient-facing practitioners when required. This could take the form of a remote (virtual) consultation service provided to primary and secondary care providers at an ICS level through multidisciplinary teams which include pharmacists and clinical pharmacologists suitably trained in pharmacogenomics. Given the degree of overprescribing in the NHS, there is also merit in introducing multidisciplinary complex prescribing clinics to primarily support medicines optimisation in patients with complex combinations of diseases and drug regimens, but with the additional remit of providing pharmacogenomic guidance to their ICS.
<table>
<thead>
<tr>
<th>Challenge</th>
<th>Mitigation strategy</th>
</tr>
</thead>
</table>
| **Pharmacogenomics clinical service design** |  > Centralised selection of key gene–drug pairs for initial national rollout (see section 5.3)  
  > Specify clinical indication(s) for testing each selected gene–drug pair in keeping with guidelines and prescribing information from regulatory agencies such as the MHRA  
  > Ensure the testing-reporting-actioning sequence fits within existing patient pathways  
  > Determine anticipated testing volumes to not overload the nascent system  
  > Plan for incremental service expansion to follow the initial implementation. This should involve incorporating additional gene–drug pairs and increasing testing capacity as awareness of the service and demand for testing rise  
  > Ensure that prescribers have regional access to expertise in pharmacogenomics (eg from clinical pharmacologists and/or pharmacists), particularly for patients with complex prescribing regimens. This may involve remote access to specialised input and/or setting up regional complex prescribing clinics. |
| **Consent processes**                  |  > Provide national standardised recommendations for consenting to tests specifically for pharmacogenomics  
  > It is expected that most prescribers will be competent to routinely request consent to pharmacogenomic testing  
  > A pharmacogenomic test should be viewed as equivalent to renal or liver function testing to guide prescribing decisions, and therefore should not routinely require genetic counselling services  
  > Where the genomic test is primarily being conducted for another indication (eg cancer or rare disease diagnosis), ensure that the appropriate consent procedures are followed for this indication |
| **Genotyping and laboratory considerations** |  > Test a panel of pharmacogenes when pharmacogenomic information is the primary indication for testing. This approach provides results relevant for the immediate indication and pre-empt future prescribing  
  > Extract pharmacogenomic information from sequence data (eg whole genome or whole exome) performed primarily for other indications (eg germline sequencing to aid cancer management or rare disease diagnosis)  
  > Ensure the test turnaround time is congruent with the chosen patient pathways  
  > Use point-of-care (POC) testing when pharmacogenomic results are required rapidly and testing is reactive – eg for warfarin, clopidogrel or aminoglycosides  
  > Although centralised genetic testing facilities such as the GLHs in England will remain the main platform for undertaking genetic testing, there should be careful evaluation of capacity and the ability to use local NHS laboratories to optimise test turnaround times  
  > Provide laboratories the freedom to decide which specific technology, platform and analytical workflow to use to deliver pharmacogene panel testing, based on local experience and expertise, test turnaround time and cost, ensuring the highest quality assurance standards |
| **Clinical decision support**          |  > Develop clinical pharmacogenomics guidance tailored to the NHS  
  > Develop a report structure that is easy to interpret, strives to avoid user alert fatigue and contains links to further information (eg just-in-time learning resources)  
  > Develop methods of providing reports across the spectrum of patient record systems, from paper-based to interruptive electronic systems  
  > Developing coding for genetic variants to allow for incorporation into the EHR  
  > Ensure that data are stored securely and confidentially  
  > Build interconnected systems that enable community-based services and hospitals to access clinically relevant pharmacogenomic results for patients  
  > Future-proof the systems so that pharmacogenomic-based recommendations can be added/amended as the research base grows |
### Table 5 (cont). Pharmacogenomics implementation challenges and proposed mitigations

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Mitigation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>&gt; Centralised funding is required for nationwide equitable implementation</td>
</tr>
<tr>
<td>Prescriber knowledge and education</td>
<td>&gt; It will be critical to upskill healthcare prescribers in pharmacogenomics. A multifaceted approach should be adopted and may include:</td>
</tr>
<tr>
<td></td>
<td>&gt; developing local champions/advisers to support the integration of genomics into practice</td>
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<tr>
<td></td>
<td>&gt; just-in-time learning resources used at or near the point of prescribing</td>
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<tr>
<td></td>
<td>&gt; access to CPD that aligns to pharmacogenomic tests available through the NHS, including online learning / short lectures / webinars</td>
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<tr>
<td></td>
<td>&gt; integrated at an appropriate level within undergraduate curricula of doctors and pharmacists</td>
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<tr>
<td></td>
<td>&gt; integration into postgraduate programmes for non-medical prescribers including, in the future, physician associates</td>
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<tr>
<td>Patient engagement, perspectives and managing expectations</td>
<td>&gt; Patient representatives should be involved throughout the implementation and service expansion phases</td>
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<td></td>
<td>&gt; Service delivery must be receptive and responsive to patient feedback</td>
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<td></td>
<td>&gt; Build public and patient trust through competent and joined-up implementation, secure data storage to preserve patient confidentiality, and upfront,</td>
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<tr>
<td></td>
<td>transparent explanations of any data breaches</td>
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<td></td>
<td>&gt; Add relevant pharmacogenomics text to NHS online guidance about medical conditions and treatments for patients and the public</td>
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<tr>
<td>Clinical governance</td>
<td>&gt; Encourage audits of local pharmacogenomic services and quality improvement programmes to spread and affirm best practice, share learning, and</td>
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<tr>
<td></td>
<td>iteratively improve service delivery</td>
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<td></td>
<td>&gt; Improvement of the recording of treatment response (eg efficacy, ADRs, adherence, reasons for changing therapy, patient reported outcome measures)</td>
</tr>
<tr>
<td></td>
<td>in clinical notes and coding to improve measures of outcome and impact</td>
</tr>
<tr>
<td>Research</td>
<td>&gt; Conduct collaborative, inclusive and multidisciplinary research to transition towards a learning healthcare system that provides equitable, clinically and</td>
</tr>
<tr>
<td></td>
<td>cost-effective, accessible and acceptable care. Collaboration between healthcare, academia and the life sciences industry will be vital</td>
</tr>
</tbody>
</table>
Aminoglycoside antibiotics – RNR1

A 23-year-old woman comes to the emergency department with acute pyelonephritis leading to severe sepsis. She is treated with an antibiotic regime which includes a single dose of intravenous gentamicin. She responds well and is discharged from hospital 3 days later. However, she notices that her hearing has declined significantly since her admission. A subsequent audiology assessment reveals that she has developed moderate sensorineural hearing loss (SNHL) and requires hearing aids.

> Aminoglycosides have proven efficacy, and can be used in combination with other antibiotics.44–46
> In addition to nephrotoxicity, sensorineural hearing loss and vestibulotoxicity are well-recognised dose-dependent adverse effects of aminoglycoside antibiotics.47
> Certain individuals have a predisposition toward aminoglycoside-induced hearing loss (AIHL), with reports of single doses causing profound bilateral sensorineural hearing loss.46,48
> This predisposition is caused by variants in the mitochondrial RNR1 gene. The most common of these variants is m.1555A>G, present in approximately 1 in 500 individuals. The less frequent m.1095T>C and m.1494C>T RNR1 variants also have strong evidence for their association with AIHL.46
> Clinical guidelines recommend that aminoglycoside antibiotics should be strictly avoided in individuals with these RNR1 variants, unless the high risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies.46,49
> Alternative antibiotic regimens should be decided upon based on clinical indication and local surveillance data in discussion with microbiology colleagues.
> Testing for m.1555A>G is available via the National Genomic Test Directory, although turnaround takes several weeks. Therefore, this is not viable in the acute setting.
> A rapid point-of-care test (POCT) has recently been developed for the m.1555A>G variant, with a turnaround time of 26 minutes. This has been trialled in neonatal intensive care units, where gentamicin is prescribed frequently.50

5.4 Consent and ethics

For a patient to consent to pharmacogenomic testing, they need to have capacity, be appropriately informed and be free from coercion. Indeed, these consent requirements are the same as for any standard medical procedure. When consenting for pharmacogenomic testing, it is helpful to both the patient and the HCP to frame the clinical settings in which pharmacogenomics results are used: namely, to guide drug and/or dose selection according to guideline recommendations to help optimise drug therapy for a diagnosed condition. Importantly, this setting is equivalent to carrying out renal or liver function tests to guide drug prescribing decisions, and that analogy might conceivably aid patient understanding. Framing pharmacogenetic testing as being similar to liver or renal function tests also guards against genetic exceptionalism, ie the belief that genetic information is special and different from other types of medical data.

The main difference between pharmacogenomic testing and renal/liver function testing is that germline genetics are unchanging and so a pharmacogenomic panel test may only need to be carried out once yet could influence multiple prescribing decisions over time, whereas renal and hepatic functions change dynamically, necessitating more frequent testing. Clearly, as research advances and/or the patient is prescribed new drugs, pharmacogenomic advice relating to specific drug–gene variant pairs will change. This may, if not already covered by the original gene panel test, require further pharmacogenomic testing.

We have drawn a distinction between the consent processes required for pharmacogenomic testing, and the more detailed consenting procedures needed for WGS/whole-exome sequencing (WES), for example in the diagnosis of rare diseases. The latter requires expert input from genetic health professionals, including
clinical geneticists and genetic counsellors, to impart information on the disease causing gene mutation(s), variants of uncertain significance (VUS) and clinically significant incidental findings (eg variants in known disease-causing genes unrelated to the test indication). Of course, WGS/WES will also contain valuable pharmacogenomic information, and this should be discussed with patients where it may make a clinically significant difference to drug choice and/or drug dose. VUS are present in pharmacogenes, and although implementation is largely based on known functional variants, further research will be essential to determine whether these VUS have any functional consequences. Some of the other relevant ethical considerations (for instance, trust, data storage conditions, patient confidentiality) are included in other parts of this report. However, it is important to mention two other ethical issues of relevance:

- Distributional justice – there should be fair distribution of scarce public health resources and thus health economic analysis should form part of the process of implementation of pharmacogenomics.
- Social justice – genetic research has largely been based on European ancestry populations, and therefore it is vital that implementation considers the diversity of our population to ensure that we do not exacerbate health and race inequalities.

### 5.5 Genotyping and laboratory considerations

The main types of genetic testing approaches available are:

- single gene testing, as employed for *HLA-B*57:01 (abacavir) and *DPYD* (fluoropyrimidines)
- testing a panel of pharmacogenes in one test (which could be based on a number of approaches including sequencing, genome-wide arrays or mass spectrometry)
- whole-exome sequencing (WES) and whole-genome sequencing (WGS).

At present, since our understanding of clinically actionable pharmacogenomics is limited to relatively few genes, the best options available are either single gene testing or panel testing. The former is simpler and can also include POC testing. However, it requires the HCP to request the test (‘a reactive approach’), and is unlikely to benefit from the gains in cost-effectiveness associated with panel testing. Specifically, incorporating a panel of pharmacogenes into a single test appears the optimal current clinical and cost strategy for the majority of drugs with a pharmacogenomic recommendation (which starts to move from a reactive testing strategy to a pre-emptive approach). This is because the genes relevant to both the immediate testing indication and potential future prescribing decisions are interrogated together, in effect future-proofing the test. It is also important to note that the cost of WES/WGS has fallen rapidly and will continue to fall, and so there may come a time when most of the population have had their whole genome sequenced. The pharmacogenomic information contained within whole exomes or whole genomes should not be ‘lost’, and should be extracted for patient benefit.

The centralised genomic laboratories are well placed to offer and coordinate panel-based pharmacogenomic testing as their consolidated resources and expertise are expected to yield high-fidelity results, appropriate quality assurance, standardised practice, access to highly secure NHS digital storage, and bioinformatics pipelines to interpret a patient’s raw genomic data to identify alleles, genetic-based gene phenotype predictions and corresponding clinical recommendations. Centralisation of genomic testing to a few laboratories also provides an economy of scale. However, given the likelihood that the demand for testing will increase over time, it is important that centralisation does not become a barrier to personalisation of prescribing, which, by definition, requires near-patient facilities.

The decision on which technology to use for genotyping/sequencing will need to be carefully considered. It may be possible to design a broad approach including biologically plausible genes/variants within panels, but initially report clinical results only on established actionable variants within pharmacogenes. Information from the broader dataset could be stored for future use once their actionability is established.
Looking to the future, it is important to state that genomics is moving at a rapid pace, and new techniques to determine disease predisposition and pharmacogenomic variation will emerge. For example, there is currently increasing interest in the role of polygenic risk scores (PRS), which can be derived from whole-genome genotyping or sequencing approaches. PRSs can be used for disease stratification, and are likely to also be used to determine the choice of drug for treatment of diseases. It is therefore important that any service specification takes into account the likely advances in this area.

5.6 Clinical decision support

For a pharmacogenomic test result to influence prescribing decisions, it must be available at the point of prescribing and easy to interpret (comparable to a drug allergy record flag). In principle, POC and preemptive testing models will ensure that most test results are available at the point of prescribing. Nevertheless, there is heterogeneity between NHS hospitals in the uptake of EHRs, and approximately two-thirds of hospitals do not currently use comprehensive clinical electronic systems. This creates significant challenges for centralised GLHs to return results compatible with the diversity of secondary care patient record-keeping systems. Although most laboratories will be returning results as text files (eg .pdf files) in the short term, this is far from ideal and every effort should be made in the medium to long term to develop systems that enable pharmacogenomic results to be coded within a patient’s EHR in an updatable (future-proof), interactive and interruptive manner, so that appropriate alerts or recommendations are provided automatically during any prescribing episode, without need for recollection from the busy prescriber (Fig 8).

In contrast to secondary care, a few main EHR providers cover the majority of GP practices, and prescribing in primary practice is already routinely electronic with an interruptive alert module (eg for interacting drugs). Therefore, primary care is likely the preferred setting for implementing pharmacogenomics interruptive clinical decision support systems at scale over the short term, particularly because the majority of prescribing happens in primary care. The bidirectional access to clinical information between local primary and secondary care services, and with community pharmacies, including pharmacogenomic test results, will help maximise the clinical and cost-effectiveness of pharmacogenomic testing, and so national initiatives to improve digitisation and interconnectedness of local NHS services will directly benefit a pharmacogenomics service, given that pharmacogenomics should be a once-in-a-lifetime test (Fig 9).

The optimal format to provide pharmacogenomic results to HCPs is currently not known, although accessibility when required, brevity, clarity and access to the recommendation rationale are likely key attributes. One popular model is the red-amber-green (RAG) or traffic light system, which colour-codes recommendations as red (strongly advise against proposed prescription), amber (use with caution) and green (proceed). Nevertheless, prescribing can be a complex decision involving integration of multiple factors (eg the patient’s age, renal function, co-medications, concomitant diseases), of which pharmacogenomics is just one. Therefore, while responsibility for the prescription will still rest with the prescriber, efforts should be made in EHR systems to integrate the different types of ‘alerts’ so that the electronic system can provide a single recommendation, rather than a series of one-dimensional warnings, with either no or conflicting recommendations. This vision will require further research, but is considered highly worthwhile.

Lastly, there is real value in incorporating high-level pharmacogenomic information into the BNF, perhaps within an appendix. While this will not necessarily provide genotype-specific recommendations, the BNF is commonly used by prescribers and can offer an alternative information source.
Codeine – CYP2D6

A 45-year-old woman undergoes an elective laparoscopic cholecystectomy and is discharged home on regular co-codamol tablets. A day later she contacts her GP complaining of ongoing pain despite taking the maximum prescribed dose. Following assessment, it is felt that no acute surgical complication underlies her pain and so she is discharged with liquid morphine to take as required. Her pain is rapidly eased and she makes a full postoperative recovery.

- Codeine is an analgesic drug frequently used to treat mild to moderate pain, and is also an antitussive and anti-diarrhoeal agent.
- Codeine is a prodrug, which is metabolised by the liver enzyme CYP2D6 to active morphine (Fig 7).54
- The gene CYP2D6 has many variants that affect its enzymatic function.
- The predicted activity of an individual’s CYP2D6 enzyme, based on the genetic variants they carry, is categorised into poor metabolisers (PMs), intermediate metabolisers (IMs), extensive metabolisers (EMs, normal function) and ultra-rapid metabolisers (UMs).
- There is a body of research evidence55 collectively reporting that CYP2D6 PMs exhibit reduced exposure to morphine after receiving codeine,56 experience reduced analgesic benefit,57,58 and CYP2D6 genotype-guided codeine prescribing results in improved analgesia for IM and PM patients compared with standard prescribing.59
- On the other hand, morphine exposure is higher after codeine intake in UMs than EMs.60,61 UM individuals appear to be at an increased risk of opioid-related adverse events,58,61 including life-threatening and fatal toxicity in young children with obstructive sleep apnoea (OSA) receiving codeine after (adenoid) tonsillectomy.62,63
- The codeine summary of product characteristics (SmPC) now states that codeine is contraindicated in both paediatric patients undergoing (adenoid) tonsillectomy for OSA and in patients known to be CYP2D6 UMs (of any age).64

Around 10% is excreted unchanged

Most is metabolised to codeine-6-glucuronide by UGT2B7, or norcodeine by CYP3A4, which both have little influence on pain

Fig 7. Codeine metabolism
5.7 Patient engagement

Patient engagement and public trust are essential for mainstreaming pharmacogenomics. Patient representatives are present on NHS GMS Alliance partnership and leadership boards, and in the corresponding structures in Scotland, Wales and Northern Ireland, with their advocacy helping to keep patient views, needs and expectations at the core of genomic decision making. Similarly, it will be essential for patient representatives to be closely involved with the decision-making infrastructure for a pharmacogenomic testing structure at both regional and national levels. For the broader patient population and general public, updating and augmenting NHS online educational material about conditions and treatments to include succinct pharmacogenomics insights should gradually raise awareness, build trust and help manage expectations.

It will be important in interactions with patients and the public to transparently appraise the merits of pharmacogenomics, describing that it is a new tool to use alongside existing practices (e.g., consideration of interacting co-medications) to help improve the chances of prescriptions being beneficial. However, messaging should be cognisant to explain that pharmacogenomics does not guarantee that a drug will definitely help without any side effects. Feedback from surveys and other patient-reported outcome measures, perhaps ascertained by quality improvement or research initiatives (see below), should be obtained as part of engaging and improving service delivery.

Lastly, there is a clear explanation that any genomic data collected by the NHS as part of clinical care are securely stored and kept confidential in line with the UK General Data Protection Regulation (GDPR). Any deviations from this must be transparently and expeditiously communicated and swiftly rectified to avoid loss of public confidence and reduced engagement.

5.8 Clinical governance and research

To maximise the potential of a national pharmacogenomics programme, quality assurance, quality improvement and ongoing research are essential. In particular, service evaluations and clinical audits will help raise practice standards across service providers, while increasing awareness of pharmacogenomics and testing indications. Quality improvement projects can be conducted across the full interlinked chain of activities that constitute a pharmacogenomics service, from identifying eligible patients for testing, optimising laboratory processes, incorporating results into individual hospital EHR systems, to improving inpatient/outpatient medication reviews. An engine of continual research is required to measure the impact of introducing pharmacogenomics at scale on health outcomes, cost-effectiveness, equity of service access and wider societal implications.

Furthermore, innovative research applying advanced analytical techniques to real-world big data in an ecosystem where researchers and healthcare services are closely aligned should drive innovation and expedite clinical translation of novel findings, including but not limited to new actionable pharmacogenes and guideline recommendations. This collective research endeavour should be collaborative, cross-cutting and encompass multiple disciplines from within the life sciences, humanities and social sciences, including health economics. Through this comprehensive approach, the full range of issues relevant to patients, healthcare providers and society pertaining to pharmacogenomics can be addressed with the aim of establishing a virtuous cycle of iterative, incremental improvements to advance the pharmacogenomics service.
Fig 8. Comparing pharmacogenomic and standard approaches to prescribing
Fig 9. Patient pathway for pharmacogenomic testing
Some red flags which increase the risk of medical malpractice have been highlighted (Table 6). It is therefore important to put into place a system that focuses on quality improvement to reduce medication errors (see section 5.8), and thereby improve patient outcomes and reduce the risk of legal challenge.

While there are individual case reports of legal cases being brought against HCPs based on the omission of pharmacogenomic testing, an interesting recent development is an $8 billion legal case brought by the state of Hawaii against the manufacturer of clopidogrel for illegal marketing. This relates to the fact that clopidogrel is a prodrug and is converted to the active metabolite by the CYP2C19 enzyme (as described below). At least 30% of the Hawaiian population carry genetic variants of CYP2C19 that cannot convert clopidogrel to its active form. In February 2021, a judge ordered Bristol Myers Squibb and Sanofi to pay over $834 million to the state of Hawaii, but the case continues pending an appeal by the manufacturers.

### Clopidogrel – CYP2C19

A 72-year-old man was diagnosed with a likely transient ischaemic attack (TIA) and commenced on atorvastatin and clopidogrel. Two months later he is taken by ambulance to his hospital emergency department with left leg weakness, and is diagnosed with a lacunar stroke. He regularly took his drugs and asks whether the clopidogrel was working for him.

- Clopidogrel is an antiplatelet drug indicated in patients with an acute coronary syndrome, percutaneous coronary intervention (PCI), transient ischaemic attack (TIA), acute ischaemic stroke and peripheral artery disease.
- Clopidogrel is administered as an inactive prodrug that is metabolised in the liver to its active antiplatelet metabolite. The drug-metabolising enzyme CYP2C19 is especially important in clopidogrel’s bioactivation (Fig 10).
- Meta-analysis in clopidogrel-treated patients (~91% underwent PCI) has highlighted the association between reduced-function variants in the gene CYP2C19, and increased risk of major adverse cardiovascular events and, in particular, stent thrombosis.66
- Randomised controlled trials have investigated the utility of CYP2C19-genotype-guided antiplatelet prescribing for cardiac conditions, with differing results.57,68
- A recent randomised controlled trial in patients with a mild ischaemic stroke or TIA carrying reduced-function CYP2C19 variants reported that ticagrelor decreased the rate of new strokes compared with clopidogrel, but with an associated increase in bleeding.69
Clopidogrel – an inactive prodrug

Absorption

Metabolism by CYP2C19 and other enzymes in hepatocytes to active clopidogrel metabolite

Inhibition of platelet P2Y12 receptors

Decreased risk of thrombosis

Fig 10. Clopidogrel metabolism

Table 6. Red flags that may increase the likelihood of malpractice cases

<table>
<thead>
<tr>
<th>Red flag</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfamiliarity and lack of training</td>
<td>There is a lack of knowledge and training on pharmacogenomics in the healthcare professions</td>
</tr>
<tr>
<td>Rapidly changing technology and standards</td>
<td>It is known that new technologies are a driver of medical malpractice, exacerbated by the fact that there are no standards</td>
</tr>
<tr>
<td>Hindsight bias</td>
<td>The circumstances surrounding a case look different to juries at the time the case is heard, compared with the time when the clinician made the decision</td>
</tr>
<tr>
<td>The more you can do, the more that can go wrong</td>
<td>The increase in genomic technologies is an opportunity to improve patient care, but at the same time represents a fertile ground to make mistakes</td>
</tr>
<tr>
<td>Differential uptake</td>
<td>Variation in uptake by postcode may put slow adopters at higher risk of medical malpractice</td>
</tr>
<tr>
<td>Expert disagreement and uncertainty</td>
<td>Given the novelty of genomic medicine and the lack of clear guidelines, disagreement and uncertainty can fuel litigation</td>
</tr>
<tr>
<td>Novel legal claims</td>
<td>Issues such as the duty to disclose incidental findings, communicate variant reclassification and inform of potential harm may become important in some circumstances</td>
</tr>
<tr>
<td>Hungry plaintiffs’ bar</td>
<td>Medical malpractice solicitors may see this as a fertile ground to pursue cases</td>
</tr>
<tr>
<td>Warnings from regulatory agencies</td>
<td>Ignoring warnings from regulatory agencies such as the MHRA, FDA and EMA can increase the chances of being sued</td>
</tr>
<tr>
<td>Ample supply of adverse outcomes</td>
<td>Case brought on the basis that an adverse drug efficacy or safety outcome could have been prevented, treated or minimised by genetic testing</td>
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</tbody>
</table>

Adapted from Marchant and Lindor69
Opportunities highlighted by the working party are outlined in Table 7. This includes not only the identification of new gene–drug pairs in the different specialty areas, but also in the refinement of existing gene–drug pairs, and the assessment of the public health benefits of pharmacogenomic implementation. There are also opportunities to reduce polypharmacy with a more targeted therapeutic approach. Due to the nature of pharmacogenomics (wide range of possible genetic variants and gene–drug combinations), the use of real-world big data and pragmatic trials will be crucial. Resources such as the UK Biobank and the 100,000 Genomes Project, as well as some of the cohort studies, should be regarded as promising assets to increase our knowledge of pharmacogenomics, in addition to specific drug–gene-related studies. As with all forms of research, it will be important to include patients and the public from the outset in order to understand their needs, uptake, acceptance, feedback, equity of access, ethical, legal and social issues, and changing perceptions of pharmacogenomics. Pharmaceutical and diagnostic industries, together with the regulators, should be involved in defining the research agenda. The implementation and further advancement of pharmacogenomics will not be possible without funding. It is therefore vital that funding is made available not only from government sources and charities, but also through private-public sector partnerships. The UK has had major success in genomics through private-public sector investment with over 50 companies now working closely with the NHS, attracting about £3.3bn in investment.

### Table 7. Opportunities highlighted by the working party

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Area of further research/opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>Immediate- and delayed-type hypersensitivity reactions</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>Exploration of any genetic component to ‘accidental awareness’ during anaesthesia</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Wider subspecialty integration of pharmacogenomics</td>
</tr>
<tr>
<td>Diabetes and endocrinology</td>
<td>Monogenic diabetes therapy / variability in response to metformin / agranulocytosis in response to thyroid-suppressing medications / adrenal suppression in response to corticosteroids</td>
</tr>
<tr>
<td>Gastroenterology and hepatology</td>
<td>Upper GI ulceration / therapies for inflammatory bowel disease / drug-induced liver injury</td>
</tr>
<tr>
<td>Haematology</td>
<td>Phenotypic vs genotypic testing</td>
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<tr>
<td>Infectious diseases</td>
<td>Antibiotics and antivirals -dosing and adverse effects</td>
</tr>
<tr>
<td>Neurology</td>
<td>Personalised approach to anti-epileptic therapy / multiple sclerosis therapies</td>
</tr>
<tr>
<td>Obstetrics and gynaecology</td>
<td>Fertility treatments / teratogenicity</td>
</tr>
<tr>
<td>Oncology</td>
<td>Efficacy of dose-reduced therapeutics in response to pharmacogenomic testing and evidence to guide dose reduction and escalation</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Steroid-induced glaucoma / treatments for macular degeneration</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>International consortium to enable research in pharmacogenomics in children</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>Role of pharmacists in all settings, and community pharmacies in implementation of pharmacogenomics</td>
</tr>
<tr>
<td>Primary care</td>
<td>Implementation of pharmacogenomics into primary care, decision support systems</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Optimising antidepressant therapy / identifying those at highest risk of adverse effects from antidepressant and antipsychotic therapies</td>
</tr>
<tr>
<td>Renal</td>
<td>Immunosuppressants in renal disease and renal transplantation / antihypertensives / antibiotics</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma treatment optimisation / targeted pulmonary fibrosis and cystic fibrosis therapeutics</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>Osteonecrosis of the jaw in response to bisphosphonates / immunosuppressants and biologics</td>
</tr>
</tbody>
</table>
Background, set-up and administration

The project was conceived by Prof Sir Munir Pirmohamed, the president of the British Pharmacological Society (BPS) and Prof Donal O’Donoghue, the registrar of the Royal College of Physicians (RCP), in 2019. It was decided to establish a working party with expertise in pharmacogenomics covering the many different medical specialties represented by the RCP, alongside representation from the RCP Patient and Carer Network and key national healthcare organisations. Representation was also sought from the Royal College of General Practitioners and Royal Pharmaceutical Society, given the instrumental role that GPs and pharmacists are anticipated to play in a broader clinical adoption of pharmacogenomics. The aim of this working party was to assess the contemporaneous evidence supporting the translation of pharmacogenomics into clinical practice and produce a succinct report to include reasonable and practical recommendations to further the clinical adoption of pharmacogenomics, where appropriate, for the advancement of patient care.

The working party was jointly set up by the BPS and RCP. The working party meeting schedules, agendas and minutes were coordinated by the BPS. It was agreed that the report would be produced by the RCP, but jointly owned by the BPS and RCP, given their mutual interest in pharmacogenomics and close productive cooperation throughout this project. The working party was initially led by Prof O’Donoghue and Prof Pirmohamed as co-chairs. The death of Prof O’Donoghue in January 2021 was an enormous loss to everyone who knew him, to the RCP as a whole, and to this working party. After consideration, it was decided that the working party should continue, be chaired by Prof Pirmohamed, and dedicate its work and this report to Prof Donal O’Donoghue.

Meetings

The initial wave of the COVID-19 pandemic in 2020 resulted in a several month delay to the start of the project, and a shift to all working party meetings being held virtually. The working party met, typically for 3 hours, as follows:

- On 1 September 2020 for the project kick-off meeting.
- For eight subsequent meetings that focused on specialty area pharmacogenomic-based deep dives, alongside planning the structure and content of the report.
- A final meeting to discuss the draft report.
- Sub-meetings were set up on an ad hoc basis, attended by at least one co-chair, co-secretary and the working party manager to revise meeting agendas to accommodate external speaker availabilities, and for further discussions as the report was being developed.

The working party membership provided pharmacogenomics-based deep dives covering the following specialty areas: allergy and immunology, cardiology, clinical genetics, oncology, renal medicine and respiratory medicine. Moreover, the membership provided in-depth perspectives on pharmacogenomics from the RCP Patient and Carer Network, Genomics England, Health Education England, NHS England, the Royal College of General Practitioners and the Royal Pharmaceutical Society.

Appendix: report methodology
External expert presenters were invited to give evidence about pharmacogenomics at working party meetings from the Royal College of Anaesthetists, Royal College of Paediatrics and Child Health, Royal College of Psychiatrists, and the following physicianly specialties: endocrinology and diabetes, gastroenterology, haematology, hepatology, infectious diseases and neurology. While it was not possible within the project timescale to solicit evidence from all specialties and royal colleges, it is hoped that the relatively wide representation achieved will nevertheless ensure that the report is both relevant and of interest to a broad audience of physicians, other healthcare professionals, and healthcare organisations.

The meetings were well attended with most working party members participating in each meeting (virtually). At each meeting, members were reminded to disclose any new potential conflicts of interest. After each meeting, detailed minutes were circulated to the working party, edits and revisions to them received by email, and approved by the working party as an accurate record at the next meeting.

Evidence

This report is based around the evidence presented in the pharmacogenomics-based deep dives at the meetings, supplemented by relevant additional literature. The deep dives were presented orally, with copies of the written slides and additional materials made subsequently available by the presenters to the working party.

Producing the report

The outline and provisional content of the report was discussed at several working party meetings, with input from all members. After the final evidence had been presented, the report was drafted by Dr Richard Turner and Dr Emma Magavern (co-secretaries), with the section on education and training drafted by Dr Michelle Bishop. Initial revisions were made by the working party chair Prof Pirmohamed and the subsequent draft was circulated to the wider working party, with collation of all responses and edits received.

A working party meeting then discussed the next draft and consensus was reached on a few key areas. The written and oral comments from the working party members were incorporated by the co-secretaries into a revised report, with input from the chair, who acted with the consent of all members, as editor to finalise the report. The graphics and production of the report were managed by the RCP Corporate Communications and Publishing team. The report was approved by both the RCP Council and the BPS Council.
Declaration of interests

A declaration of interests form was completed by all members of the working party and deep dive specialty presenters. Members were reminded to disclose any new potential conflicts of interest at each meeting.

### Members of the working party

<table>
<thead>
<tr>
<th>Name</th>
<th>Conflict of interest statement</th>
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<tbody>
<tr>
<td>Professor Sir Munir Pirmohamed (co-chair)</td>
<td>I was a member of the NHS England Pharmacogenomics working group which looked at implementation of pharmacogenomics into the NHS, and which drug–gene pairs need to be included in the testing registry. I was not paid for this work. For the duration of the working party, I was president of the British Pharmacological Society, co-sponsor of the working party. I am also a non-executive director for NHS England. I receive research funding from various organisations, including the MRC, NIHR, EU Commission and Health Education England. I have also received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); a PhD studentship jointly funded by EPSRC and AstraZeneca; and grant funding from Vistagen Therapeutics. I also have unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol Myers Squibb and UCB. I have developed an HLA genotyping panel with MC Diagnostics, but do not benefit financially from this. None of this funding is directly relevant to these guidelines.</td>
</tr>
<tr>
<td>Dr Richard Turner (co-secretary)</td>
<td>During the setting up and running of the working party, and during most of the development of the report, I was an academic clinical lecturer at the University of Liverpool. While the report was being finished, I independently moved to begin working at GSK. I am a member of the BPS.</td>
</tr>
<tr>
<td>Deborah Roebuck</td>
<td>I am employed by AbbVie Ltd</td>
</tr>
<tr>
<td>Dr Paul Ross</td>
<td>I have received fees for the following work: participation in advisory boards from AstraZeneca, Roche, Sirtex and Eisai; speaker fees from Amgen, Merck, Servier and Roche; financial support to attend conferences from Amgen, Bayer, Roche, and Servier; research funding from Sanofi and Bayer. I am a member of NHS England Chemotherapy Clinical Reference Group; the Adjuvant and Advanced disease subgroup of the NCRI Colorectal Clinical Studies group; the hepatobiliary subgroup of the NCRI Upper GI Clinical Studies group. I am senior medical editor for Macmillan Cancer Support.</td>
</tr>
<tr>
<td>Dr Joyce Popoola</td>
<td>Member of the BMA. Grants/meeting sponsorship/honorarium: Chiesi Limited, Astellas Pharma, Alexion Pharmaceuticals, Kidney Care UK, Kidney Research UK</td>
</tr>
<tr>
<td>Dr Shuaib Nasser</td>
<td>Member of the British Society for Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>Professor Sir Mark Caulfield</td>
<td>Previously chief scientist of Genomics England (2013–21), a wholly owned DHSC company</td>
</tr>
<tr>
<td>Ravi Sharma</td>
<td>Director of England, Royal Pharmaceutical Society</td>
</tr>
<tr>
<td>Dr Imran Rafi</td>
<td>I am currently an unpaid GP adviser to Congenica, a DNA analytical company interested in pharmacogenomics. Member of the Academy of Medical Royal Colleges Genomic Medicine Partnership Group. Note that Dr Shuaib Nasser, also on the working party, is my brother-in-law.</td>
</tr>
<tr>
<td>Dr Jude Hayward</td>
<td>I am an unpaid adviser to Congenica, a DNA analytical company interested in PGx. Member of the Academy of Medical Royal Colleges Clinical Genomic Medicine Partnership Group</td>
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</table>
## Deep dive specialty presenters (individuals not included above)

<table>
<thead>
<tr>
<th>Name</th>
<th>Conflict of interest statement</th>
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<tr>
<td>Dr Mario Juruena</td>
<td>Advisory board/honoraria from Daiichi Sankyo, Lundbeck, Pfizer, GSK, Sanofi, Janssen (J&amp;J), Abbott, Bionomics, Libbs and Livanova. CNPq, FAPESP, UKRI, MRC and NIHR. I have received grants/clinical trial payments from the Academy of Medical Sciences/Royal Society, Wellcome. KCL (UK); European Commission (EU); UNESCO (France); NARSAD (USA); CNPq and Sao Paulo Research Foundation (Brazil). I have paid positions at King’s College London and NHS, UK</td>
</tr>
<tr>
<td>Dr Dan Hawcutt</td>
<td>Member of expert advisory groups at the Medicines and Healthcare Devices Regulatory Agency (MHRA) and chair the joint Royal College of Paediatrics and Child Health / Neonatal and Paediatric Pharmacists Group Joint Standing Committee on medicines. I am a section editor for Archives of Disease in Childhood.</td>
</tr>
<tr>
<td>Professor Jaideep Pandit</td>
<td>Fellow of the Royal College of Anaesthetists and member of the Association of Anaesthetists</td>
</tr>
<tr>
<td>Professor Sanjay Sisodiya</td>
<td>Honorary consultant neurologist and director of genomics at the Epilepsy Society, member of the Scientific Advisory Board of Dravet Syndrome UK and Alternating Hemiplegia of Childhood UK (UK charities)</td>
</tr>
<tr>
<td>Professor Ewan Pearson</td>
<td>I have received honoraria from Lilly, Sanofi and Illumina. I have received grant funding from Novo Nordisk</td>
</tr>
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</table>

All other contributors had no interests to declare.
References


21 Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology* 2014;83:2077–84.


This report considers the barriers as well as the opportunities provided by increasing pharmacogenomic testing. It includes a set of recommendations encompassing steps along the pathway to embedding pharmacogenomics in the NHS. It covers understanding the evidence for each test, working with patients and the public to understand their needs and communicate potential benefits of testing, training healthcare professionals to exploit advances in pharmacogenomics, working with leaders to commission testing, and ensuring that it is implemented effectively in practice.

The ultimate goal is to make pharmacogenomic-based prescribing a reality for all. This will empower healthcare professionals to deliver better, more personalised care, and in turn improve outcomes for patients and reduce costs to the NHS.


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