Pharmacogenomics

Although the Medicines Learning Portal aims to support NHS hospital pharmacists in their first 1,000 days of practice, this specially commissioned tutorial is to support all pharmacists and pharmacy technicians working in primary and/or secondary care who currently have limited experience working with pharmacogenomic information.

After completing this tutorial, you will be able to:

- Discuss how genomic data may be used in the prediction, prevention, diagnosis and treatment of disease.
- Describe how pharmacogenomic information is currently used in the NHS to support safe and effective personalised prescribing of medicines for patients.
- Discuss the practical and ethical considerations around applying, handling and storing the pharmacogenomic information of individual patients.

Why this subject matters…

Listen to Dr Hayley Wickens, Consultant Pharmacist Genomic Medicine from the Central and South Genomic Medicine Service Alliance (GMSA) explain the importance of pharmacogenomics in ensuring that patients benefit from their medicines and their risk of adverse effects is reduced.

Remind me of the science

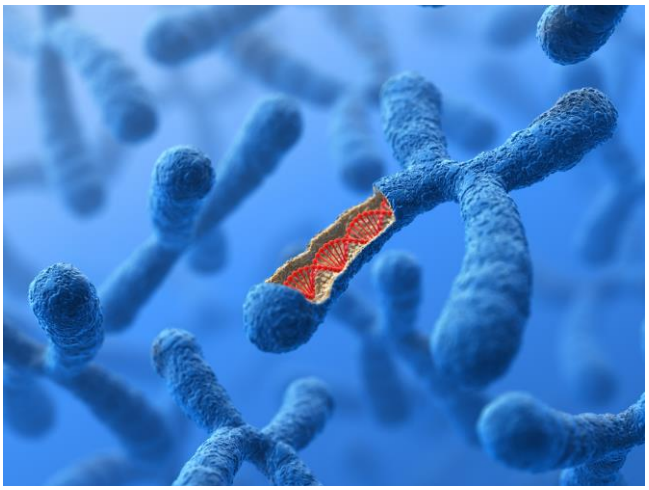
If some time has passed since you have had to think about genes, chromosomes, proteins and all things in between, then you may find it helpful to refresh your memory about some of the basics. Fortunately the NHS England Genomics Education website has a range of excellent resources including short videos and a genomics glossary to help you get back up to speed quickly. We have signposted to some of the most relevant content below.

You can skip to page 3 if you feel confident with this fundamental knowledge.

What is genomics?
Includes a video on the structure of DNA, definition of a gene and a variant, how genomics differs to genetics, and how the order of the 3 billion letters in a human genome is read, compared to a reference genome and then applied to individual patients.

What is a genome?
Short, animated video describing the role of genes, where a genome is found in the body and how the small variation between the genomes of all humans is of interest in the prediction, prevention, diagnosis and treatment of disease.

Where does our genome come from?
Revision of how paternal and maternal DNA combine to form an offspring's genome, and the significance of (potential) parents carrying a genomic variant.



How are proteins synthesised?
Refresh your knowledge about how amino acids and proteins are made using DNA and mRNA and transcription and translation.

Do genes govern our fate?
A useful page that covers the concepts of penetrance and expressivity.

In addition to the NHS England Genomics Education website, the BBC bitesize website also has some useful content including:

The genome
Several pages of text covering the genome, variation, DNA structure, protein synthesis, and mutations.

Genetic inheritance
Includes a short video explaining genetic inheritance, dominant and recessive alleles, and homozygous and heterozygous alleles.

You may also find it helpful to use the glossary on the NHS England Genomics Education website to revise any terminology as you work through this tutorial.

Genomics and the NHS

Personalised and precision medicine

There is currently a shift within medicine towards more personalised treatments, tailoring care specifically to an individual patient. This has been particularly seen in the treatment of various cancers, but is rapidly expanding into other areas. Genomics can play a key role in personalised and precision medicine and has a wide range of potential applications within healthcare including in;

- **Precision diagnosis** - rare diseases (e.g. Gaucher disease, achondroplasia).
- **Risk screening** or **cascade testing** within families for identified genetic conditions (e.g. familial hypercholesterolaemia).
- **Personalised treatment** - targeted cancer therapies, tailoring dosage or drug choice through pharmacogenomics, avoiding adverse drug reactions.
- **Infectious diseases** – pathogen identification and outbreak tracing (e.g. tracking variations of COVID-19 strains using RNA sequencing, antimicrobial resistance prediction using whole genome sequencing in *Mycobacterium tuberculosis* (TB) infection).
- **Research** – drug design and big data science.

NHS strategy

The NHS has a strategic focus on embedding genomics in practice. In England, this is outlined in the 2022 document Accelerating genomic medicine in the NHS. Its priorities are:

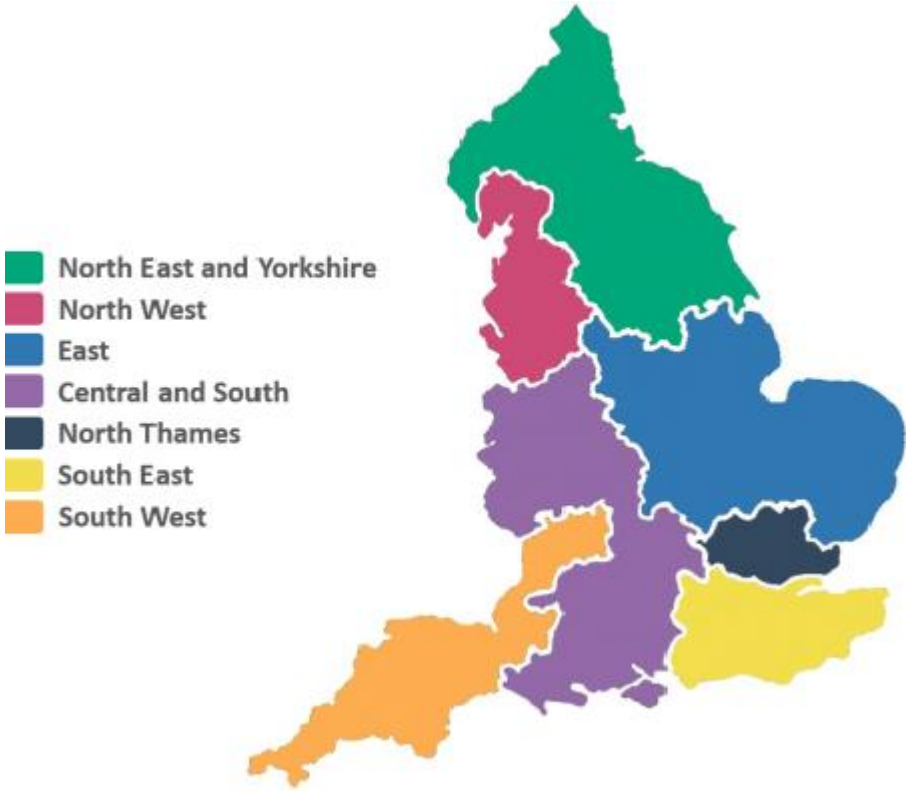
- Embedding genomics in NHS from primary/community care through to specialist and tertiary care.
- Delivering equitable genomic testing in cancer, rare, inherited and common diseases, enabling precision medicine and reducing adverse drug reactions.
- Enabling genomics to be at the forefront of the data and digital revolution, ensuring genomic data can be interpreted and informed by other diagnostic and clinical data.
- Evolving the service through cutting-edge science, research and innovation to ensure that patients can benefit from rapid implementation of advances.

Pharmacy professionals across all sectors have the potential to significantly contribute to the implementation of personalised medicine and genomics. This could be through helping to implement genomics within the NHS, using evidence-based genomic testing to optimise the prescribing of medicines or reduce toxicity such as in our online case studies, or supporting patients in their understanding of the options available to them and aid in shared decision-making. This potential has been recognised by pharmacy leaders as a key area for development and is already incorporated into foundation and advanced frameworks. In April 2023 the Royal Pharmaceutical Society in collaboration with other

pharmacy organisations published a position statement on pharmacy and genomics. This describes current and future roles for pharmacy teams in genomic medicine.

Each of the devolved nations in the UK has developed its own approach to genomics. NHS England have created seven regional Genomic Medicine Service Alliances (GMSAs) across England to co-ordinate the integration of genomics into routine healthcare, ensure equity of access and provide faster diagnosis and more effective, personalised treatments for patients. NHS-commissioned genomic tests are listed in the National Genomic Test Directory (NGTD) for England and Wales. This is described in more detail on the Commissioned tests page.

In England, GMSAs bring together research and clinical staff and the regional Genomic Laboratory Hubs as part of the NHS Genomic Medicine Service. Each GMSA has two dedicated pharmacist posts; a Chief Pharmacist for strategic input, and a clinical specialist Consultant Pharmacist for Genomics. If you would like more information on your regional NHS GMSA and their contact details you can e-mail england.genomics@nhs.net.



The 7 GMSAs in England
Image courtesy of NHS England

Genomics services in Wales are co-ordinated by Genomics Partnership Wales and the All Wales Medical Genomics Service. The Scottish Strategic Network for Genomic Medicine Laboratory co-ordinates services in Scotland. More information for Northern Ireland Regional Genetics Laboratories – Molecular Genetics can be found on their website.

Taking and sequencing a sample

Taking a sample

The first step in genomic testing for any individual is acquiring a biological sample, typically blood, saliva or tissue biopsy (the latter particularly for cancer). The sample has the genomic material extracted for testing either for single nucleotide polymorphisms (SNPs) or longer stretches of DNA (for exome or genome sequencing). RNA sequencing is also possible, along with other measurements of cell function (protein synthesis, metabolic activity), although these are less common clinically.

Sequencing a sample

An understanding of the different types of sequencing, when or why they might be used and what they can and can't be used to identify is helpful when presented with genomic data.

1. Targeted gene panel/SNP analysis

- Only looks at specific genes or SNPs that are known to be associated with a particular disease, phenotype or symptoms (e.g. monogenic diabetes).
- Looking for something you already suspect. Won't pick up novel causative genes.
- Can't reanalyse data if new genes are found. A new panel has to be created and retested.

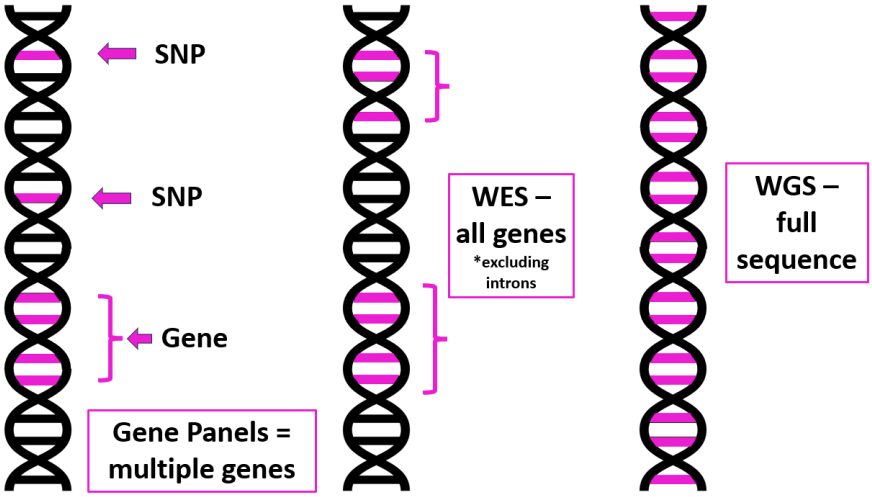
2. Whole exome sequencing (WES)

- Exome represents ~2% of human genome, but captures all protein coding regions.
- Majority of disease causing variants are thought to be found in the exome.
- Misses copy number variants or variants outside the exome.
- Can be reanalysed if new genes are identified without need for further sequencing.
- Can be used for 'virtual targeted panels' looking for specific gene variants.

3. Whole genome sequencing (WGS)

- The genome includes the whole DNA**:** exons, introns and all bits in between.
- Large amount of data requiring costly analysis / storage.
- Can be used for diagnosis, prediction, prevention or treatment of disease.
- WGS can also be used to sequence the genome of tumours and infectious agents to allow effective diagnosis and treatment.
- An example of WGS in practice is the Newborn Genome Programme.

You can read further information on sequencing on the Genomics Education Programme website.



Targeted gene panels, SNP analysis, WES and WGS compared.
Image courtesy of Dr Hayley Wickens, Consultant Pharmacist Genomic Medicine

Examples of genomic sequencing in practice

1. Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a common autosomal dominant genetic disease that increases the likelihood of coronary artery disease, heart attacks and sudden cardiac death at a young age. Early detection and genetic diagnosis can enable early intervention with effective treatments (e.g. statins) and decrease the risk of cardiovascular disease (CVD), leading to better outcomes and reduced morbidity for patients. It can also allow identification and treatment of affected family members.

A small targeted panel test is used to identify known gene variants. Patients usually have a functional mutation of one of 3 genes;

- Low-density lipoprotein receptor gene (LDLR or apoB/E receptor) - ~85-90%
- Proprotein convertase subtilisin kexin 9 gene (PCSK9) – 2-4%
- Apolipoprotein B gene (principally APOB3500) – 1-12%

All impair LDL receptor-mediated catabolism resulting in higher LDL-C levels.

Heterozygous FH (person has one copy of a pathogenic variant out of their two copies of the gene) is a common disorder, with an incidence of ~ 1 in 250 individuals in the UK. In England, it is estimated that >150,000 people are affected by FH. Around 7% of those with FH in England have been identified and the aim has been to improve this to 25% by 2024/5. Genetic testing for FH is part of the NHS Long Term Plan (2019).

FH is also currently part of a primary care initiative incentivised by PCN DES IIF 22/23 (CVD-04). This rewards the identification of patients aged 29 and under with a total cholesterol greater than 7.5 mmol/L OR aged 30 and over with a total cholesterol greater than 9.0 mmol/L who have been:

- diagnosed with secondary hyperlipidaemia; or
- clinically assessed for familial hypercholesterolaemia; or
- referred for assessment for familial hypercholesterolaemia; or
- genetically diagnosed with familial hypercholesterolaemia

Pharmacists and pharmacy technicians working in GP practice are ideally placed to facilitate patient identification and prioritisation, counsel and support patients and their families and prescribe and manage therapy.

2. Gene therapy

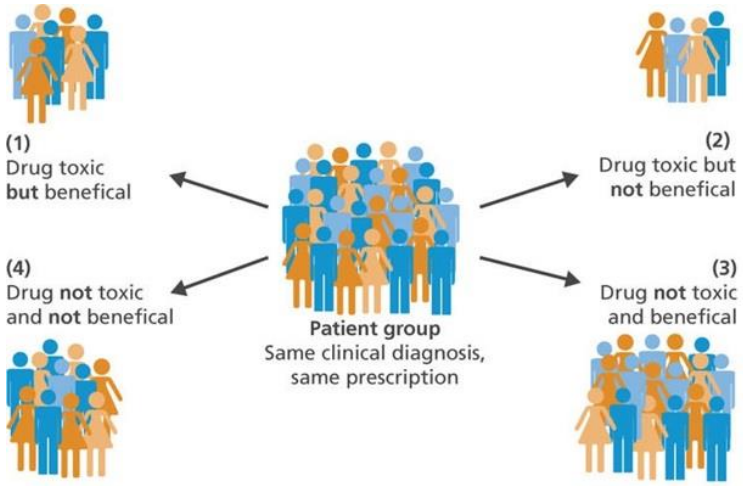
Another area using genomics and personalised medicine is gene therapy. The idea behind gene therapy is often to treat the underlying genetic cause of a disease rather than the symptoms. There is potential for gene therapy in areas such as inherited single gene disorders. One real world example is onasemnogene abeparvovec (Zolgensma) for treating spinal muscular atrophy in babies.

Another application is in cancer therapy. Here a patient's own white blood cells can be reprogrammed to target their cancer. One example of this, CAR-T (chimeric antigen receptor T-cell) therapy, is already available on the NHS for some cancers.

Making decisions about medicines

What is pharmacogenomics?

Pharmacogenomics is the branch of genomics concerned with the way in which an individual's genetic attributes affect their likely response to medicines. When we give a patient a medicine, we want it to have benefit without causing harm. In practice it can be difficult to predict how an individual will respond to any given drug as shown in the image below. Pharmacogenomics can be used to ensure patients receive medicines that are effective while reducing the risk of certain adverse effects.



Potential patient outcomes when given a medicine
Edited image courtesy of HEE Genomics Education Programme

Pharmacogenomics is important to pharmacy practice as it can help to remove the 'trial and error' aspect of treatment choice or effective dosing, ensuring better outcomes for patients. As experts in medicines, the pharmacy workforce are ideally placed to advise on how pharmacogenomic information can be used to adjust or manage a patient's treatment. An example is hepatitis C (HCV) which has seven distinct genotypes and multiple subtypes. Genotyping of the virus can help when selecting appropriate antiviral therapy.

How pharmacogenomics can influence the response to medicines

- **Pharmacokinetics** - where a genetic variant alters drug metabolism, affecting plasma concentration (e.g. cytochrome p450 isoenzyme polymorphism).
- **Pharmacodynamics** - where a genetic variation reduces binding of the drug to its receptor, thereby decreasing therapeutic efficacy. (e.g. warfarin and VKORC1).
- **Adverse reactions** – for example altered susceptibility to a hypersensitivity reaction to a certain drug (e.g. HLA-mediated reactions).
- **Effects on disease pathogenesis or severity and how they respond to specific therapies** (e.g. ovarian cancer and BRCA mutations, NTRK gene fusion in various cancers).

How pharmacogenomics can affect efficacy

1. Pharmacokinetics

Cytochrome p450 (CYP) isoenzymes

In practice one of the most common applications of pharmacogenomics that pharmacy professionals will come across as services develop will involve CYP450 isoenzymes. Many drugs are metabolised by CYP450 isoenzymes, and there are at least 57 CYPs encoded by the human genome, and these are organised into 18 families, with families 1,2 and 3 responsible for over 50% of the metabolism of common drugs (e.g. CYP2C19, CYP3A4). More information can be found here.

Some medicines are pro-drugs which rely on these enzymes for activation (e.g. clopidogrel), while others rely on these enzymes to break them down and inactivate them (e.g. voriconazole). Individual drugs are not metabolised exclusively by one isoenzyme, although one often predominates. Many drug – drug interactions are mediated by these enzymes (see the Interactions tutorial).

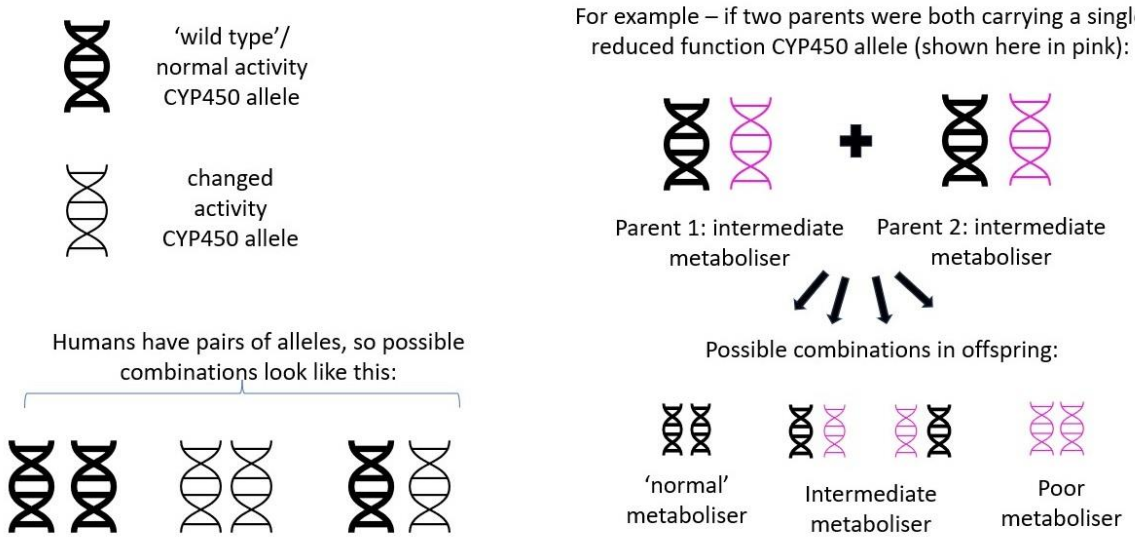
CYP450 isoenzymes are subject to genetic polymorphism which can result in changes in the enzyme activity. There can be many variations in a specific isoenzyme, some having no appreciable effect, whereas others can have a pronounced effect on how an individual patient metabolises a particular drug. The expression and activity of CYPs can vary considerably among individuals and ethnicities. This can lead to instances of loss of efficacy or decreased plasma levels, increased plasma levels or adverse effects, some of which may require dose changes or a need for alternative therapies depending on the impact.

Alleles and diplotypes

Most reporting of genetic polymorphism of CYP450 isoenzymes is done in terms of alleles and diplotypes and uses the star (*)-allele nomenclature.

Each allele is defined by a genotype at one or more specific single-nucleotide polymorphisms resulting in variable enzyme activity. Each different variant has a different *number and, whilst nomenclature can vary, these are usually divided into increased activity, active, decreased activity, or loss-of-function variants. ***1 is used to denote the 'wild type' variant, which would represent 'normal' function.**

The combination of the same alleles from each chromosome pair is used to determine a patient's diplotype (sometimes also referred to as genotype), which can be used to infer an individual's metaboliser status. **A diplotype of *1/*1 is usually inferred to be a 'normal' status.**



How metaboliser status is passed from parent to offspring
Image courtesy of Dr Hayley Wickens, Consultant Pharmacist Genomic Medicine

Different combinations of alleles can result in the same metaboliser status so in practice diplotypes are usually assigned one of the following functions to describe a patient's metaboliser status for that specific CYP450 isoenzyme:

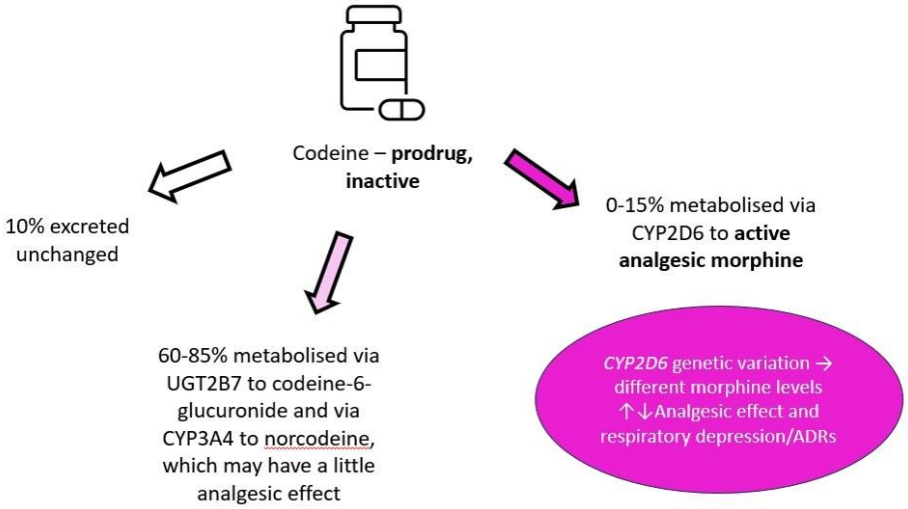
- **Poor metaboliser**
- **Intermediate metaboliser**
- **Normal metaboliser**
- **Extensive / rapid metaboliser**
- **Ultra-rapid metaboliser**

The reliability of the predicted genotype 'normal metaboliser' will depend on the number of variants tested for. The more variants analysed the stronger the prediction as rarer variants are more likely to be picked up.

A caveat is that around 80% of data in genome-wide association studies are based on individuals of European ancestry. Some CYP variants occur at different rates in different ethnic groups. This means that tests that only identify the most common variants in European populations may not be as accurate for non-European populations. Efforts are being made to increase the proportion of genomic research and clinical data coming from patients of non-European ancestry. More information on this can be found here.

CYP2D6 is an example isoenzyme with hundreds of known genetic variants. **Codeine is a pro-drug**, which relies on metabolism by CYP2D6 to its active metabolite morphine for its analgesic effect.

Poor metabolisers of CYP2D6 -> convert less codeine to its active metabolite - > reduced analgesic effect -> poor pain control.



Metabolism of codeine
Image courtesy of Dr Hayley Wickens, Consultant Pharmacist Genomic Medicine

2. Pharmacodynamics

Genetic variation can lead to differences in therapeutic response even when the level of drug itself is unchanged. These pharmacodynamic effects are often more complex than pharmacokinetic effects. This is in part because of the complexity of drug target pathways compared to pharmacokinetic ones. In practice this means that for now there are fewer practical clinical applications based on genetic variations in drug pharmacodynamics.

An example is the VKORC1 gene which encodes the vitamin K epoxide reductase protein. This enzyme catalyses the conversion of vitamin K-epoxide to vitamin K. **Warfarin acts as an inhibitor of VKORC1** reducing the amount of available vitamin K for clotting proteins.

Variants in this gene can alter a patient's sensitivity to warfarin, with common variants in VKORC1 accounting for up to 30% of stable warfarin dose variance in people of European ancestry. Different variants have been found in populations of different ancestry. Genomic effects on warfarin are multifactorial, but in combination with specific CYP2C9 diplotypes, VKORC1 status has been used to guide optimal initial warfarin dosing. However due to population differences these data cannot be assumed to apply across the board. Testing isn't routinely offered in the UK.

3. Cancer care targeted therapy and personalised medicine

Personalised medicine or targeted treatment is becoming more common in cancer care. Genetic variation of cancer cells can be used to select a more targeted therapy. Some variants can make a person more, or less, likely to respond to a specific treatment.

For example, variants in the epidermal growth factor receptor (EGFR) gene can change how a tumour will respond to EGFR-inhibitor drugs. In lung cancer, treatment may differ depending on if there are changes in the EGFR gene or the anaplastic lymphoma kinase (ALK) gene. Melanoma treatment can differ depending on whether there are changes in the BRAF gene.

A final example is in chronic myeloid leukaemia (CML) which is usually characterised by an abnormal BCR-ABL fusion gene on chromosome 22 (Philadelphia chromosome). An abnormal BCR-ABL results in an 'always on' tyrosine kinase enzyme with associated effects on cell proliferation.

In CML tyrosine kinase inhibitors (TKI) specifically target the ATP-binding site of BRC-ABL, reducing progression of chronic disease to the acute phase and improving survival. Imatinib was the first TKI of this kind, but this was followed by second generation drugs such as nilotinib and bosutinib. However resistance to some TKIs can develop through the T315I gene mutation. Knowing if this mutation is present or not, can help guide treatment choice.

How pharmacogenomics can affect the risk of adverse drug reactions

Adverse drug reactions (ADRs) account for around 1 in 16 hospital admissions. There are a number of different ways that genomics can influence an individuals' susceptibility to ADRs. Understanding the underlying genetic causes of adverse effects and an individual's predisposition can help guide medicine choices in personalised medicine.

As part of this the MHRA and Genomics England are collaborating on the Yellow Card Biobank project. Currently this is focusing on bleeding with direct oral anticoagulants and severe skin reactions with allopurinol.

Being aware of how a patient's genomics may affect their risk of ADRs is useful for all pharmacists and pharmacy technicians. Some examples of pharmacogenomic influenced adverse effects are given below.

1. CYP-related effects

CYP enzyme variants can influence safety of medicines as well as efficacy. Using an example from above, as codeine is a pro-drug, which relies on metabolism by CYP2D6 to its active metabolite morphine, increased metabolism can lead to increased levels of morphine. Ultra-rapid metabolisers of CYP2D6 convert more codeine to its active metabolite and there is an increased risk of toxicity from increased morphine levels.

Some medicines specifically require genetic testing for CYP enzymes before treatment is started with the results influencing the dose or whether the drug is contraindicated.

An example is **siponimod** which is a specialist drug used in the management of **secondary progressive multiple sclerosis**. It is extensively metabolised by **CYP2C9** (79.3%) and to a lesser extent **CYP3A4** (18.5%). Patients who have specific poor metaboliser statuses for CYP2C9 have much higher plasma levels (up to 284%) of siponimod resulting in increased risk of adverse effects. Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status.

Based on these results siponimod may be;

- contraindicated (CYP2C9*3*3 genotype)
- a lower dose may be recommended (CYP2C9*2*3 or *1*3 genotype)
- or the standard dose may be appropriate (all other CYP2C9 genotypes)

2. Human leukocyte antigen

The human leukocyte antigen (HLA) system is a complex of genes involved in the regulation of the immune system. HLA genes are highly polymorphic, vary widely across populations and several variants have been associated with immune adverse reactions to various drugs.

They are particularly implicated in dermatological reactions such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Drugs associated with HLA-mediated adverse effects include carbamazepine and allopurinol.

Another example is **abacavir** which is a nucleoside reverse transcriptase inhibitor (NRTI) used in the treatment of **HIV**. It is associated with a serious immune-mediated hypersensitivity reaction that occurs in 5-8% of patients and requires the immediate cessation of therapy.

It has been shown that this **hypersensitivity reaction** is more common and more severe in patients with the **HLA-B*57:01 allele**. Testing for this HLA allele is mandated for all patients who may benefit from starting abacavir. Patients with a positive HLA-B*57:01 allele can then be offered alternative therapy without risking a severe adverse effect or having effective treatment delayed.

3. Mitochondrial mutations

Changes in mitochondrial DNA are another way that genomics can alter a patient's susceptibility to adverse effects. One example, as outlined in a 2021 MHRA Drug Safety Update, is where rare mitochondrial mutations have been associated with an increased risk of deafness when patients are given aminoglycoside antibiotics. The most common of these is the MT-RNR1 m.1555A>G variant which has an estimated prevalence of 1 in 500 in the UK population.

4. Other examples of pharmacogenomic-mediated adverse effects

SCLO1B1 gene variants can alter the risk of developing myopathy with statins.

Information technology, data transfer and clinical responsibility

As pharmacogenomic testing services develop, new questions will arise for healthcare systems. Future things to consider as genomic knowledge and these services develop;

- Where would this information be held?
- What about information transfer?
- Who would be able to see any results/genomic information?
- Would this information have any relevance to existing treatment?
- Will pharmacogenomic information be incorporated into prescribing systems?
- What happens as testing improves?
- Would existing results need to be retested or reclassified?
- Who would be responsible for reviewing this data?

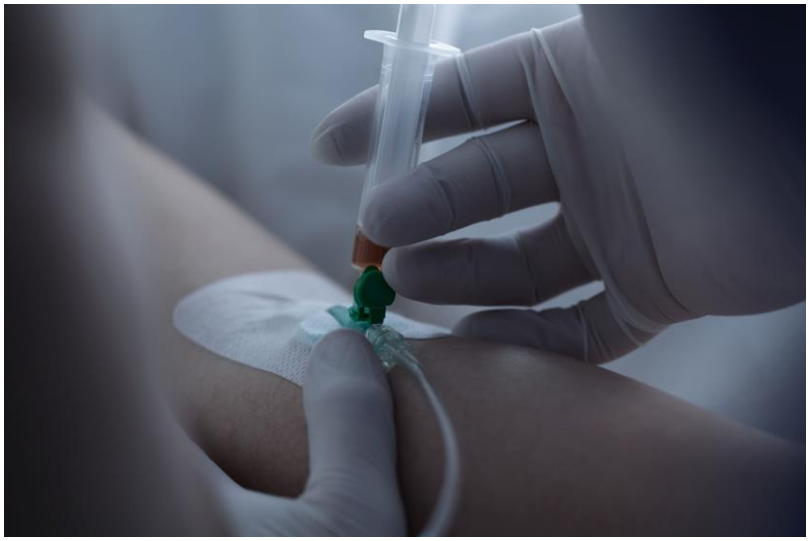
Commissioned tests

Only a few pharmacogenomic tests are currently commissioned by the NHS. However as more genomic information becomes available, personalised medicine becomes more embedded in healthcare and more drugs requiring genomic testing are licensed this is likely to change.

In England, information on what tests are commissioned can be found in the National Genomic Test Directory (NGTD). There is no directory specifically for pharmacogenomic tests: you will need to check either the directory for rare and inherited diseases, or the one for cancer. Currently the NGTD includes the following;

1. Dihydropyrimidine dehydrogenase gene (DPYD)

Some patients carry specific variants in the DPYD gene which can result in deficiency of dihydropyrimidine dehydrogenase (DPD), which is an enzyme responsible for metabolising systemic fluoropyrimidine cancer chemotherapy (e.g. capecitabine, 5-fluorouracil). Use of these drugs in these patients could result in severe or life-threatening adverse effects (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity). Therefore patients who require systemic fluoropyrimidines must undergo pharmacogenomic testing before starting treatment. If they are found to have a variant that results in reduced activity of the enzyme, then patients may be offered alternative therapy or a lower dose of the drug.



2. Thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) in patients with ALL

6-mercaptopurine is prescribed for patients with acute lymphoblastic leukaemia (ALL). It is extensively metabolised by the enzymes TPMT and NUDT15. Variants in the TPMT and/or NUDT15 genes can result in reduced enzyme activity and increased risk of toxicity (e.g. bone marrow suppression). Therefore genetic testing for TPMT and NUDT15 is commissioned for patients with ALL who require treatment with 6-mercaptopurine.

Note that genetic testing is **not** commissioned for other indications requiring 6-mercaptopurine or azathioprine (e.g. autoimmune disorders) which rely on biochemical testing of the activity of the enzymes.

3. Aminoglycoside exposure posing a risk to hearing (R65)

As described on above systemic aminoglycoside use (e.g. gentamicin, amikacin and streptomycin) can result in rare cases of ototoxicity and there is some evidence to suggest an association with specific mitochondrial mutations. Currently the commissioned test looks specifically for the presence of the MT-RNR1 m.1555A>G variant (estimated prevalence 1 in 500). Further variants are being added to the NGTD in April 2024.

Tests in the NGTD have a clinical indication identifier code: this test is R65 and you may hear or see it referred to in this way. Patients who have this variant have an increased risk of hearing loss. The test has a 4-6 week turnaround time and so is not suitable for use in acute situations and treatment should not be delayed.

If an individual with a variant of the MT-RNR1 gene has previously received aminoglycosides and not developed hearing loss, this does not exclude them from developing it with subsequent doses. A normal test result does not eliminate the risk of aminoglycoside-induced hearing loss as there are other mechanisms that can cause this.

It may be considered for patients with a predisposition to gram negative infections, for example, due to known respiratory disease (e.g. cystic fibrosis, bronchiectasis) or due to structural or voiding genitourinary disorders. It may also be relevant for patients with hearing loss who have been exposed to aminoglycosides.

Testing for the human leukocyte antigen variant HLA-B*57:01 in patients needing abacavir predated the creation of the NGTD. However it routinely happens in the NHS and is usually available through tissue typing laboratories. Other HLA testing (e.g. for allopurinol, carbamazepine/oxcarbazepine) may be available locally if required.

Some medicines such as siponimod for multiple sclerosis, and mavacamten for symptomatic obstructive hypertrophic cardiomyopathy require genetic testing to guide dosage for their use, but testing is currently provided by the drug manufacturer and is not commissioned by the NHS.

For the devolved nations, the All Wales Medical Genomics Service offers tests listed in the NGTD. The Scottish Strategic Network for Genomic Medicine Laboratory offers genomic tests in accordance with Scottish Genomic Test Directory for Cancer and the Scottish Genomic Test Directory for Rare and Inherited Disease. More information for Northern Ireland Regional Genetics Laboratories – Molecular Genetics can be found on their website.

Direct-to-consumer (DTC) testing

DTC tests can be arranged by patients themselves via non-NHS routes without going through a clinician, usually through a private company, and are becoming more widely available. While many tests are concerned with ancestry or heritage, companies may also offer testing for genetic predisposition to certain diseases, carrier testing for inherited conditions (e.g. cystic fibrosis) or for variants within known disease-causing genes.

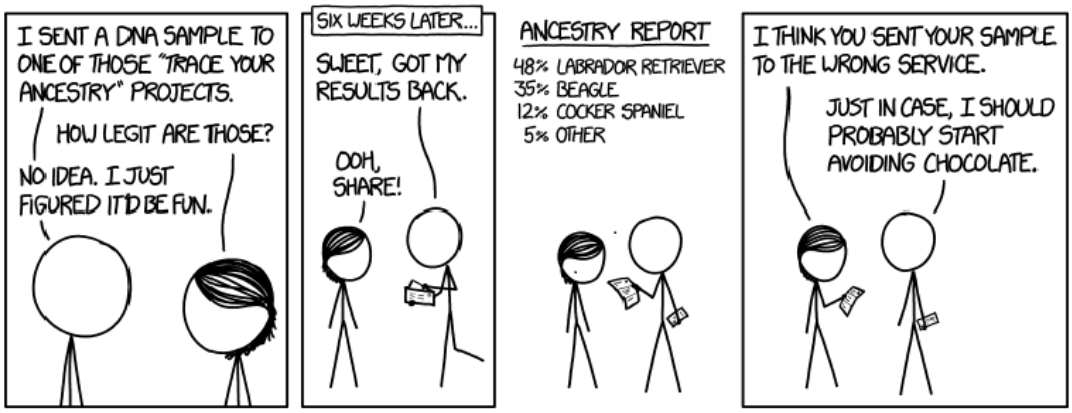


Image courtesy of xkcd.com

DTC pharmacogenomic tests relating to variants that might affect drug metabolism are also becoming more commonly available. These may offer a breakdown of a patient's metaboliser status for various CYP enzymes and other enzymes involved in drug metabolism. However the validity, sensitivity, and utility of private DTC tests, including pharmacogenomic tests, are not subject to the same regulation or standards as NHS laboratories so may significantly vary, resulting in risks of false positive or false negative results. It is also unlikely that any counselling or interpretation for the results will be offered.

The Royal College of General Practitioners (RCGP) and the British Society for Genetic Medicine (BSGM) have produced a genomic position statement about DTC genomic or genetic testing.

Information sources

There are a range of information resources to support you in the field of pharmacogenomics.

Some **Summaries of Product Characteristics** may contain helpful information about prescribing medicines according to a patient's genomic profile (e.g. allopurinol, clopidogrel, citalopram, simvastatin). These may be accessed via the emc or MHRA websites.

The **MHRA** have published multiple alerts relating to pharmacogenomics and drug safety. These include:

Carbamazepine, oxcarbazepine and eslicarbazepine: potential risk of serious skin reactions [2012]
Tamoxifen for breast cancer [2010]
Statins: benefits and risks [2014]
Phenytoin: risk of Stevens-Johnson syndrome associated with HLA-B*1502 allele in patients of Thai or Han Chinese ethnic origin [2010]
Codeine: restricted use as analgesic in children and adolescents after European safety review [2013]
Codeine-containing pain relief in children [2012]
5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity [2020]
Aminoglycosides (gentamicin, amikacin, tobramycin, and neomycin): increased risk of deafness in patients with mitochondrial mutations [2021]

The National Genomics Education Programme's GeNotes site has an A-Z Knowledge Hub which you can use to refresh your memory or learn about different genomic concepts. The site also has a series of clinical scenarios including some on pharmacogenomics.

The PharmGKB site is a specialist pharmacogenomic resource funded by the National Institute of Health in the United States (US). New users can take a tour of the site here and get advice on searching here.

If you have time you can listen to Rachel Huddart, Scientific Curator at PharmGKB, provide a more detailed walkthrough of how to use the site (17 minutes). The site includes prescribing information, clinical guidelines and diagrams. Particularly helpful if you are new to pharmacogenomics are the overviews of very important pharmacogenes (VIPs).

A related site is the Clinical Pharmacogenetics Implementation Consortium. Also funded by the US government, this resource aims to support healthcare professionals make decisions about medicines based upon the results of pharmacogenetic testing. The menu bar signposts you towards guidelines, an alphabetical list of medicines together with genes that may impact upon their efficacy or safety, and lots of other helpful information. Again, you can listen to Dr Mary Relling explain more about the site (17 minutes).

Several of NICE's Clinical Knowledge Summaries may also be helpful to pharmacists and pharmacy technicians working with pharmacogenomic data including that on Familial hypercholesterolaemia, carbamazepine for trigeminal neuralgia and allopurinol for gout.

Genomics England have an independent **Participant Panel** who have produced a useful guide on language and terminology when communicating with patients and their families. It is intended for Genomics England staff but may be helpful for healthcare professionals conducting consultations.

Next steps in learning…

In addition to the entry level content signposted to on the Remind me of the science page of this topic, NHS England Genomics Education has a range of more advanced material including online courses, videos and podcasts. You can click on the 'resource type' or the 'curated collection' and select 'pharmacy' as a profession to view content. A recommended listen on this site is Prof. Anneke Lucassen's podcast on the considerations around ethics and data in relation to genomic healthcare; the target audience is the nursing profession but it is also relevant to pharmacists and pharmacy technicians.

The Genomics England site also has lots of really helpful information about the topic more broadly including a range of podcasts and blogs. Their diverse data initiative aims to improve access to personalised medicine for all patients regardless of their background.

CPPE have launched an e-learning programme on consulting with patients on the topic of genomics. Allow 2.5 hours to complete the programme.

The PharmGKB site has a range of training exercises, videos and tutorial papers and signposts to some external resources.

Read the Personalised prescribing report (2022) from the Royal College of Physicians and British Pharmacological Society which is gives recommendations on how the NHS should optimise medicines use for all patients using pharmacogenomics.

The elearning for healthcare website has a module on Advanced Therapy Medicinal Products. If you have had limited experience of working with genomic information, you may find the introductory modules including the one on CAR-T interesting.

Explore the PharmVar website which is a repository for pharmacogenomic gene nomenclature used by other sites.

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