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Workshop D: Genomics in Healthcare

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Developing people for health and healthcare

www.hee.nhs.uk

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Expectations for this session

Overview: synopsis of genomics in the NHS

Interactive: opportunities for discussion/ questions

Signposting: providing links to guidance and learning opportunities

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Why is genomics important?

> *All doctors will need to be able to understand when to use genomic testing and how to interpret the results they get back from the lab in practice.*

Photo credit: MRC Mitochondrial Biology Unit

Professor Patrick Chinnery

The Telegraph, 30 December 2017

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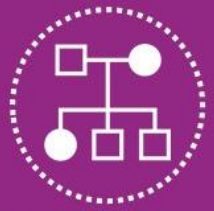
Genomics – what is it, where is it used?

Genomics

- The study of an organism's complete set of genetic information
- The genome includes both genes (coding) and non-coding DNA
- 'Genome' is the complete genetic information of an organism

vs



Genetics

- The study of heredity
- The study of the function and composition of single genes
- 'Gene': specific sequence of DNA that codes for a functional molecule

Rare and inherited disease

Cancer

Pharmacogenomics

Direct to consumer testing

Infectious disease

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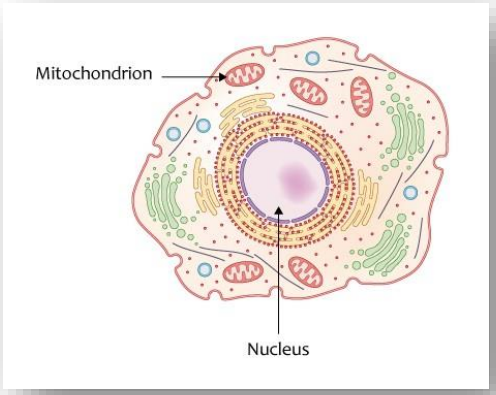
The science



- 46 nuclear chromosomes (pairs) plus mitochondrial DNA
- Nuclear chromosomes: autosomes and sex chromosomes
- Pairs of chromosomes = pairs of genes

Germline DNA: DNA derived from germ cells

- ‘Constitutional DNA’
- Any change in germline DNA is present in every cell in body (including germ cells) → pass on to the next generation

Somatic DNA: All cells except for germ cells

- Changes to DNA in somatic cells – will only affect that cell and subsequent daughter cells following mitosis
- The effect depends on when the change occurred during development:
  - Early in development: more cells show the change = mosaic form of a genetic condition (e.g., Down syndrome)
  - Later in life: somatic changes can lead to cancer development

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Genomic variation

We all have variation

- 3-5 million variants
- Change in the DNA sequence
  - Small (one base) to large (entire chromosome – dosage)
- Not all associated with health and/or clinical management
  - Benign
  - Natural variation
  - Drug effects (pharmacogenomics)
  - Disease susceptibility
  - Cause of a genetic condition

Terms

Variant or mutation

- Use the term variant ('mutation' still used in some areas)

Pathogenic/non-pathogenic/ VUS: -

- Pathogenic – cause of genetic condition

- Non-pathogenic – not associated with the condition

- **V**ariation of **U**ncertain **S**ignificance – association with disease/condition is unclear

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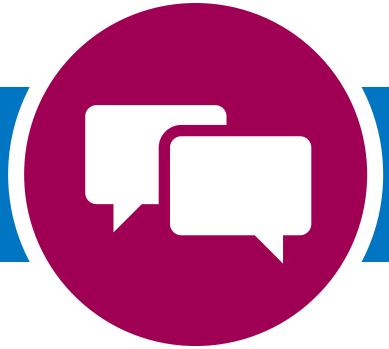
Discussion: Your experiences with genomics?



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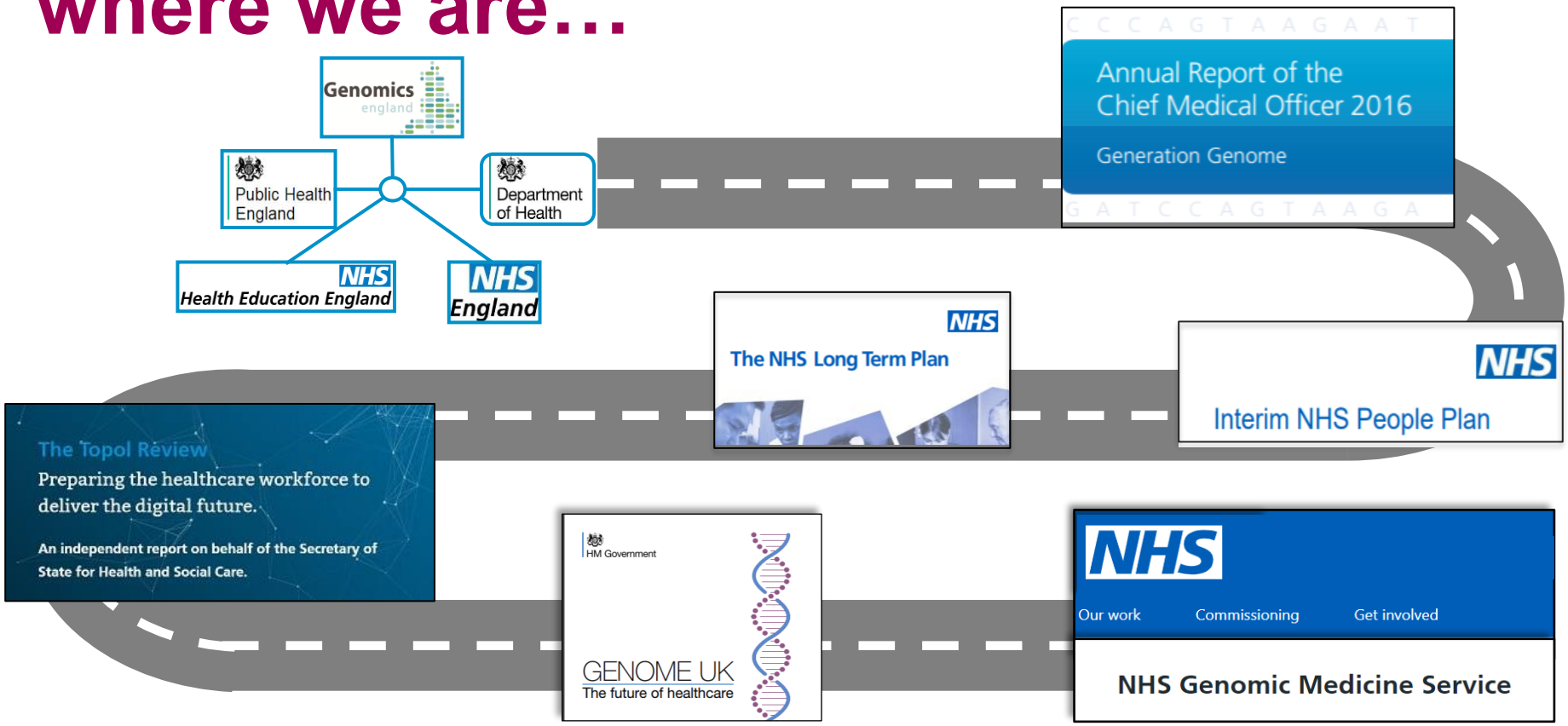
Genomics in the NHS: How we got to where we are…



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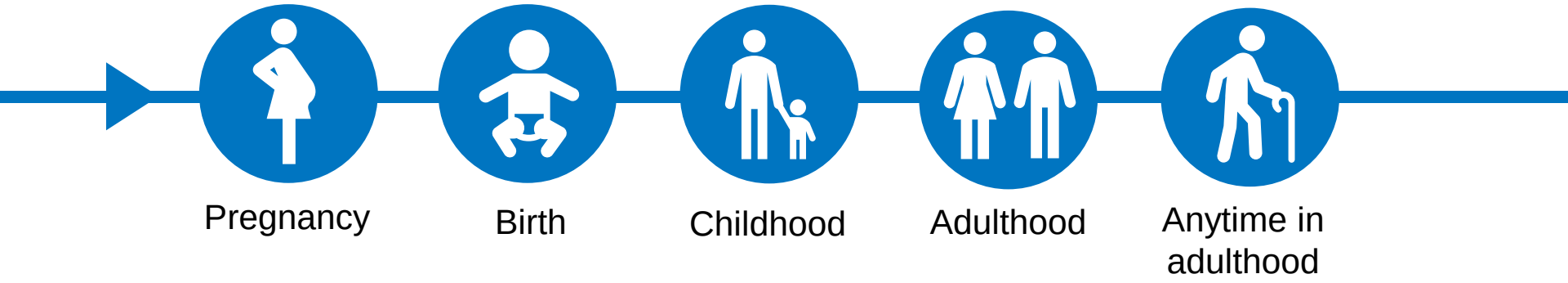
‘Rare and inherited disease’ – genetic conditions

- Any genetic condition due to **a change in germline DNA**
- Single gene conditions or Mendelian conditions
  - Inheritance patterns: autosomal dominant, autosomal recessive, X-linked recessive.
- Genetic conditions **seen in almost all specialties**, and **across the lifespan of an individual**
  - Individual conditions may have different manifestations at different points in life
  - Some conditions are adult onset only



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How can you identifying someone who may benefit from a genomic test

From the patient's presentation: recognition of clinical signs and symptoms.

From the family history: recognising a pattern of affected people (collecting family history information).

Because they tell you: there is a known genetic diagnosis in the family.

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Taking and drawing a family history

Genetic family history

Overview of the family medical history

Identifies biological relationships

Discussion: How many here have ‘drawn’ a pedigree/family tree?

https://www.genomicseducation.hee.nhs.uk/taking-and-drawing-a-family-history/

- Even if don’t draw a pedigree, important to know how to ‘read’ one

- **Know how you would act on the information**
  - Know what would trigger a referral/genomic testing in your area
    - Referral guidelines (department/regional/NICE guidance)
    - National Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/)
  - If in doubt, call regional genomic services (geneticalliance.org.uk/information/service-and-testing/nhs-genetic-services-in-the-uk-2/)

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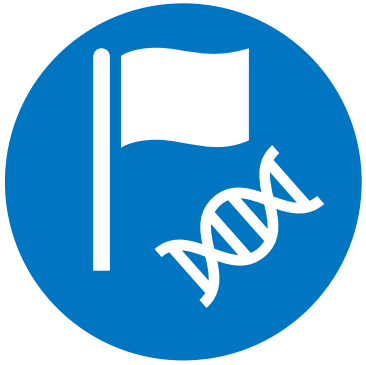
Features which are suggestive of a genetic condition in the family

- Multiple closely related people affected with the same condition.
- Disorders with earlier age of onset than typical:
  - Cancer;
  - Heart disease.
- Bilateral disease in paired organs.
- Sudden cardiac deaths in people who seemed healthy.
- Three or more pregnancy losses.
- Stillbirths or babies who have died in neonatal period.
- Multiple congenital anomalies, dysmorphic features, developmental and growth delay.
- Two or more medical conditions occurring together.
- Medical problems in offspring of parents who are related by blood.



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What can genomic testing can offer: Shortening the diagnostic odyssey

The process of diagnosis, the so called "diagnostic odyssey", can be a difficult and frustrating experience that comes with **uncertainty**, **multiple referrals**, diagnostic **wrong turns**, and unnecessary and sometimes **invasive tests**.

For those with rare diseases, the journey to a final diagnosis is often long, and difficult.

On average…

Four years for final diagnosis

Three misdiagnoses

Five different doctors

Receiving a diagnosis can:

- **Offer certainty and empower** families to feel in control of the situation.
- Allow the family to **form realistic expectations** about the disease.
- **Give valuable information** for others in the family who may be at risk, and for future pregnancies.
- **Increase understanding** of the disease and **allow access** to tailored treatments.

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What else can genomic testing offer?

- **Tailored treatment** (in some cases), e.g. cystic fibrosis
  - 2,000 different variants in *CFTR* gene
  - Ivacaftor and Tezacaftor/ivacaftor made available for CF treatment
    - Only effective for certain variants

- **Prevention (pre-symptomatic testing):** e.g. familial hypercholesterolaemia
  - Relatively common condition (1 in 250)
  - Identify early, prevent symptoms through medical management

- **Information:** e.g. reproductive choices
  - Options available for prenatal testing or pre-implantation genetic testing for various conditions*
  - Need to know the familial variants, clinical genomic services can coordinate testing process.

*hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/approved-pgd-and-ptt-conditions/

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Different types of testing

- Diagnostic
- Pre-symptomatic or predictive
- Carrier
- Prenatal
- Pre-implantation

Genetic testing of children:

Beneficial if:

- confirming a suspected diagnosis.
- removing need for invasive procedures.
- condition occurs in childhood and there is treatment that can be offered.

Problematic if:

- carrier testing a healthy child.
- predictive or pre-symptomatic testing for adult-onset condition.

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Complexity of genomic tests

Targeted tests

Looking for specific variants (e.g., familial variant, or small number of known variants associated with a condition)

Results:

Yes, a variant was found (positive result)

No, the variant wasn't found (negative result)

Genomic tests

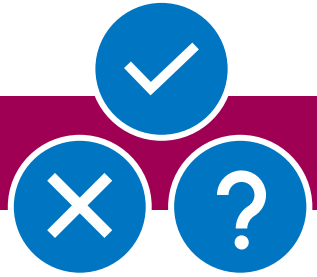
- Panel tests (looking at multiple genes at the same time)
- Whole exome sequencing (looking at all protein coding regions)
- Whole genome sequencing (looking at entire genome)

Possible results:

- Pathogenic variant identified
- No pathogenic variant identified (normal or negative result)

Doesn't mean that there is no variant present, just can't find it yet

- Variant of uncertain/unknown significance: association with disease/condition is unclear



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It's not just about the science…..

What does this mean for me?

If a variant is found – what does this mean for prognosis

If a variant is not found – challenging result for the patient/family

What does this mean for my family

Communicating information to family members

Can I pass this on to my children?

Reproductive choices

Utilise the specialist services:

https://www.genomicseducation.hee.nhs.uk/careers/

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Resources and guidance

National test directories

The NHS Test Directories outline the genomic tests available, eligibility criteria and who can order the tests within the NHS.
england.nhs.uk/publication/national-genomic-test-directories/

Consent and confidentiality

Report of the Joint Committee on Genomics in Medicine, providing guidance on the use of genetic and genomic information in the clinic.
rcplondon.ac.uk/projects/outputs/consent-and-confidentiality-genomic-medicine

Competency frameworks

Framework that outlines the core competencies required to facilitate and consent patients for germline genomic tests.
genomicseducation.hee.nhs.uk/consent-a-competency-framework/

Online learning resources

A series of clinical guides and online learning resources to support clinicians integrate genomic tests into their practice.
genomicseducation.hee.nhs.uk/supporting-the-nhs-genomic-medicine-service/

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Common conditions

Development of common disease is thought to be influenced by many genomic variants each with small individual effect sizes.

Note on terminology:

Polygenic: variants in multiple genes (compared with monogenic)
Multifactorial: ‘multiple factors’ such as genomic variants and environmental factors

Polygenic risk scores (PRS) are a tool that combines the genomic information to provide a probabilistic risks, like other biomarkers such as cholesterol and blood pressure.

Not used in clinical practice yet - Watch this space

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What questions do you have?

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Cancer

Cancer is a genomic condition

- **Germline variants** versus **somatic mutations** seen in the tumour

- Inherited cancer syndromes
  - predisposition due to a germline variant (e.g., *BRCA1/2*, Lynch syndrome, hereditary RB, etc.)
  - cancer development due to additional somatic mutations

- ‘Sporadic’ cancers – due solely to somatic changes

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Inherited cancer syndrome

Clinical clues that may suggest an inherited cancer syndrome	- Young age of diagnosis - Bilateral disease in paired organs (e.g. RB) - Clinical/histological features
What you are looking for in a family history	- Patterns of cancers in the family • *BRCA1/2*: Breast and/or ovarian • Lynch syndrome: bowel, endometrial, ovarian - Blood relatives, on the same side of the family - Criteria 'high risk family' – more likely to identify germline variant
Familial germline variant – other members of the family can be offered predictive testing	- **Positive predictive test result:** screening and/or prophylactic management - **Negative predictive test result:** population risk

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Testing cancer genome (somatic changes): when and why

Diagnosis	Treatment	Prognosis	Monitoring	Clinical Trials
Refine a diagnosis and may provide insights into how the cancer may progress and respond to treatment.	Molecular information may influence treatment choices, including identify cancers that may become resistant to treatment.	Molecular signature may indicate prognosis at time of diagnosis.	Undergoing treatment (to see of treatment is working) and those in remission (catch potential disease progression).	Some eligibility criteria is based on presence (or absence) of genomic variants in the tumour.

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Case examples

BRCA variants and PARP inhibitor ovarian cancer

Patients with platinum sensitive relapsed ovarian cancer and germline or somatic mutations in *BRCA1/2* may benefit from treatment with the PARP inhibitor Lynparza (Olaparib).

nice.org.uk/guidance/ta598

EGFR mutation and treatment for non-small cell lung cancer

Identification of an *EGFR* mutation increases confidence that the cancer will respond to a range of tyrosine kinase treatments including gefitinib and dacomitinib.

nice.org.uk/news/article/life-extending-lung-cancer-treatment-recommended-for-use-on-the-nhs

NTRK gene fusion and 'tumour agnostic' drug (larotrectinib)

Driving treatment due to tumour's genomic make-up rather than where it originated (when standard treatments have failed). *NTRK* gene fusions are commonly seen in some rare cancers, but occur in less than 1% of the common solid tumours, such as lung, colorectal and breast cancers.

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Key point

- Somatic changes – cannot be passed down in families
- BUT – may identify a germline variant – which will impact on families

Discussion: How you would describe the difference to a patient?

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What questions do you have?

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The next set of slides will cover….

- Pharmacogenomics
- Direct to consumer testing
- Infectious disease

Discussion: What experiences have you had in these areas?

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Pharmacogenomics (PGx)

- How genomic variants affect a person's response to drugs.
- Efficacy and/or adverse drug reactions
- Limited PGx testing in NHS
  - Variability of use between specialisms
  - Expand in the coming years

Note on terminology:

- **Pharmacogenetics**: variation in one gene influences response to a single drug
- **Pharmacogenomics**: broader view, considers how variants across the genome can influence drug response
- Not to be confused with 'personalised medicine' or targeted treatment

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Case example #1: Avoiding adverse reactions

Abacavir and gene variation *HLAB*5701*

- Abacavir used in combination therapy for HIV.
- 5% of people having the treatment
  - hypersensitivity reaction which can be fatal
  - Gene variant *HLAB*5701*

NICE guidelines state patients must be tested for this variant prior to commencing treatment

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Case example #2: Avoiding adverse reaction

Fluoropyrimidines and *DPYD* gene variants

- Fluoropyrimidines are antimetabolite chemotherapy drugs used in the treatment of various cancers.
- Enzyme DPD has a role in the metabolism of these drugs
- Reduced level of DPD, due to variants in the *DPYD* gene
  - Increased risk of severe or fatal toxicity

Clinical guidance: All patients, prior to commencing treatment with a fluoropyrimidine based therapy (5- fluorouracil, capecitabine or tegafur) should be screened for four *DPYD* gene variants which have been associated with fluoropyrimidine-associated toxicity.

www.england.nhs.uk/wp-content/uploads/2020/11/1869-dpyd-policy-statement.pdf

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Case example #3: Deciding dosage

Thiopurines and the TPMT enzyme

- Thiopurines – applications in chemotherapy and in immunosuppression for autoimmune disease
- Dosage matters – when in excess, severe side effects plus need to pause treatment
- Enzyme TPMT – involved in metabolism of thiopurines
  - 3 in 1000 people have no working copy of *TPMT* gene = no working enzyme
  - 10% people have a version of the TPMT gene – enzyme is less active
  - For these people – standard treatment → extremely ill

NICE guidelines: “consider **measuring TPMT activity** before starting azathioprine, mercaptopurine, or tioguanine therapy. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.”

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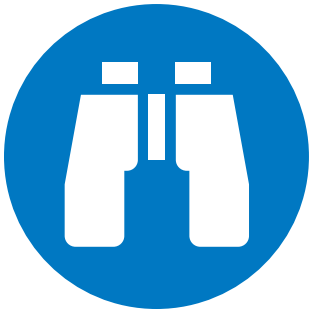
Forward view

- Currently, small number of gene/drug pairs that require testing prior to prescribing
- Area that will grow in the coming years, but work to consider
  - Which tests will be included (clinical utility)
  - Clinical workflows (who does the test and when)
    - Turn around time (consider point of care testing)
  - Where do the results get recorded
- Need to remember that PGx will not be the pharmacy ‘utopia’
  - PGx test results will provide important and clinically relevant information that needs to be consider alongside other factors that could affect efficacy (including compliance) and adverse drug reactions.



Watch this space

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Pharmacogenomics - resources

- GEP – experts blogs
- FutureLearn MOOC: Using Personalized Medicine and Pharmacogenetics
- GEP MSc module: Pharmacogenomics and Stratified Healthcare

Later this year: 'Pharmacogenomics in the NHS' report from the RCP – overview of current situation and recommendations

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Direct to consumer testing (DTC)

- Any ‘genetic’ test that can be purchased directly by the public.
- DTC vs clinical tests:
  - Clinical – order a test to answer a specific question
  - DTC – looks at areas of genome where variation known to occur.
    - Good at identifying common variants, unlikely to identify rare variants accurately
  - DTC: The risk of false reassurance
    - 3 common *BRCA* variants – miss 80% people who have a *BRCA* variant.

> *Genetic tests sold online and in shops should absolutely not be used to inform health decision without further scrutiny”*
>
> Professor Anneke Lucassen

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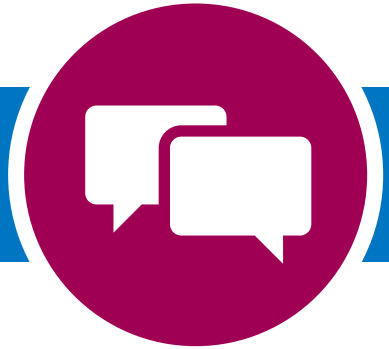
Discussion: Consider what you would do if a patient presented their results to you – what would be your first step?



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Practical tips for clinicians

Key points:

- Family history matters
- Don’t be reassured by negative (‘nothing found’) results
- Results found by re-processing raw data from DTC tests are often inaccurate

Guidance:

- RCGP/BSGM joint position statement*

> *Health professional should exercise caution when asked to offer, or provide, clinical expertise about the results of DTC genetic testing.*

*https://www.rcgp.org.uk/policy/rcgp-policy-areas/genomic-position-statement.aspx

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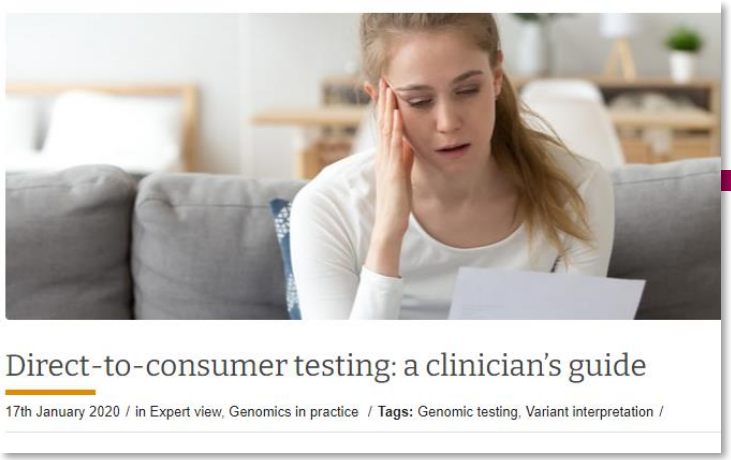
Direct-to-consumer testing: resources

GEP expert blog



BMJ Practice Pointer: https://www.bmj.com/content/367/bmj.l5688 includes a BMJ Talk Medicine Podcast

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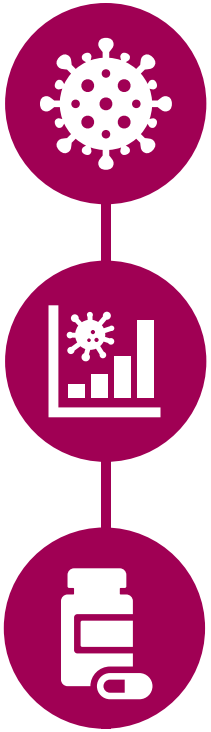
Infectious disease and the NHS

Number of examples including:



Identifying the pathogen

Panel looking for a whole range of respiratory viruses, for example, and identify the specific viruses (if they're there).

Tracking outbreaks

- Viruses (e.g., COVID) and bacteria (e.g., TB).
- Or concluding that it is a coincidence not an outbreak (e.g., Clostridium difficile).

Antibiotic resistance (e.g., TB treatment)

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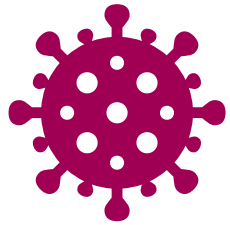
COVID-19 – identifying and tracking new variants



- Identified because genomic sequencing forms significant part of the pandemic response
- Tracking – e.g., surge testing for ‘South African variant’

https://www.genomicseducation.hee.nhs.uk/blog/genomics-and-the-new-covid-19-variant/

Note on terminology:

- Variant of the virus vs genomic mutations
- ‘UK variant’ of COVID-19 → 23 different mutations

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GenOMIC study

- Identifying **germline variants** – why some people have more severe illness due to COVID-19 infection
  - Matched study
  - Recruitment for those mild illness
- Outcomes not clear yet, but may include:
  - Prediction
  - Prevention
  - Treatment and management

https://covid.genomicc.org/

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What questions do you have?

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Continue your learning: Where to get started

General information: Genomics 101

- Nine courses, covering scientific information, clinical skills (e.g. family history) etc.
- 30-40 minutes per session
- Certificate of completion available
- E-Learning for Healthcare site – free to access

www.genomicseducation.hee.nhs.uk

Genomics in your practice

GEP: collections of resources tailored to your profession or specialty and access our range of guides and clinical tools https://www.genomicseducation.hee.nhs.uk/genomics-in-healthcare/

Review your specialities training curricula – highlights relevant areas of genomics

Current issues and controversies

- GEP blog: expert opinion (www.genomicseducation.hee.nhs.uk/blog/
- Range of podcasts

Horizon scanning

- Think tank reports
  - PHG Foundation

phgfoundation.org/

phg foundation
making science work for health

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Opportunities for further development

The Masters in Genomic Medicine framework:

- an educational programme designed to provide healthcare professionals with a multidisciplinary perspective on genomics and its applications in healthcare; and
- a flexible framework offering a range of qualifications.
  - Individuals can undertake CPPD modules, PGCert, PGDip, or a full Master's degree.
- Funding has been available from HEE's Genomics Education Programme to cover course fees → likely to continue 2021/22

Further information:
www.genomicseducation.hee.nhs.uk/about-us/masters-in-genomic-medicine/

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- Just-in-time resources, e.g., factsheets
- Links to all our courses

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