# Genomics in Pharmacy

## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Presenter</th>
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<tr>
<td>18.00</td>
<td>Welcome and introductions</td>
<td>Mandeep Butt (Clinical Medicines Optimisation Lead UCLPartners)</td>
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<td>18:05</td>
<td>Genomics Medicine Service Alliances &amp; The Role of Pharmacy</td>
<td>Prof Mike Roberts (Managing Director, UCLPartners Academic Science Partnership)</td>
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<td>18:15</td>
<td>Genomics in pharmacy practice</td>
<td>Hayley Wickens (Lead Pharmacy Training Programme Director (South), Genomics Specialist, HEE)</td>
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<td>18.30</td>
<td>Genomics in CVD prevention</td>
<td>Helen Williams (Consultant Pharmacist for CVD, South East London CCG)</td>
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<td>18:45</td>
<td>Q&amp;A and Poll</td>
<td>Mandeep Butt</td>
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<td>18.55</td>
<td>Studying genomics</td>
<td>Aiysha Saleemi (Pharmacist Advisor)</td>
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<td>19:05</td>
<td>Quiz and Q&amp;A</td>
<td>Aiysha Saleemi / Mandeep Butt</td>
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<td>19.15</td>
<td>Close</td>
<td>Mandeep Butt</td>
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NHS Genomic Medicines Service Alliance (GMSA)

• NHS GMS North Thames Alliance is one of seven GMS Alliances in England and is:
  • Hosted by UCLPartners, 10 North London Trusts as Partners
  • Covers North London, Essex, and Herts population 9.2 million

• Role of GMS alliances includes:
  • Working with patients and the public to build trust in genomics
  • Clinical leadership to enable the workforce to use genomics safely, effectively and efficiently
  • Systematic implementation of genomic medicine into the NHS
  • Delivery of the NHS Long Term Plan ambitions:
    o Creating a learning environment to support the rapid adoption and spread of scientific advances.
NHS GMSA

• Genomic Medicine Service: Update for chief pharmacists published in July 2020

• All hospital chief pharmacists and CCG lead pharmacists should:
  • be aware of the NHS Genomic Medicine Service (GMS), implications for pharmacy and development of NHS GMS alliances
  • identify members of their team with specialist expertise in genomics
  • support the development and delivery of GMS alliance pharmacy transformation
  • encourage members of their pharmacy teams to learn about genomics and personalised medicine via: https://www.genomicseducation.hee.nhs.uk/.
Timelines

• Submission of N Thames bid – completed last week
• Review by NHSE/I within 2 working weeks (11\textsuperscript{th} December latest)
• Launch of newly commissioned GMSAs mid January 2021

• Recruitment of new Clinical Director End December 2020
• Recruitment of other roles advertised next week to be appointed January-February 2021
• Job descriptions available via Rebecca.graham@uclpartners.com

• Business cases for transformation programmes for the new GMSAs to be submitted mid February!!
The GMSA builds on the existing GLH, GMC and clinical genetics infrastructure

- A regional Clinical and Scientific Directorate will enable clinical and scientific partners to work with the executive team to ensure delivery of the business plan (including transformation plans).
- Membership of the Directorate will be adjusted as appropriate once the business plans and transformation projects have been agreed. For example, there will be additional non-recurrent resources that will be put in place for delivery of the transformation plans that may be asked to join the directorate.
- In addition, given the number of specialty leads, attendance may be requested of specific individuals rather than the full cohort. Given they all feed into the Clinical Director, there will be access to clinical leadership for all specialties.

The speciality leads for Genomics Testing ensure clinical leadership is wide reaching. In partnership with the executive team, including Clinical Director, Chief Nurse, Chief Midwife, and Chief Pharmacist, this provides further opportunities to bring together the existing genomics work with the ambitions of the GMSA.
Within each GMS Alliance:

**Pharmacy System Leaders**
Chief Pharmacists in GMS Alliance strategic governance structure

- Strategic system leadership
  - Infrastructure & networks across region
  - Oversight of pharmacy transformation
  - Workforce development

**Pharmacy Clinical Leads**
Pharmacists with genomics expertise embedded in GMS Alliance clinical leadership groups

- Delivering against GMS priorities
  - Operational leadership & policy implementation
  - Pharmacy Transformation Programme
  - Education & Training

Working with regional pharmacy & medicines optimisation networks across primary & secondary care

**Pharmacy Genomics Collaborative**
National network to share best practice and advise on:

1. Workforce development strategy
2. Role of pharmacy in pharmacogenomics
3. Pharmacogenomics implementation and evaluation
Practical steps

• Map stakeholders and networks

• Undertake a review of awareness and engagement

• Design a workforce development strategy

• For transformation projects focusing on pharmacogenomics consider: a) Which pharmacogenomic tests are currently offered within the region and is there any variation? b) Are there existing projects or research activity on pharmacogenomics in the region and how would these link in? c) Are there opportunities to develop the role of the pharmacist within pharmacogenomic pathways? d) Implementation issues for pharmacogenomics: i) Clinical guidance ii) Information for patients and the public iii) Data to measure the uptake and clinical impact of pharmacogenomics iv) Implementation across different sectors in primary and secondary care e) DPYD testing implementation as an example pathway.
Key Priorities for North Thames GMSA 2021
Aligned to the LTP

• 100,000 genomes project

• Familial Hypercholesterolaemia

• Lynch Syndrome

• Local priority: screening for DPY deficiency in the prescription of methotrexate
Thank you

For more information please contact:

Mike Roberts

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www.uclpartners.com
@uclpartners
Genomics and the Pharmacy Team

Dr Hayley Wickens
Pharmacy Training Programme Director, HEE South
Hon Consultant Pharmacist Anti-infectives, University Hospital Southampton
MSc Genomic Medicine 2018

Any uncredited graphics courtesy of https://www.flickr.com/photos/genomicseducation/

Developing people for health and healthcare
www.hee.nhs.uk
Some serious **genetic** conditions, such as **sickle cell disease** and **achondroplasia**, are caused by a change to a **single letter** of DNA out of **3 billion**.
GENOMICS IN DIAGNOSIS AND TREATMENT
To personalise treatment and surveillance we can use genomic information...

- from a person
- from a person’s cancer
- from an infective organism

- To sub-classify their disease
- To assess their susceptibility
- To predict their response to drugs
- To choose the best treatment
- To make a prognosis
- To target therapy to its genomic profile
- To diagnose the type of infection
- To choose appropriate treatment
- To track epidemics
Example of a ‘genomic’ drug class: Chronic Myeloid Leukaemia

- Characterised by BCR-ABL fusion gene
  - ‘Philadelphia Chromosome’ t(9:22)
- ABL is an auto-inhibited Tyrosine Kinase
- BCR-ABL is an ‘always on’ TK
  - Role in cell division, growth etc.
- TKIs reduce progression to ‘blast phase’ and improve survival +++
  - Bind the ATP-binding site of BCR-ABL
  - Imatinib (Glivec) – identified via HTS
  - 2nd Gen: nilotinib, dasatinib, bosutinib, ponatinib
  - T315I mutation gives TKI resistance – apart from ponatinib
Example of genomics in AMR testing: TB

• “...This is the first time that WGS has been used as a diagnostic solution for managing a disease on this scale anywhere in the world...”

• “…Where previously it could take up to a month to confirm a diagnosis of TB, confirm the treatment choices and to detect spread between cases, this can now be done in just over a week by PHE’s Birmingham laboratory...”

PHARMACY AS PHARMACOGENOMICS EXPERTS
Flucloxacillin: HLA-B*57:01:01 associated with risk of liver injury

Carbamazepine: HLA-B*15-02 → TEN & SJS, Asians/Han Chinese (94% PPV, 100% NPV)
• HLA*A:31-01 ↑ risk in Europeans/Japanese (range of severity)
• screening not yet routine in European populations, but mandated in Asian populations.

Azathioprine: TPMT inactivates azathioprine/5-MP
• 90% homozygous high metabolising / 10% heterozygous
• 0.33% homozygous low-metabolising: dramatic, rapid myelosuppression, and suffer from secondary leukaemias and myelodysplasias
• Functional TPMT testing of RBC possible

56 drugs have a genetic testing requirement in their SmPC...
Pharmacogenomics: PharmGKB.org

Pretty cool right? Tell me more...

Learn more about PharmGKB
Pharmacogenomic Passports?

- Groningen (UCMG)
  - 36 variants in 15 genes, using Dutch national guidelines for drug selection and dosing.
  - 300 outpatients screened, clinical decision support ‘PGxConsultor’ with supervision by a clinical pharmacist

- Leiden
  - Implementing PGx in Primary Care Project - IP3
  - 8 gene panel (CYP2C9, CYP2C19, CYP2C6, CYP3A5, DPYD, SLCO1B1, TPMT, VKORC1)
  - 200 individuals tested
    - 95% had ≥1 one actionable genotype
    - 10% had ≥4
    - 30% were either closely monitored, had a dose adjustment or drug changed

“For this to work well, a multidisciplinary approach, including clinicians, geneticists, and pharmacists, needs to be used...”
Stratification using genomics

**Clinical diagnosis**
**HIV/AIDS**
Drug (Abacavir) is known to be beneficial

Test for genetic variant

- **Absent**: prescribe Abacavir (not toxic) (3)
- **Present**: do not prescribe Abacavir (is toxic) (1)

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(1) Drug toxic but beneficial

(2) Drug toxic but not beneficial

(3) Drug not toxic and not beneficial

(4) Drug not toxic and beneficial
Pharmacist roles:

- Recommend PG testing to aid drug and dosage selection.
- Design a patient-specific drug and dosage regime based on the patient’s PGx profile that also considers PKPD of drug, co-morbidities and lab data etc
- Educate patients, pharmacists, and HCP about PG and testing, cost-effectiveness
- Communicate PGx-specific drug therapy recommendations to the health care team, including documentation in notes.

Plus (if specialist):

- Design decision support, write guidelines, service development/strategy, evaluation, R&D….
PHARMACY WORKFORCE DEVELOPMENT IN GENOMICS
Workforce Development

• Current offer variable and person- rather than system-led
  – Formation of GMSAs needing trained staff
  – HEE and NHSE/I joint working
• Pharmacy should be ‘front and centre’ in Genomics
  – Experts in science, data and communication with patients
  – e.g. formulary, MDT, pharmacogenomic ‘passports’
• Need service specification(s) for pharmacists in Genomics
  – Roles are emerging and being defined; level of training required will vary
  – Remodelling of services e.g. cancer – from organ/system to mutation-based
Genomics training available for Pharmacy staff

- HEE Genomics Education Programme
  - Free online courses, teaching resources, bitesize
  - Plus in-person training (MSc/modules)
- Genomics MOOCs FutureLearn
  - HEE, St. George’s
- *new* CPPE Genomics module

Genomicseducation.hee.nhs.uk / e-lfh.org.uk (search “genomics”) / cppe.ac.uk
Pharmacists in Antimicrobial Stewardship (AMS)

New speciality¹ 6 specialist ph in UK

UKCPA-IMG (PIN) launched 12 members

Imperial MSc launched

141 posts in 125 Trusts²

187 posts in 120 Trusts³

1st Cons Ph (infection)

Hospital Pharmacy Initiative


Publications, Masterclasses, Curriculum, joint work with infection societies

…Genomics – following the path of AMS?

Challenges for Pharmacy

- Building in development for the whole pharmacy workforce
- Initial Education and Training – already a full programme, what do we drop?
- Science moving faster than societal discussion
- Be bold – understand the potential of pharmacy in the emerging genomics field
- What will you do in the next 6 months?
Further reading

- www.genomicseducation.hee.nhs.uk
- https://www.genomicsengland.co.uk/the-100000-genomes-project/
- https://www.pharmgkb.org/

- Hayley.wickens@hee.nhs.uk
- Twitter: @BugHayleyW

THANK YOU
Genomics and CVD Prevention
Familial Hypercholesterolaemia

Helen Williams
Consultant Pharmacist for CVD & Clinical Adviser, UCLP
National Speciality Adviser for CVD Prevention, NHSE&I
10 year cardiovascular disease ambitions for England

**Atrial fibrillation (AF)**
- 85% of the expected number of people with AF are detected by 2029
- 90% of patients with AF who are already known to be at high risk of a stroke to be adequately anticoagulated by 2029

**High blood pressure**
- 80% of the expected number of people with high blood pressure are diagnosed by 2029
- 80% of the total number of people already diagnosed with high blood pressure are treated to target as per NICE guidelines by 2029

**High cholesterol**
- 75% of people aged 40 to 74 have received a formal validated CVD risk assessment and cholesterol reading recorded on a primary care data system in the last five years by 2029
- 45% of people aged 40 to 74 identified as having a 20% or greater 10-year risk of developing CVD in primary care are treated with statins by 2029
- 25% of people with Familial Hypercholesterolaemia (FH) are diagnosed and treated optimally according to the NICE FH Guideline by 2024
Current detection and management of High Cholesterol and Familial Hypercholesterolaemia (FH)

High Cholesterol
- Now: 49% Detection
- 2029: 75% Detection
- Now: 35% Management
- 2029: 45% Management

Familial Hypercholesterolaemia (FH)
- Now: 5% Detection
- 2024: 25% Detection
Why FH?

- FH is a dominantly inherited genetic disorder affecting approximately 1 in 250 individuals
- Characterized by markedly elevated low-density LDL-C and accelerated atherosclerotic cardiovascular disease
- People with FH have a 2.5- to 10-fold increased risk of ASCVD compared with controls
  - Studies have shown that the risk of developing coronary heart disease is up to 13 times higher in people with untreated FH
- When FH is diagnosed and treated early in life, the risk is greatly reduced (≈ 80%)
- Most people with FH have never been diagnosed or treated
50% If left untreated, men have a **50% risk** of having a heart attack by age 50.

30% Untreated women have a **30% risk** of having a heart attack by age 60.
Effect of statins on outcome in FH

BMJ 2008; 337 doi: https://doi.org/10.1136/bmj.a2423
Heterozygous and Homozygous FH

- Heterozygous FH – one mutation in one allele
- True homozygous FH – same mutation in both alleles of the same gene
- Compound heterozygous FH – different mutations in the two alleles of the same gene
- Double heterozygous FH – different mutations in two alleles of different genes
Chance of inheriting

If 2 people with heterozygous FH (HeFH) have a family of 4 children, on average:

- 2 children will inherit the normal form of FH (HeFH) by inheriting one faulty gene and one healthy gene
- 1 child will inherit the more severe form of FH (HoFH) by receiving a faulty gene from each parent
- 1 child will not inherit FH at all because they receive a healthy gene from each parent

(This is an average situation. It is possible that all the children in the family could have FH or none of the children will have it)
1. This may be you – the ‘index case’.
2. One of your parents will have FH.
3. Approximately half your children will have FH.
4. Approximately half your siblings will have FH.
5. Approximately half the children of your affected siblings will have FH.
6. If you don’t have FH your children can’t have FH.
Broad Spectrum of LDL-C levels in FH

Simon Broome criteria

Definite FH

• Cholesterol as below and tendon xanthomata, or evidence of these signs in a 1st or 2nd degree relative

OR

• DNA-based evidence of an LDL-receptor mutation, familial defective apoB-100 or a PCSK9 mutation

Probable FH

• Cholesterol as below and at least one of the following
  • FH MI: aged < 50 in 2nd degree or <60 in 1st degree relative
  OR
  • FH raised total cholesterol:
    • > 7.5 mmol/L in adult 1st or 2nd degree relative
    • > 6.7 mmol/L in child, sibling under 16

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<th>Total Chol</th>
<th>LDL-C</th>
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<tr>
<td>Child/young person</td>
<td>&gt;6.7</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>Adult</td>
<td>&gt;7.5</td>
<td>&gt;4.9</td>
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Screening for familial hypercholesterolaemia.
Bender, Robert; Bell, Damon; Hooper, Amanda; Edwards, Glenn; van Bockxmeer, Frank; Watts, Gerald; Burnett, John
Pathology. 44(2):122-128, February 2012. DOI: 10.1097/PAT.0b013e32834efa07
FH Is Most Frequently Caused by *LDLR* Mutations

- Mutation in *LDLR* are found in ~95% of the confirmed cases of HoFH
- More than 1,000 *LDLR* mutations have been reported
- Based on the mutations patients can be divided in receptor negative (<2% activity) or receptor defective
- The type of mutations affect the LDL-C levels and the response to treatment
Molecular Causes of FH

~95% due to mutations in LDLR gene
~5% due to other mutations in APOB, PCSK9 and LDLRAP1 (ARH) genes

**LDLR (chr 19p13):** Primary familial hypercholesterolemia OMIM: 143890

**APOB (chr 2p24):** Familial defective Apo B OMIM: 144010

**PCSK9 (chr 1p32):** Proprotein convertase subtilisin/kexin type 9 OMIM: 603776

**LDLRAP1 (chr 1p36):** Autosomal recessive hypercholesterolemia OMIM: 603813
Cascade testing

- Cascade screening identifies people with FH by a process of family screening. It is less costly and more efficient than systematic screening in the population.
- It can be done with or without genetic testing but genetic testing is the best approach to identify patients.
- Once specific gene defect has been identified in index case (~£250 per test) – can just screen for that defect in family members (£40-50 per test).
- It needs dedicated staff, storage facilities, electronic database.
- Cascade screening in the Netherlands was associated with a dramatic increase in the number of patients treated with statin (from 38% to 90%).
Genetics of FH

Figure 1 Dominant pattern of inheritance of familial hypercholesterolemia due to mutations in the LDL-receptor gene (LDLR). (A) The index patient in this family (arrow) is a child with a clinical phenotype of homozygous familial hypercholesterolemia. The dark half-filled symbols indicate individuals heterozygous for the Asp461Asn mutation in LDLR; the light half-filled symbols indicate individuals heterozygous for 21-base-pair duplication in exon 4 of LDLR. Total plasma cholesterol before treatment is shown below each symbol in mmol/l. The patient’s mother was married three times (symbols marked 1–3). Note that cholesterol levels in the patient’s father and in his daughter by his second wife are much lower than those in the family of the patient’s mother, but other unrelated patients with this same mutation (Asp461Asn) have severely increased plasma cholesterol (AK Soutar, unpublished data). (B) Mean plasma cholesterol levels in unaffected, heterozygous and ‘homozygous’ members of the same family.


Figure 1 Dominant pattern of inheritance of familial hypercholesterolemia due to mutations in the LDL-receptor gene (LDLR). (A) The index patient in this family (arrow) is a child with a clinical phenotype of homozygous familial hypercholesterolemia. The dark half-filled symbols indicate individuals heterozygous for the Asp461Asn mutation in LDLR; the light half-filled symbols indicate individuals heterozygous for 21-base-pair duplication in exon 4 of LDLR. Total plasma cholesterol before treatment is shown below each symbol in mmol/l. The patient’s mother was married three times (symbols marked 1–3). Note that cholesterol levels in the patient’s father and in his daughter by his second wife are much lower than those in the family of the patient’s mother, but other unrelated patients with this same mutation (Asp461Asn) have severely increased plasma cholesterol (AK Soutar, unpublished data). (B) Mean plasma cholesterol levels in unaffected, heterozygous and ‘homozygous’ members of the same family.
Where are we now?

• 7 national genomics hubs identified
  • North Thames Genomic Laboratory Hub led by Great Ormond Street Hospital for Children NHS Foundation Trust
• Awaiting confirmation of funding for genetic testing in FH
• Pathway redesign to optimise genetic testing
  • Identification of patients in primary care – search tools, triage, referral
  • Genetic counselling and cascade testing
  • On-going management – high intensity statin, ezetimibe, PSCK9i
• Pilots of child-parent screening programmes
Q&A and Poll
Studying Genomics

Aiysha Saleemi, Pharmacist Advisor, UCLPartners

26th November 2020
Career Background

• Hospital pharmacy (2007-2016)
  • Post-graduate diploma
  • Independent prescribing

• GP practice part-time (2015)

• CCG (2016-2018)
  • PRINCE2 project management

• Academic Health Science Network (2018-date)
  • Darzi Fellowship
  • Post graduate certificate in genomics
Genomics course

• Masters (8 modules + research project)

• Postgraduate diploma (8 modules)

• Postgraduate certificate (4 modules)
  • An introduction to human genetics and genomics
  • Genomics of common and rare inherited diseases (Dec 2020)
  • Molecular pathology of cancer and application in cancer diagnosis, screening and treatment (Feb 2021)
  • Pharmacogenomics and stratified medicine (March 2021)
My Experience

- Full-time work, part-time study, again!
- New databases to understand – ClinVar, OMIM
- Find genomics buddies
- Easier if you find it interesting
Quiz

1. How similar are human genomes?
   • 96.9 – 97.1%
   • 98.7 – 98.8%
   • 99.8 - 99.9%

2. If you read 5 letters every second, how long would it take to read a human genome?
   • 7 years
   • 19 years
   • 23 years

3. What percentage of the genome contains genes?
   • 73%
   • 47%
   • 2%
Thank you

For more information please contact:

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Quiz and Q&A
Thank you

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