Genomics in Pharmacy

UCLPartners
26th November 2020

Genomics in Pharmacy

Agenda

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

Genomics Medicine Service Alliances & The Role of Pharmacy

Prof. Mike Roberts, Managing Director, UCLPartners Academic Science Partnership

26th November 2020

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:
    - Creating a learning environment to support the rapid adoption and spread of scientific advances.

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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/.
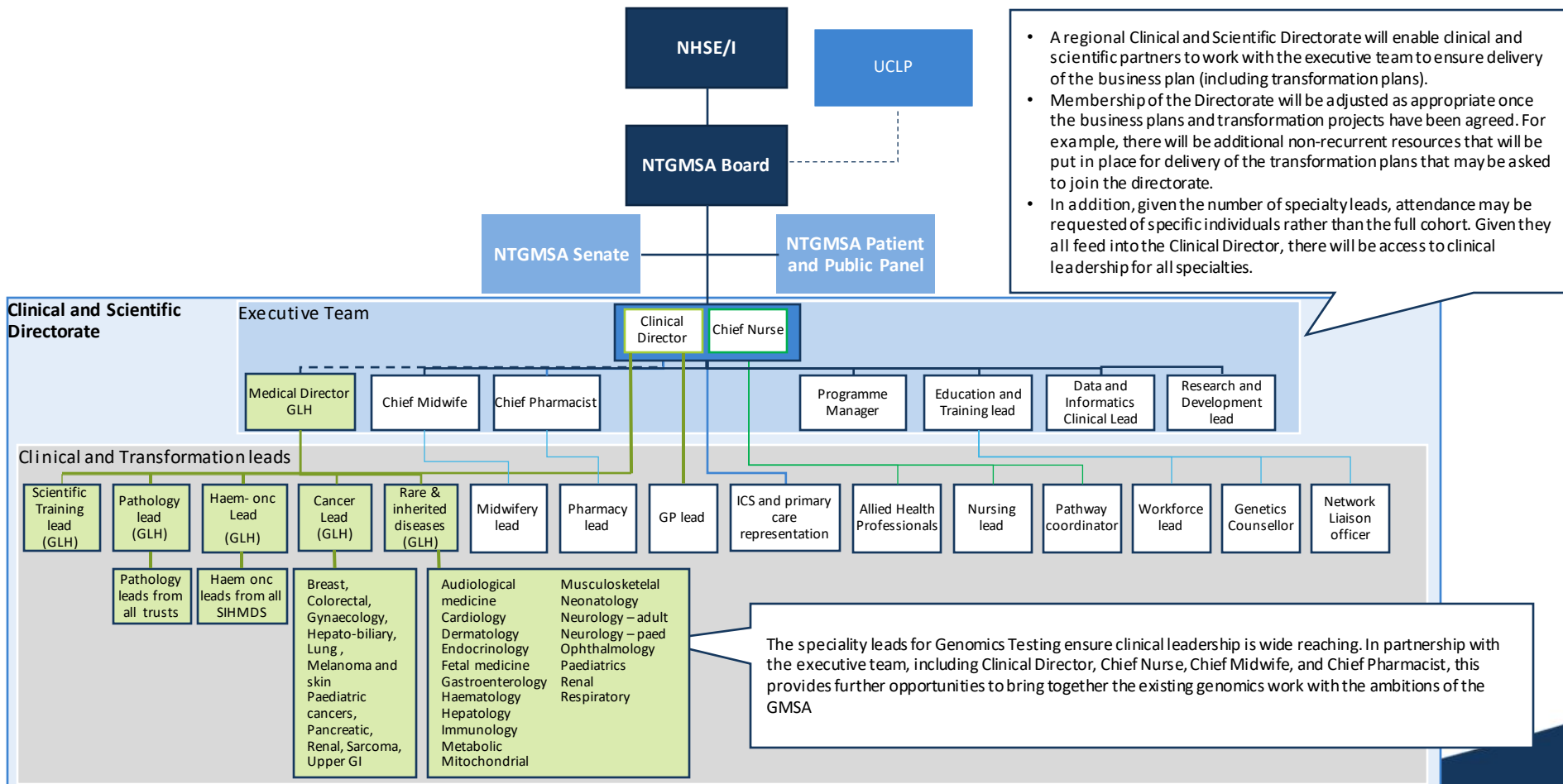
Timelines

- **Submission of N Thames bid – completed last week**

- **Review by NHSE/I within 2 working weeks (11th 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!!**

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The GMSA builds on the existing GLH, GMC and clinical genetics infrastructure

NHSE/I

UCLP

NTGMSA Board

NTGMSA Senate

NTGMSA Patient and Public Panel

Clinical and Scientific Directorate

Executive Team

Clinical Director — Chief Nurse

Medical Director GLH — Chief Midwife — Chief Pharmacist — Programme Manager — Education and Training lead — Data and Informatics Clinical Lead — Research and Development lead

Clinical and Transformation leads

- Scientific Training lead (GLH)
- Pathology lead (GLH)
- Haem- onc Lead (GLH)
- Cancer Lead (GLH)
- Rare & inherited diseases (GLH)
- Midwifery lead
- Pharmacy lead
- GP lead
- ICS and primary care representation
- Allied Health Professionals
- Nursing lead
- Pathway coordinator
- Workforce lead
- Genetics Counsellor
- Network Liaison officer

Pathology leads from all trusts

Haem onc leads from all SIHMDS

Breast, Colorectal, Gynaecology, Hepato-biliary, Lung , Melanoma and skin Paediatric cancers, Pancreatic, Renal, Sarcoma, Upper GI

Audiological medicine
Cardiology
Dermatology
Endocrinology
Fetal medicine
Gastroenterology
Haematology
Hepatology
Immunology
Metabolic
Mitochondrial

Musculosketelal
Neonatology
Neurology – adult
Neurology – paed
Ophthalmology
Paediatrics
Renal
Respiratory

- 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

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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

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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.

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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

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Thank you

For more information please contact:

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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/*
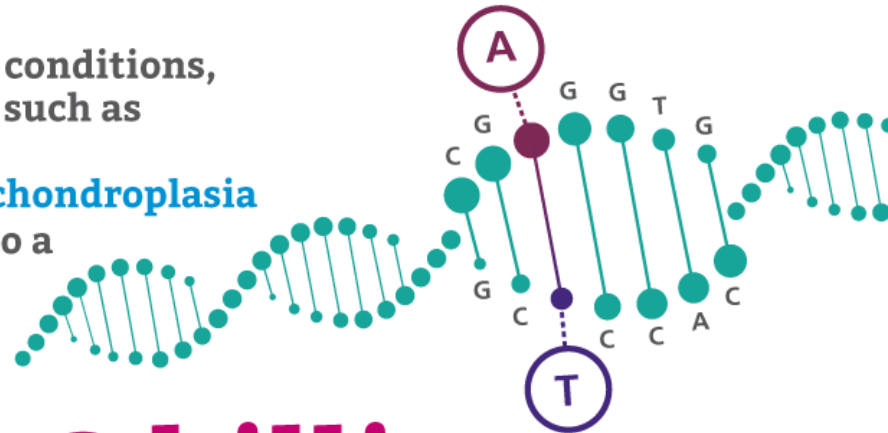
GENOMICS IN DIAGNOSIS AND TREATMENT

To personalise treatment and surveillance we can use genomic information...

from a person
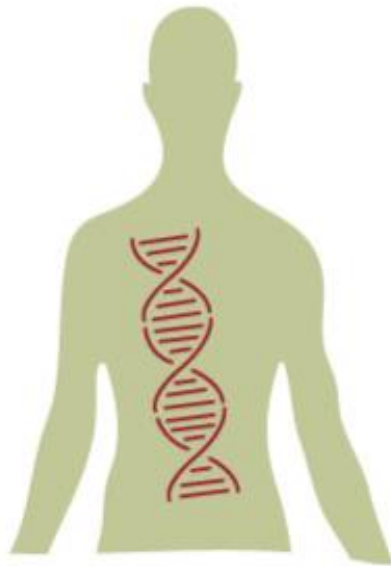
- To sub-classify their disease
- To assess their susceptibility
- To predict their response to drugs
- To choose the best treatment

from a person's cancer

- To make a prognosis
- To target therapy to its genomic profile

from an infective organism

- 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
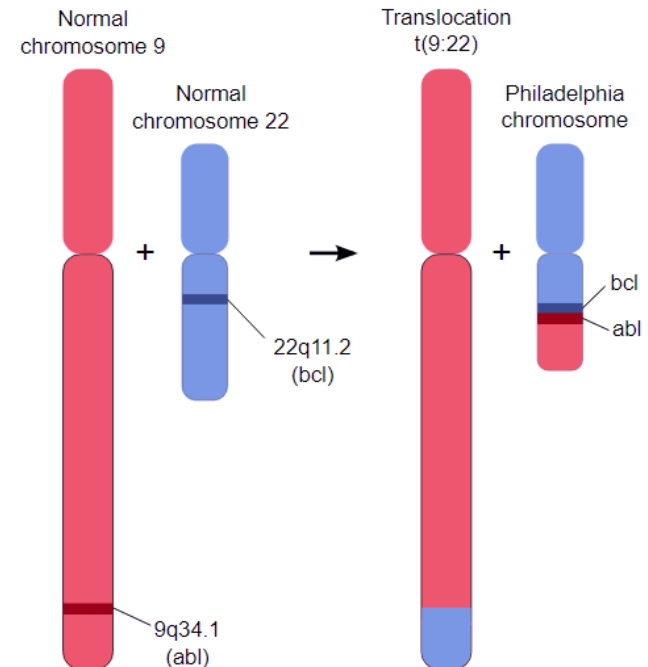
Example of genomics in AMR testing: TB

GOV.UK

Press release

England world leaders in the use of whole genome sequencing to diagnose TB

Whole genome sequencing (WGS) is now being used to identify different strains of tuberculosis (TB), announced Public Health England today.

Published 28 March 2017
From: **Public Health England**

- *"…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..."*

https://www.gov.uk/government/news/england-world-leaders-in-the-use-of-whole-genome-sequencing-to-diagnose-tb

PHARMACY AS PHARMACOGENOMICS EXPERTS

The effect of more than 100 drugs is influenced by genetic variatio

codeine

carbamazepine

azathioprine

warfarin

flucloxacillin

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…
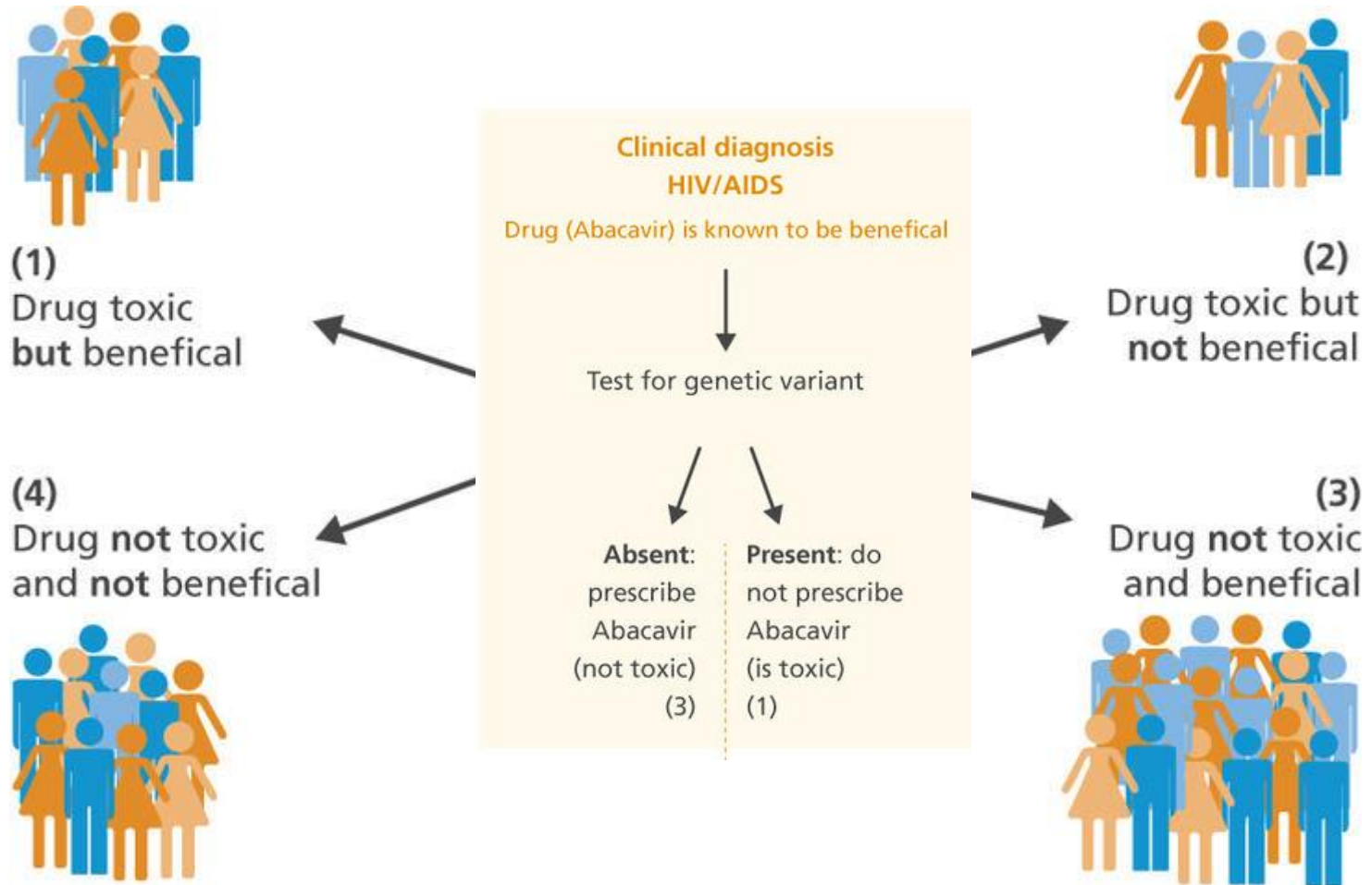
Pharmacogenomics: PharmGKb.org

Pharmacogenomic Passports?

"...For this to work well, a multidisciplinary approach, including clinicians, geneticists, and pharmacists, needs to be used..."

- 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 - IP[3]
  - 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

Stratification using genomics

(1)
Drug toxic
but benefical

(4)
Drug **not** toxic
and **not** benefical

Clinical diagnosis
HIV/AIDS

Drug (Abacavir) is known to be benefical

Test for genetic variant

Absent:
prescribe
Abacavir
(not toxic)
(3)

Present: do
not prescribe
Abacavir
(is toxic)
(1)

(2)
Drug toxic but
not benefical

(3)
Drug **not** toxic
and benefical

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.
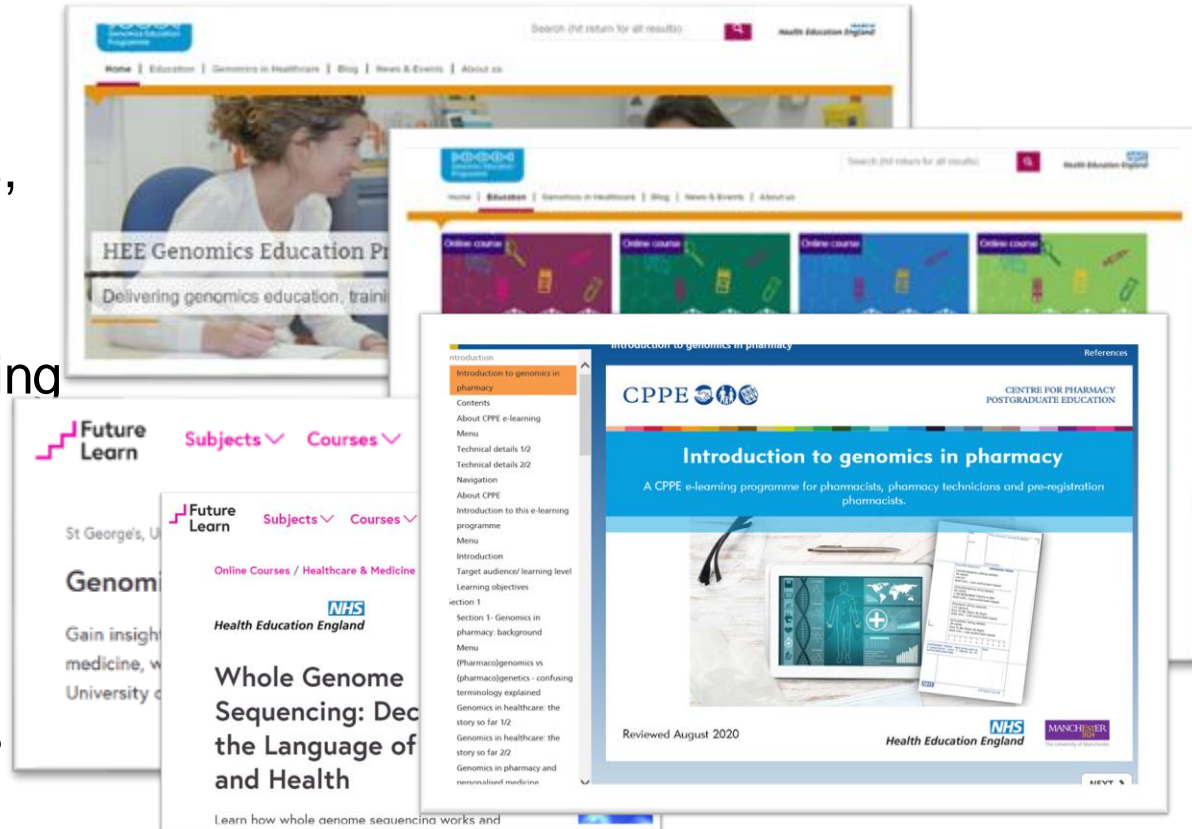
Plus (if specialist):
- Design decision support, write guidelines, service development/strategy, evaluation, R&D….

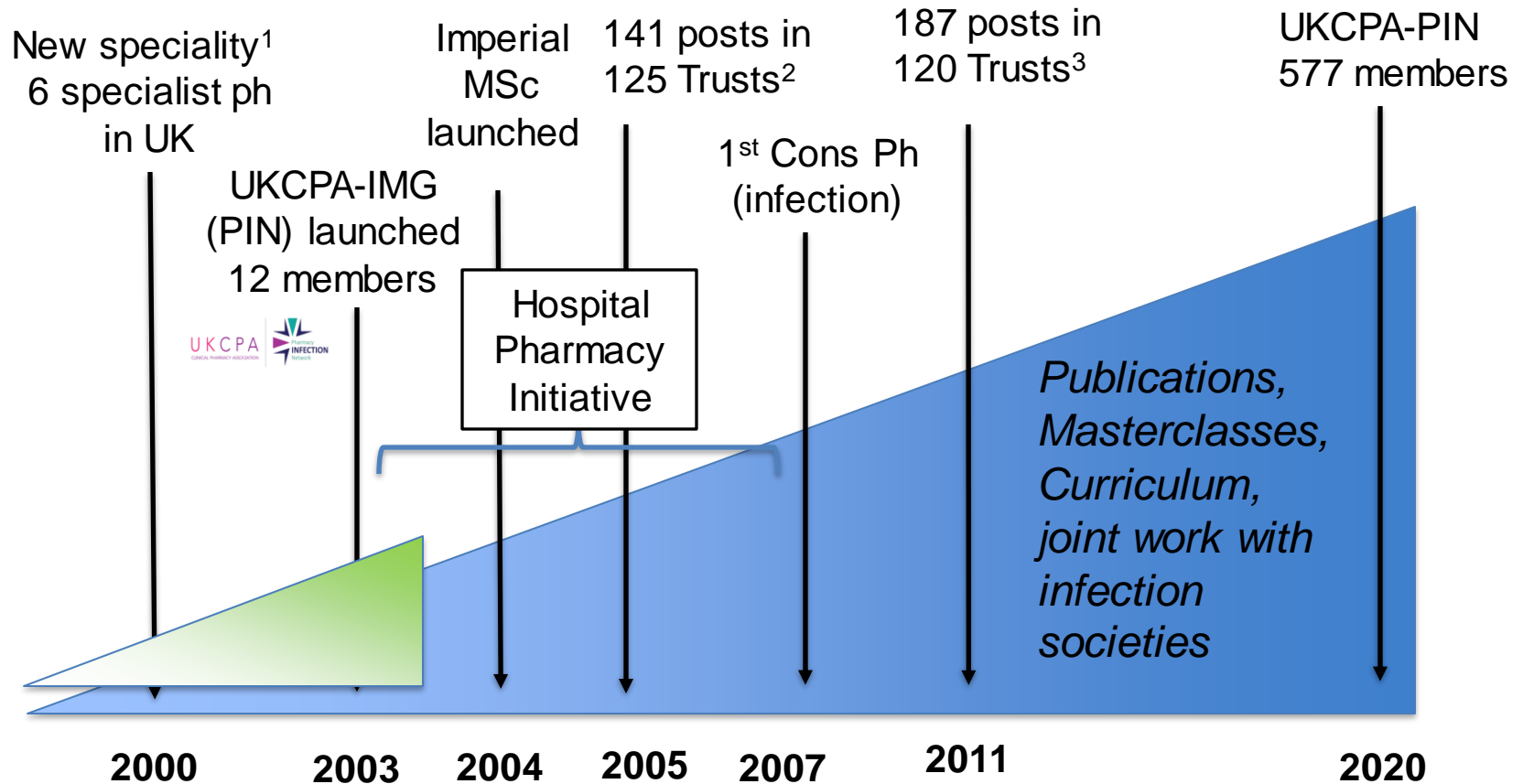**PHARMACY WORKFORCE DEVELOPMENT IN GENOMICS**

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)

NHS
Health Education England

New speciality[1]
6 specialist ph
in UK

UKCPA-IMG
(PIN) launched
12 members

Imperial
MSc
launched

141 posts in
125 Trusts[2]

1st Cons Ph
(infection)

187 posts in
120 Trusts[3]

UKCPA-PIN
577 members

UKCPA CLINICAL PHARMACY ASSOCIATION Pharmacy INFECTION Network

Hospital
Pharmacy
Initiative

*Publications,
Masterclasses,
Curriculum,
joint work with
infection
societies*

2000   **2003**   **2004**   **2005**   **2007**   **2011**   **2020**

…Genomics – following the path of AMS?

[1.] *Jepson A & Wickens HJ (2003) Pharm. J. 271(7278):774-775*
[2.] *Wickens HJ & Jacklin A (2006) J. Antimicrob. Chemother. 58 (6): 1230-1237*
[3.] *Wickens HJ et al (2013) J. Antimicrob Chemother. 68(11):2675-81*

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

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)

High blood pressure

High cholesterol

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**

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**

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
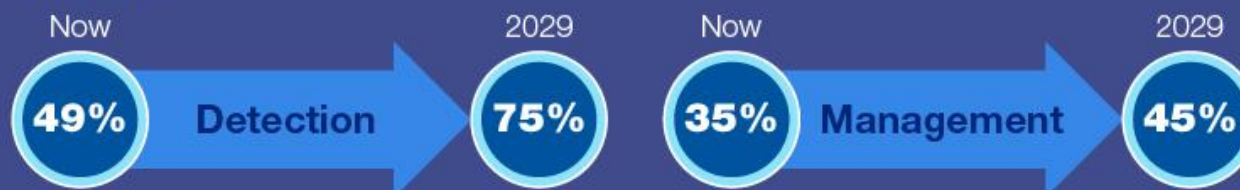
Why FH?

- 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
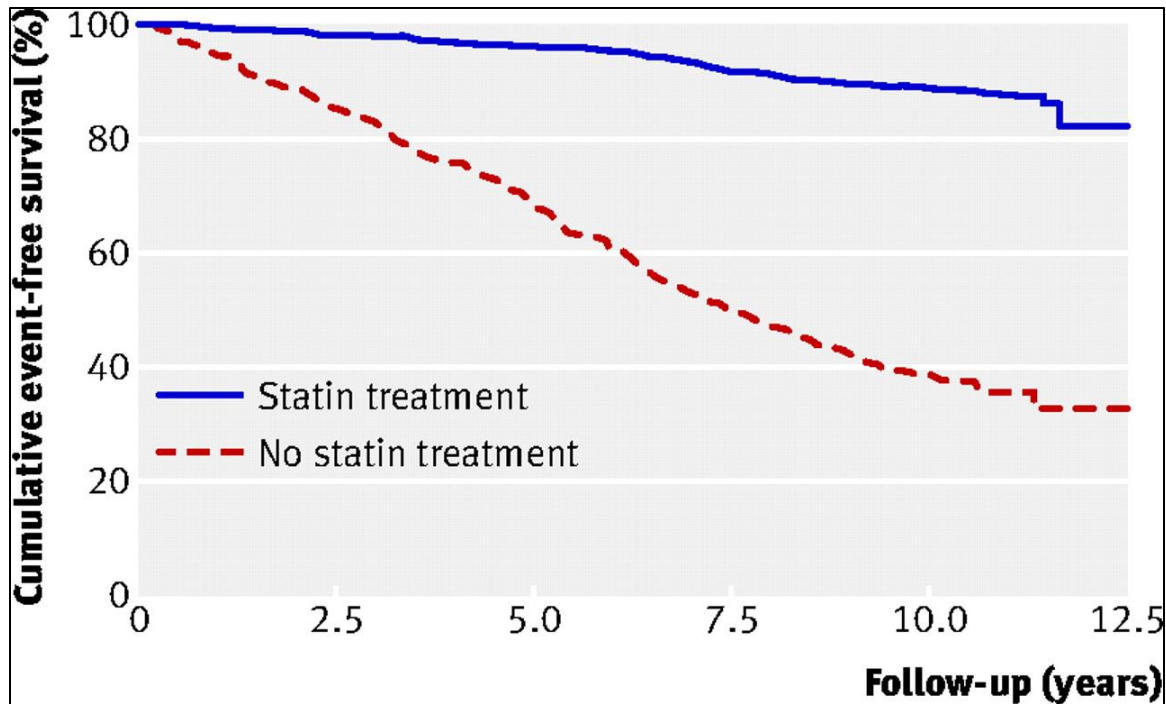
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50% If left untreated, men have a **50% risk** of having a heart attack by age 50.

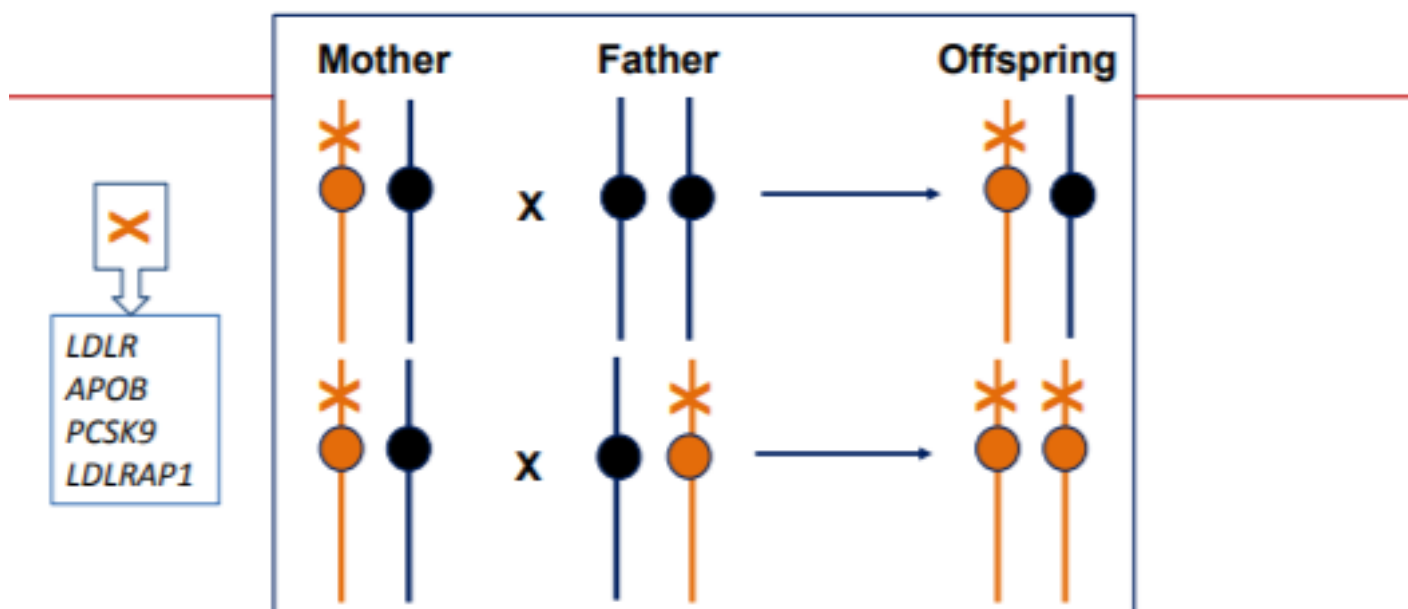Untreated women have a **30% risk** of having a heart attack by age 60. **30%**

Effect of statins on outcome in FH

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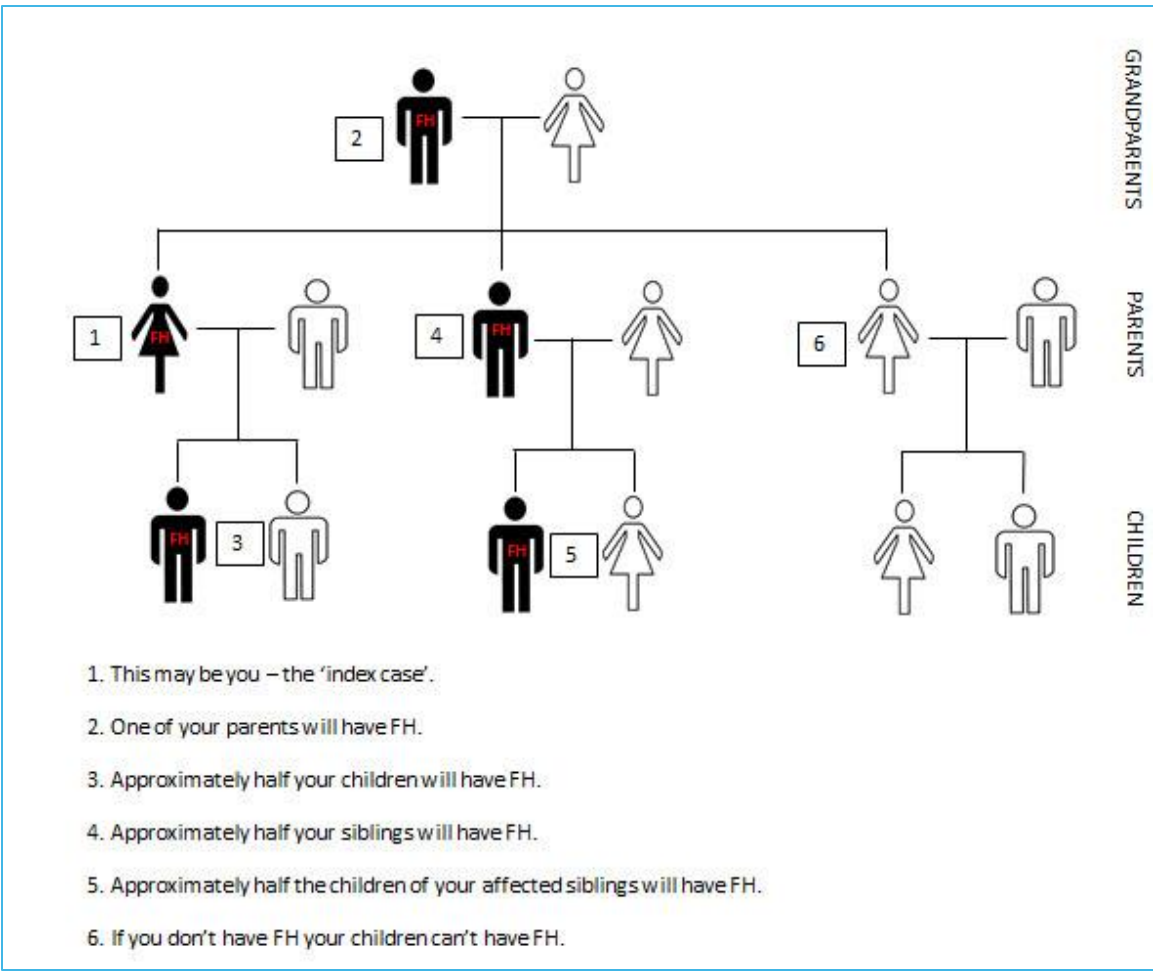
Heterozygous and Homozygous FH

- Heterozygous FH – one mutation in one allele
- True homozygous FH – same mutation in both alleles of 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

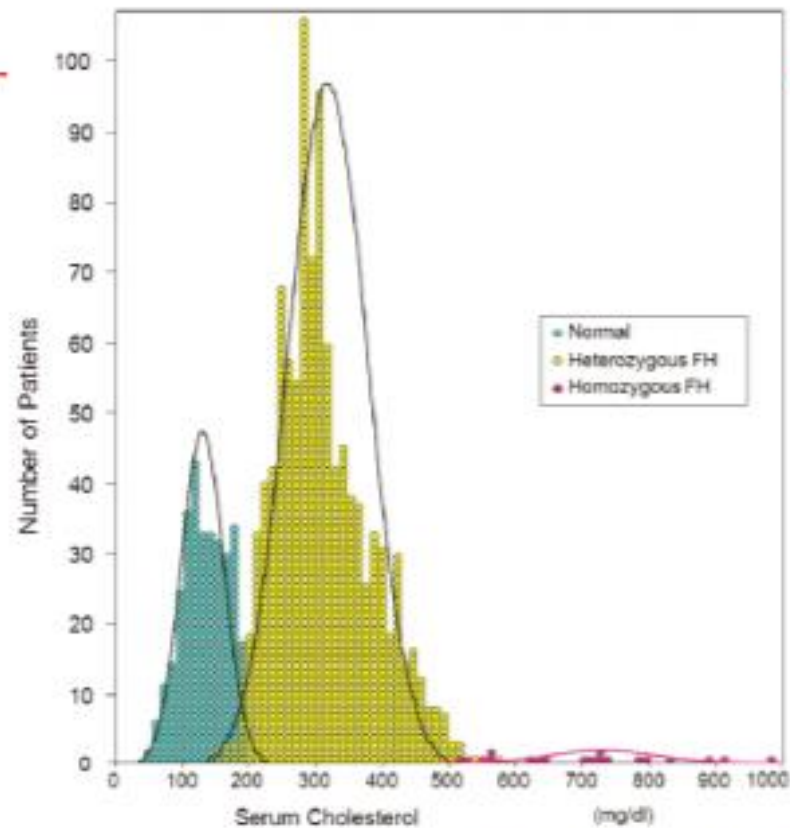If 2 people with heterozygous FH (HeFH) have a family of 4 children, on average:

- 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)

Heart UK 2018

GRANDPARENTS

PARENTS

CHILDREN

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.

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Broad Spectrum of LDL-C levels in FH

Harada-Shida et al. J Ateroscler Thromb, 2012; 19:1043-1060

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

	Total Chol	LDL-C
Child/young person	>6.7	>4.0
Adult	>7.5	>4.9

(A) Extensor tendon xanthomata

(C) Corneal arcus

(B) Achilles tendon xanthoma

(D) Xanthelasmata

FH Is Most Frequently Caused by *LDLR* Mutations

1. Ligand-Binding Domain
2. EGF Precursor Homology Domain
3. O-Linked Sugar Domain
4. Membrane-Spanning Domain
5. Cytoplasmic Domain
NH₂
COOH
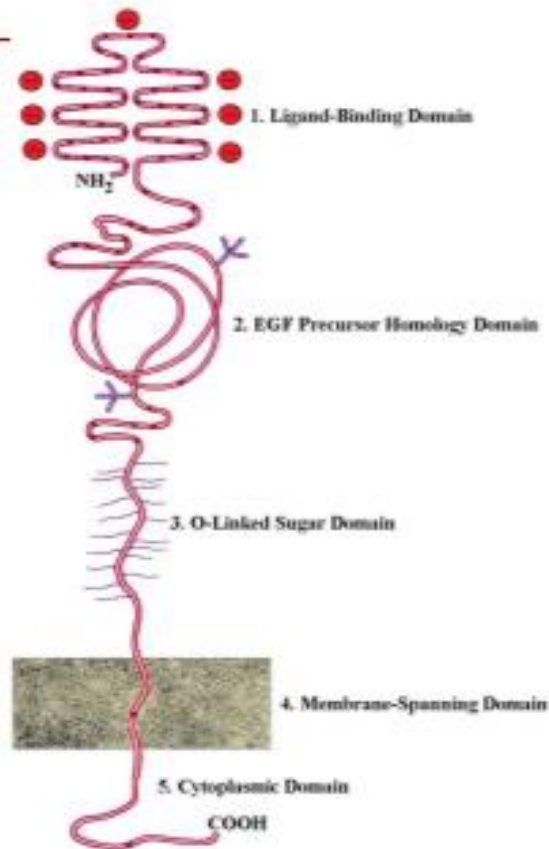
- Mutation in *LDLR* are found in ~95% of the confirmed cases of HoFH

- 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

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
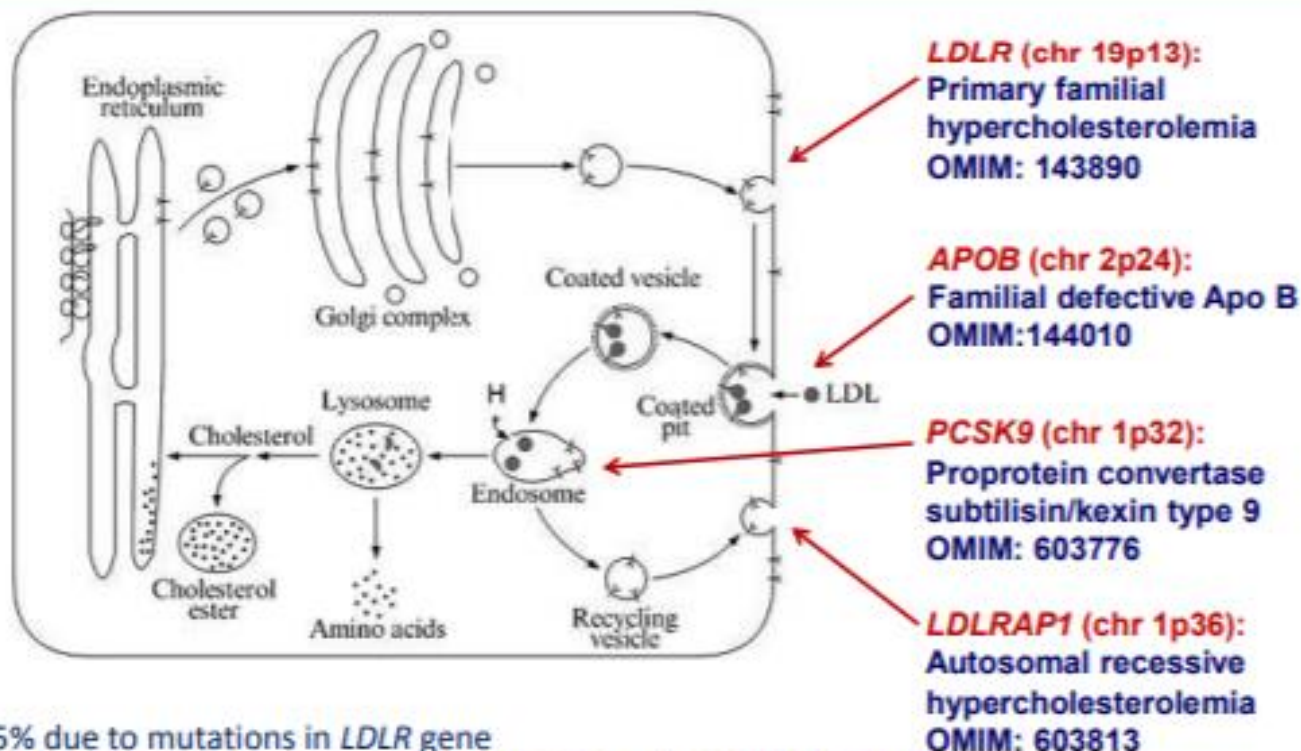
~95% due to mutations in *LDLR* gene

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

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%)

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Genetics of FH

Soutar AK and Naoumova RP (2007) Mechanisms of Disease: genetic causes of familial hypercholesterolemia
Nat Clin Pract Cardiovasc Med **4**: 214–225 doi:10.1038/ncpcardio0836
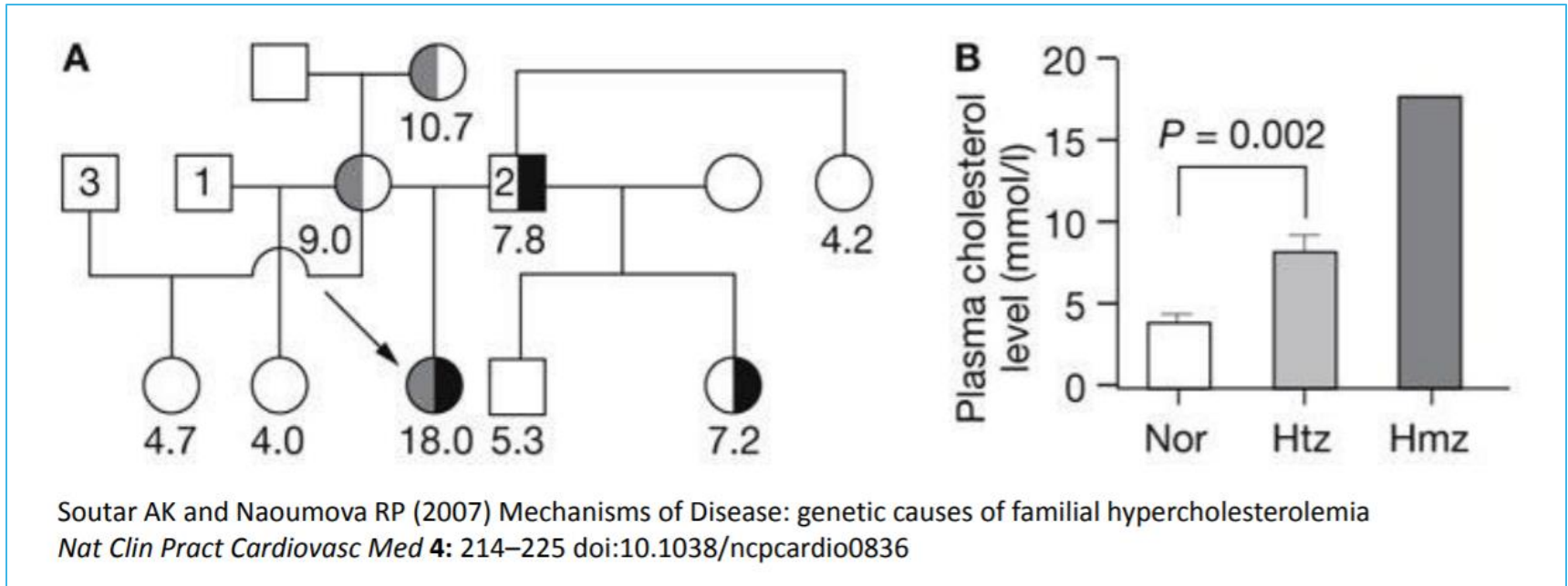
Figure 1 Dominant pattern of inheritance of familial hypercholesterolemia due to mutations in the LDL-receptor gene (LDLR). (A) The index patient in this family (arrow) is a child with a clinical phenotype of homozygous familial hypercholesterolemia. The dark half-filled symbols indicate individuals 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

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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%

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Thank you

For more information please contact:

Aiysha Saleemi

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Quiz and Q&A

Thank you

For more information please contact

Primary Care enquiries Primarycare@uclpartners.com