Genomics and Primary care

Dr Imran Rafi FRCGP FRCP BSc MSc MSt PhD DFMS
Joint RCGP Clinical Champion for Genomics with Dr Jude Hayward
and
Academy of Medical Royal Colleges
Genomic Champions

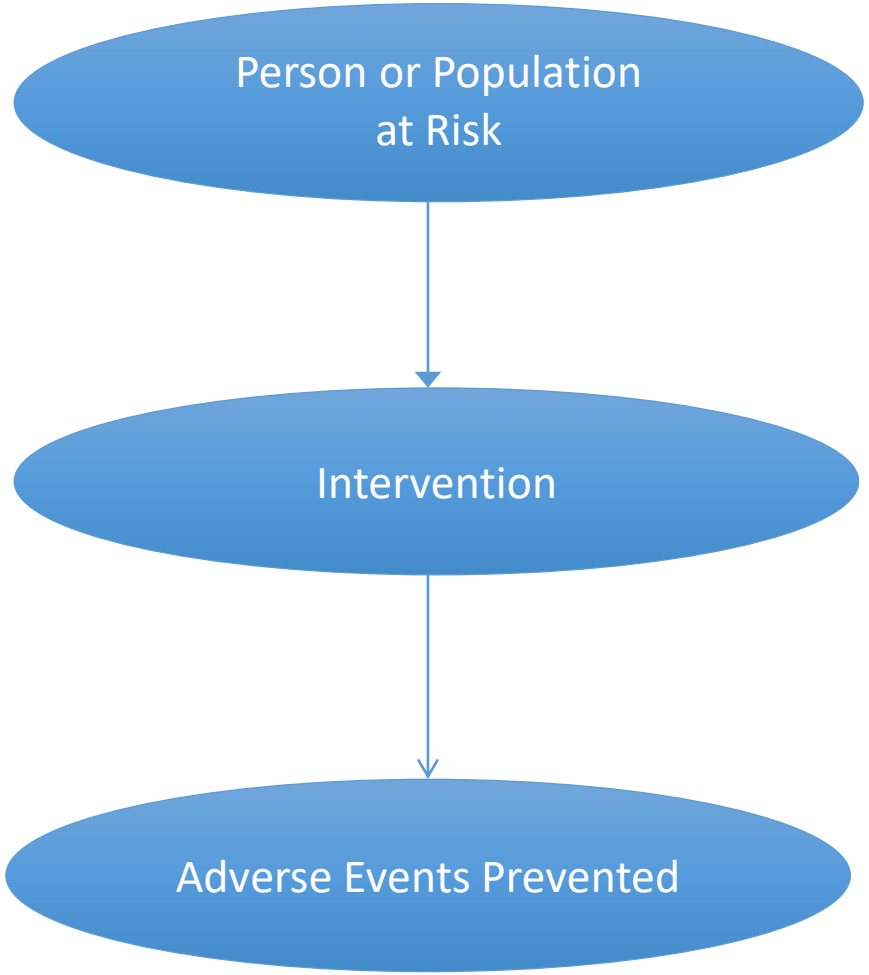
Thank you to:

- Dr. Michelle Bishop: Education Lead, HEE Genomics Education Programme

Mainstreaming Genomics

- Laboratories: Genomic Laboratory Hubs
- Genetic Test Registry
- Direct Access testing
- Mainstreaming Genomic testing

We think prevention looks like this



But really it looks like this…

Intervention

Genomics live in Primary Care

How could genomics issues present now?
What do we in Primary Care need to know?
What do we not need to know?

How could Genomics issues present?

- Family History: at increased risk of having a genetic condition
- Consideration of test: increased risk or concern
- Red flags
- Direct-to-Consumer Test results (DCT)
- Management of patient with genetic condition
- Coding of genomic information and results

Knowledge, skills and attitudes

- Core to General Practice
- Genetic conditions, modes of inheritance
- Referral indications and pathways
- Accessing resources and signposting

What's new?

- Understanding of genomics services
- Genomic tests: nomenclature, information, availability, limitations, clinical management
- Ethical, legal and social implications
- Common complex conditions: Risk stratification, disease sub-typing

Unlikely to present currently?

5 years

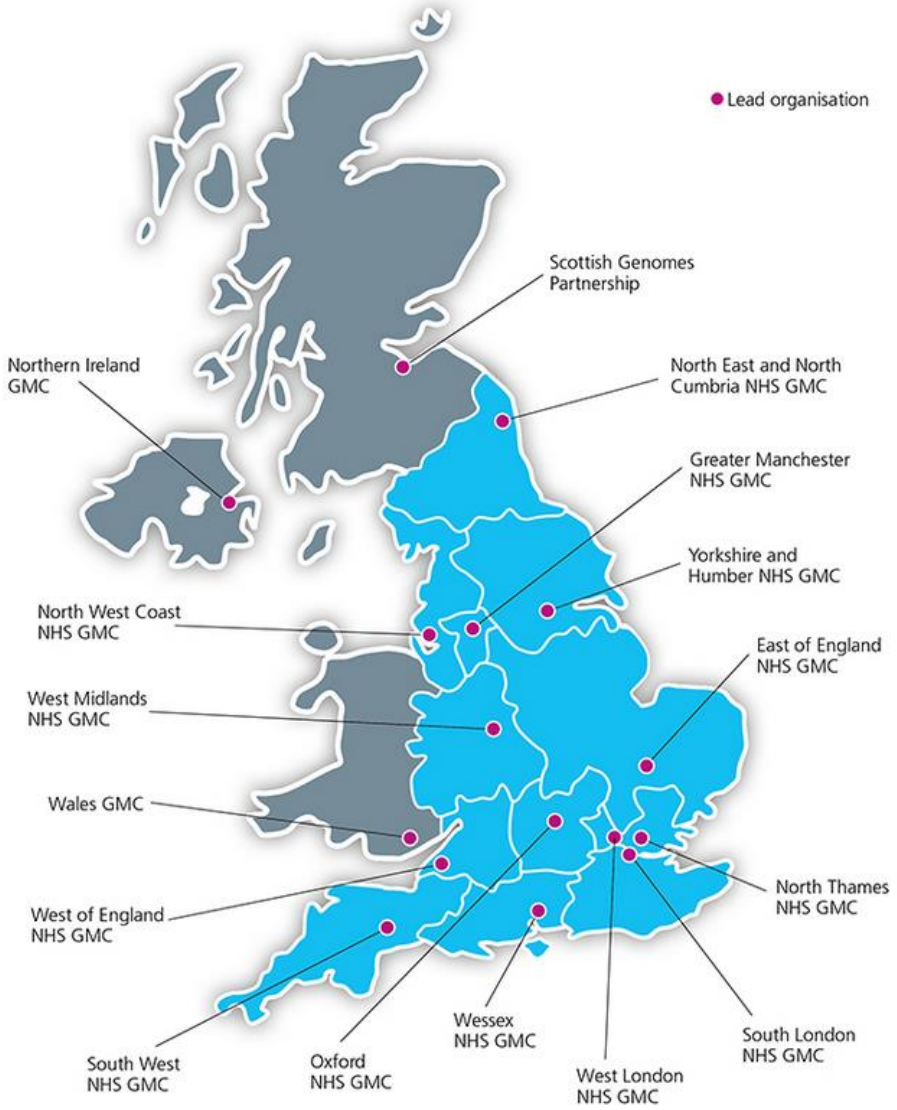
- Genomic literacy
- Risk stratification
- Diagnosis
- Pharmacogenomics
- New biomarkers/targets/ in Multimorbidity
- Patient ownership

10 years

- Desk top sequencers
- Age appropriate screening
- Artificial intelligence applications around interrogation and applications of the EHR e.g rare diseases
- Databases that utilises epigenetics influenced by social factors

Genomics Medicine Centres:

- 7 nationally
- Established by Genomics England
- Formed by Regional Genetics Services



Pathogenic variant:

- An alteration in genetic sequence that increases an individuals' susceptibility or predisposition to a certain disorder

Benign variant:

- An alteration in genetic sequence which is not disease-causing

Variant of unknown significance:

- A variation in a genetic sequence whose association with disease risk is unknown.

REASON FOR REFERRAL: Genetic testing for *HFE*-related hereditary haemochromatosis

PATIENT GENOTYPE: CY HH*
INTERPRETATION This patient carries a single copy of the C282Y mutation. The H63D variant has not been detected. Therefore, **this patient is unlikely to be affected with *HFE*-related hereditary haemochromatosis but is a carrier.** Please note that this test will not exclude other forms of haemochromatosis and iron overload. There is a 50% chance that this patient will pass the C282Y mutation on to any of their children. The likelihood of a predisposition to *HFE*-related hereditary haemochromatosis in any children will depend on the genotype of both parents.

What's needed?

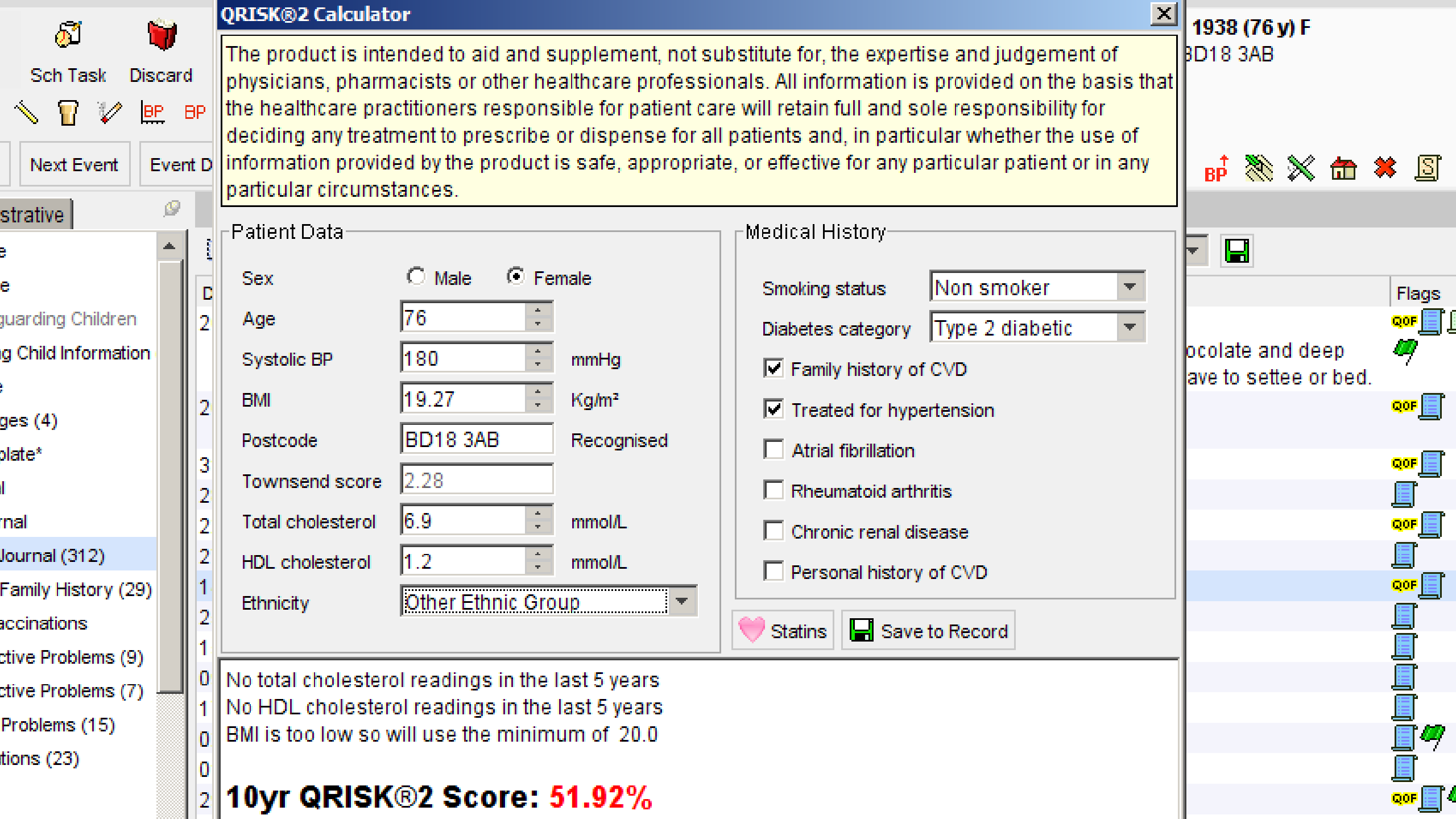
1. Facilitate adoption and diffusion of new knowledge
2. Education and training requirements
3. Models of Care and new ways of working, primary and secondary care taking into account current demands

MRCGP Curriculum

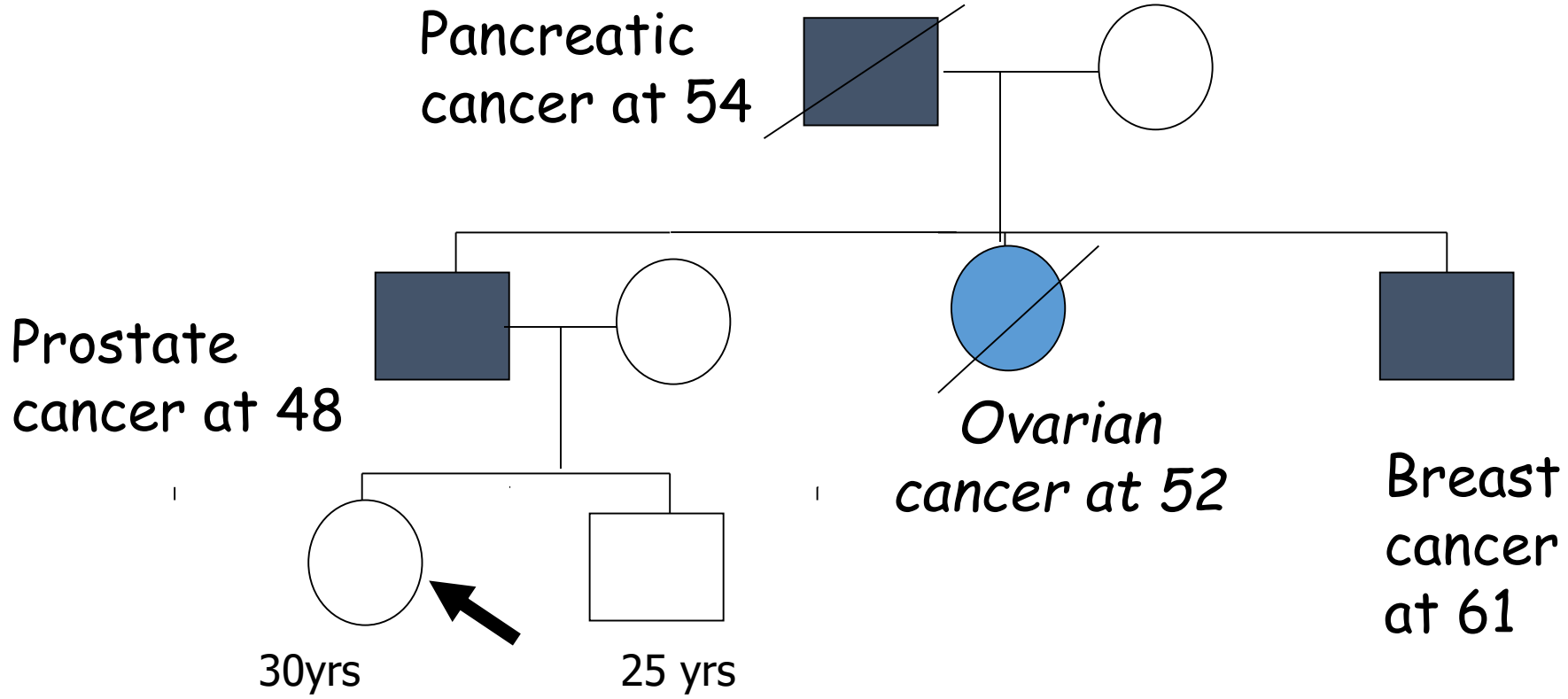
- Overview of the common genetic conditions
- The importance of family history
- Attitudinal and holistic care
- The societal impact of genetics
- Awareness of the impact of new technology

How Non Invasive Prenatal Testing (NIPT) fits into the screening pathway:

- The UK National Screening Committee (UK NSC) has recommended introducing NIPT to the fetal anomaly screening pathway. There will be an evaluative rollout
- NIPT will be an additional option, for those women who have a higher chance (1 in 2 to 1 in 150) of having a baby with Down`s, Edwards` or Patau`s syndrome following combined or quadruple screening (singleton pregnancy only).
- **NIPT will not be offered as a standalone test**


QRISK®2 Calculator
The product is intended to aid and supplement, not substitute for, the expertise and judgement of physicians, pharmacists or other healthcare professionals. All information is provided on the basis that the healthcare practitioners responsible for patient care will retain full and sole responsibility for deciding any treatment to prescribe or dispense for all patients and, in particular whether the use of information provided by the product is safe, appropriate, or effective for any particular patient or in any particular circumstances.
Patient Data
Sex
Male
Female
Age
76
Systolic BP
180
mmHg
BMI
19.27
Kg/m²
Postcode
BD18 3AB
Recognised
Townsend score
2.28
Total cholesterol
6.9
mmol/L
HDL cholesterol
1.2
mmol/L
Ethnicity
Other Ethnic Group
Medical History
Smoking status
Non smoker
Diabetes category
Type 2 diabetic
Family history of CVD
Treated for hypertension
Atrial fibrillation
Rheumatoid arthritis
Chronic renal disease
Personal history of CVD
Statins
Save to Record
No total cholesterol readings in the last 5 years
No HDL cholesterol readings in the last 5 years
BMI is too low so will use the minimum of 20.0
10yr QRISK®2 Score: 51.92%
1938 (76 y) F
BD18 3AB
Flags
Sch Task
Discard
Next Event
Event D
Journal (312)
Family History (29)
Problems (15)

Risk stratification



Pharmacogenomics in Practice: embracing technology, stratifying and personalising

Why?:

- **Prescribing safely**
  - An average GP authorises 200 repeat prescriptions each week
- **Manage Multimorbidity and Polypharmacy**
  - GPs have an average of 41.5 patients a day – higher than the 25 recommended as safe by European GPs
- **Promote Patient adherence** (Approximately 50% of all GP appointments are for patients with long term conditions)
- **Because we have** :
  - Decision support/the Electronic Health Record (EHR)

I: Has the case for the evidence been made?

Curated, peer-reviewed guidelines that translate laboratory test results into actionable prescribing decisions ?

- The Dutch Pharmacogenetics working group which has published guideline on over 53 drugs and 11 genes .
- Clinical Pharmacogenetics Implementation Consortium
- PharmGKB remains a good repository for such guidance.
- Role of regulators e.g FDA labelling – does this not signal strong evidence?
- NIHR portfolio studies and guidance on genomics research in practice

II: What model of care should we use?

- **In primary care, a feasibility study** using pharmacogenetics testing with clinical decision has been done and research activity continues (Dawes et al 2016). Patients were identified and stratified into the commonest presenting in primary care with actionable pharmacogenetics tests
- **Primary Outcome**: was ability to obtain and genotype samples
- **Secondary outcome**: The secondary outcomes were yield and purity of DNA samples, ability to link results to decision support software and use of the decision support software.

  Results: Genotyping resulted in linking of 189 patients (99%) with pharmacogenetic reports to the decision support program. A total of 96.8% of samples had at least 1 actionable genotype for medications included in the decision support system.

SUMMARY OF RESULTS

RED CATEGORY

Based upon the patient's results, the medication has **potentially reduced efficacy or increased toxicity**.

Medication change or dose adjustment with increased monitoring is highly recommended with this drug.

Drug	**Findings**
Clopidogrel (Plavix)	Reduced Response to Clopidogrel

- Genotype: CYP2C19 *1/*9

Evidence Level: Actionable

- **Adult Guidelines**

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

Pediatric Guidelines

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Pediatric Guidelines

The pharmacogenetic recommendations for clopidogrel based on CYP2C19 genotypes in adults may be used with caution in children and adolescents and should be accompanied by close monitoring and testing of platelet function.

Potential benefits of genetic profiling Over the counter testing

- More information
- allows early intervention
- allows more personal control
- possibility of saving public healthcare resources if testing and treatment conducted privately
- can alert relatives to important genetic conditions

Potential harms of genetic profiling

- The test results can be unreliable and difficult to interpret
- ‘Good’ results may lead to complacency in lifestyle
- Learning about risk of disease could be upsetting, particularly if no treatments are available
- There is potential for misuse of personal genetic information
- People may seek unnecessary further tests or advice from their doctor

Report of Molecular Genetic Analysis for Targeted Gene Panel

Patient name:		Referred by:	
		Unit:	Yorkshire Regional Genetics Service
DOB:		Date requested:	13 Jul 2018
Sex:	Female		
NHS No.:		Leeds Pedigree:	
Patient no.:		Leeds Lab no:	
Sample type:	Blood		
Test reason:	BRCA1 & BRCA2 analysis. Affected with ovarian and breast cancers. Family history of ovarian cancer.		

Results and Interpretation:

Test	Result	Lab Ref
Targeted gene sequencing	**BRCA1 c.2560_2561dup heterozygote**	NGS18-143
Targeted gene dosage analysis	**no mutation detected**	NGS18-143

This patient has been screened for variants in BRCA1 and BRCA2 by sequence and dosage analysis. This patient is heterozygous for the pathogenic BRCA1 variant c.2560_2561dup p.(Gln855fs).

This result is consistent with the patient's affected status, and the patient is at high risk of developing further BRCA1-related cancers.

This result may have important implications for other family members and testing is available if appropriate. We recommend that those relatives are referred to their local Clinical Genetics department.

Summary:

This patient is heterozygous for the pathogenic BRCA1 variant c.2560_2561dup.

Test reason: Analysis of cancer predisposing genes.
Affected with breast cancer. Family history of cancer.

Results and Interpretation:

Test	Result	Lab Ref
Targeted gene sequencing	**MSH6 c.17C>G heterozygote**	NGS18-105
Targeted gene dosage analysis	**no mutation detected**	NGS18-105

This patient has been screened for variants in the following cancer predisposing genes by sequence and dosage analysis:

ATM*, BRCA1, BRCA2, BRIP1, CHEK2*, MLH1, MSH2, MSH6, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53.

This patient is heterozygous for the MSH6 sequence variant c.17C>G p.(Thr6Ser). This variant is predicted to cause the conservative substitution of a highly conserved amino acid residue and in silico analyses are inconclusive[1]. It has not been reported in patient cohorts, but is absent in population control datasets[2]. In the absence of further evidence, this variant is of uncertain clinical significance. Predictive testing is not indicated for relatives.

Please note: sample labelling did not comply fully with laboratory acceptance criteria; identity was confirmed by the requester.

Summary:

This patient is heterozygous for a MSH6 variant of uncertain clinical significance.
This finding in isolation is insufficient to justify change in clinical management.

Resources

RCGP Genomics page:

- www.rcgp.org.uk/clinical-and-research/our-programmes/innovation/genomics-in-medicine.aspx

4 webinars:

- Familial Cancer, Rare Disease, NIPT, Ethics

4 podcasts

Resources

HEE Primary Care area: Disease summaries

- www.genomicseducation.hee.nhs.uk/resources/genetic-conditions-factsheets/

Gen-Equip Genetics education for primary care: modules / webinars

- www.primarycaregenetics.org:

For patients:

- www.geneticalliance.co.uk
- Condition-specific websites (www.hda.org.uk)

Thank you!