

January 2016

Dr Imran Rafi
Dr Judith Hayward

Contact
irafi@sgul.ac.uk

General practice and genomics

Clinicians have always personalised patient management. There is a growing momentum to improve this further through the integration of genomic information into clinical care. This will incorporate powerful new tools through which clinicians can further tailor healthcare, improving disease prevention, prediction, diagnosis and treatment.

Advances in genetic technology and understanding, coupled with an increasing patient demand for genetic and genomic investigation, is driving this momentum. The healthcare workforce including General Practitioners (GPs) needs to be empowered to identify the opportunities for genomic medicine and feel confident in their skills to deliver personalised care effectively and compassionately. They will need to have sufficient understanding of genomics to communicate effectively, support their patients and institute appropriate management.

Making a detailed diagnosis

This requires an understanding of pathology at a molecular level, which is now made possible by rapid, affordable sequencing of the genetic code (human and microbial / viral). Deciding when to use these tests and how to interpret their results will become important parts of medical practice. Even where GPs are not using these tests directly, they need to be aware of the implications for patients and their families going through secondary and tertiary care.

Cancer

It is perhaps in the area of cancer where GPs are currently experiencing the greatest impact from genomics. With over 330,000 new cases diagnosed in the UK each year across a range of different sites, GPs have an important role to play both in supporting patients through diagnostic and treatment processes (see example 1) and in using knowledge of genomics for disease prevention. Testing of both the patient's own genetic makeup ('germline' DNA) and the tumour DNA ('somatic' testing) are important here.

A small proportion of cancers (around 5%) are due to familial cancer syndromes such as breast or ovarian cancer associated with mutations in the *BRCA1* or *BRCA2* genes. This is relevant for the care of the patient with cancer, and also for the identification of risk in family members so that prevention, in the form of increased monitoring, screening (e.g. mammography) or treatment (e.g. chemotherapy or prophylactic mastectomy) can be offered. Such syndromes should be suspected in families who have multiple members affected with cancer, particularly at younger ages, with specific cancer types or with unusual cancers such as male breast cancer.



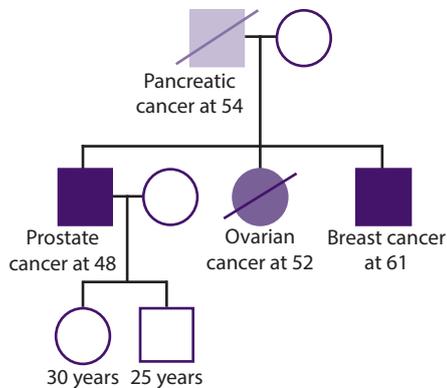
Example 1

Testing the germline DNA in ovarian cancer patients for *BRCA1* or *BRCA2* mutations influences the choice of chemotherapeutic agent. So-called Poly ADP ribose polymerase (PARP) inhibitors are more efficacious in individuals who carry a *BRCA* gene mutation.

"My mother had breast cancer when she was only 47, and I'm 40 now. Can I have a mammogram? Her brother had it in his 60s but I don't think that's relevant as he's a man."

*"My sister has had a *BRCA1* gene test and carries a gene change. What does this mean for me and can I have a test too?"*

Recognising the high risk cancer family



Key

-  Square indicates male
-  Circle indicates female
-  Line Indicates individual is deceased
-  Shading indicates individual is affected by the condition

"My father and brother both have a problem with learning or picking up things quickly. Is it hereditary?"

"My mother had the same type of epilepsy as me. Does this mean my children are at risk?"

Advances in genetic knowledge and sequencing have led to the development of new genetic tests for rare monogenic diseases. With older technologies, these tests were expensive and time-consuming, and were usually offered as single-gene tests as determined by genetics specialists. Increasingly, new technologies allow for these single genes related to the suspected condition to be gathered together into multiple 'panels' of genes and tested in parallel, at vastly reduced time and cost.

As more patients get access to testing either through research programmes, as part of clinical care, or by direct to consumer testing from commercial companies they will turn to primary care for discussion and advice.

The detection of a tumour's genetic signature may be used to make a precise diagnosis, enabling a more accurate prognosis and better tailored treatment. Increasingly, drugs are available that are targeted to the genetic features of a cancer, requiring genetic testing of the cancer cells to determine their potential response.

Rare diseases

Rare diseases, which are predominantly genetic in origin, affect 1 in 17 of the population and therefore make up a proportion of the clinical caseload in all specialties including primary care.

Making a detailed diagnosis is increasingly important for rare disease as there is now much greater understanding of underlying pathology, likely natural history, responsiveness to various treatments and best forms of overall management. Genomic tests now increasingly make this possible.

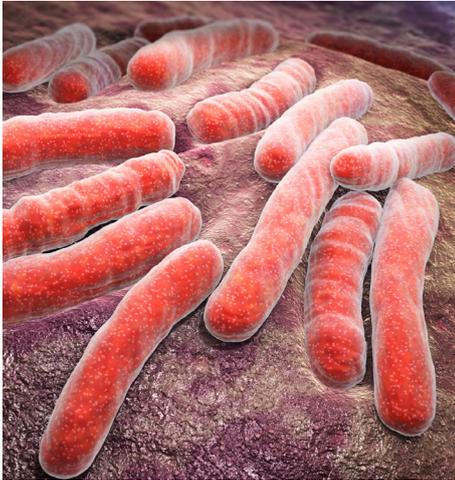
Once detailed diagnosis of a rare condition is made, one of the important roles in general practice is to be alert to the complications and monitor and manage appropriately. For example, in polycystic kidney disease (PKD) patients need regular and tailored surveillance involving monitoring of blood pressure and renal function, particularly close care during pregnancy and being alert to other complications such as intracranial cerebral problems.

Another important dimension of rare genetic disorders is the familial element. The GP must always be aware of the potential for disease in relatives of affected patients and should give appropriate advice.

Common complex diseases

All diseases result from a combination of genetic and environmental factors. Common disorders such as diabetes, obesity, heart disease and most cancers are all influenced by underlying susceptibility as well as the surrounding environment and the lifestyle the individual chooses to adopt. Whilst background public health measures and general health promotion are key to better health at the population level, as the potential of personalised medicine develops it is likely that prevention (for example diet or weight loss programmes) will also become increasingly tailored to the particular individual and interventions such as breast or prostate screening may be offered according to underlying risk.

'Where did this outbreak originate from?'



Mycobacterium Tuberculosis

"I would like to start a statin, but am concerned as it gave a friend of mine lots of pain."

Example 2

Statin induced myopathy is a reported side effect for some patients. There are variants in the genes involved in statin pharmacokinetics linked to statin-induced myopathy. A gene variant which encodes for a hepatic carrier transporter can predict a high risk of myopathy associated with simvastatin use. Guidelines advocate avoiding the prescribing of the 80mg strength dose of simvastatin and / or prescribing an alternative statin (Wilke RA *et al.* 2012) in patients who are known to have a 'poor metaboliser' genotype - such genetic information will be increasingly available at the point of care.

Infectious diseases

In infectious disease, genome sequencing of the pathogens can, in principle, be used to diagnose infections and determine likely susceptibility to antimicrobials. For example, genomics is likely to become a key part of TB management within the next few years, as genome sequencing provides diagnostic and drug susceptibility information more rapidly (potentially within 2-3 weeks) than current laboratory methods. For most infections managed in primary care or other community settings, however, diagnosis and treatment management using genomic information will only have an impact once suitably accurate, cheap and reliable point of care diagnostic devices based on sequencing are available.

The detailed and high-resolution information obtained by sequencing a pathogen from a patient can be used to make a diagnosis and inform treatment, but is also important in a public health context for understanding how diseases spread in the community. Public Health England has already established a service using whole genome sequencing (WGS) to investigate community outbreaks of Salmonella infections, using genomic information to detect outbreaks, rule cases in and out of the outbreak and to identify the source of infections. They are also piloting this approach for enhancing the effectiveness of epidemiological investigation of potential TB outbreaks.

Pharmacogenetics and treatment

With the development of rapid sequencing assays, and multiple gene panels, it is anticipated that testing for relevant genetic variants that influence both drug efficacy and drug safety will be increasingly used to aid both drug and dosage selection and this will be relevant with different population groups.

Developing intelligent decision support systems that allow the use of genomic and clinical information to aid prescribing drugs at the right dose will be important in the future. Such information is being incorporated into the summary of product characteristics of individual drugs, and is reflected in the guidance provided by regulatory agencies such as the European Medicines Agency (see example 2).

Ethical, legal, social and organisational implications

There are a number of broader challenges that will influence the use of genomic medicine. These include:

- Developing skills and expertise in genomics within the wider health professional workforce
- Issues relating to patient communication, privacy and consent (particularly for genomic testing in children)
- Handling uncertain, unexpected or incidental findings from genomic tests in clinical practice

Further Information and Resources

The Royal College of General Practitioners. MRCGP Curriculum statement on Genetics 3.02.

www.rcgp.org.uk/training-exams/gp-curriculum-overview/~media/Files/GP-training-and-exams/Curriculum-2012/RCGP-Curriculum-modules.ashx

Cancer genetics module on the RCGP elearning platform:

elearning.rcgp.org.uk/course/

HEE Genomics Education Programme
Health Education England
Information on genomics education including HEE sponsored MSc., Diploma, PG Certificate and CPPD genomics courses

0121 695 2374

genomicseducation@wm.hee.nhs.uk

www.genomicseducation.hee.nhs.uk

Online module, St George's, University of London, The Genomics Era: the future of genetics in medicine

www.futurelearn.com/courses/the-genomics-era

UK Genetic Testing Network (UK GTN)

0203 350 4999

ukgtn@nwlcslu

ukgtn.nhs.uk

UK Pharmacogenetics and Stratified Medicine network.

www.uk-pgx-stratmed.co.uk

Statins benefit and risks drug safety update

www.gov.uk/drug-safety-update/statins-benefits-and-risks

Wilke RA, Ramsey LB, Johnson SG *et al*. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther.* 2012;92:112–117.

- Implications of significant results for other family members
- Bioinformatics provision and secure genomic data storage and access within the health service
- Impact of genomics on current healthcare services, resources and patient pathways (including equity of access to genomic tests)
- Developing intelligent decision support systems that allow the use of genomic and clinical information to aid in the prescribing of drugs at the right dose
- Clarifying risks and benefits associated with using genomic tests for opportunistic screening

The future

The last two decades have seen unprecedented investment in life sciences in the UK. Advanced technologies are now available to sequence the entire genome at a cost of a few thousand pounds in as little as 24 hours, and it is envisaged that this cost will fall considerably over the next few years. More recently, the Government has signalled its confidence in the power of genomic science to produce major health benefits for the population through its investment in the 100,000 Genomes Project. However, achieving these benefits will depend on the ability of clinicians to use these new technologies effectively, efficiently and responsibly, for the population as a whole. Genomics can no longer be left to specialists and enthusiasts, but must be grasped by every clinician throughout the NHS.

Through the 'Clinical Champions' network, the Royal College of Physicians aims to promote education and training in genomics within every specialty. This will ensure that clinicians of the future are ready to capitalise on all of these new developments to provide personalised care for their patients.



Health Education England



**Royal College
of Physicians**

phgfoundation
making science work for health