

September 2016

Ian A Cree

University Hospitals Coventry and
Warwickshire, Coventry**Contact**

iancree@gmail.com

Pathology 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 diagnostic tools through which clinicians can further tailor healthcare, improving disease prevention, prediction, diagnosis and treatment.

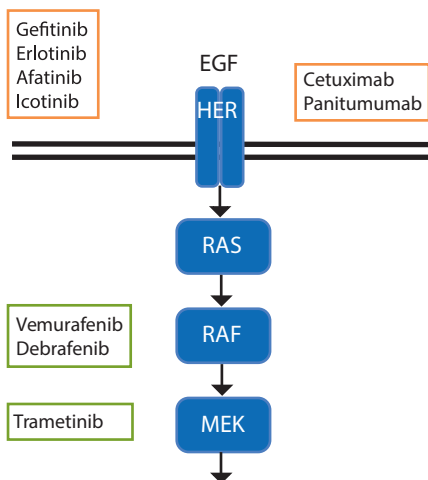
Advances in genetic technology and understanding, coupled with an increasing patient demand for genetic and genomic investigation, is driving this momentum. All those working in pathology need to identify the opportunities for genomic medicine that affect their specialty and feel confident in their skills to deliver and explain molecular diagnoses to their clinical colleagues.

Making a detailed diagnosis

Disease diagnosis alone is increasingly insufficient: pathologists are asked to provide information on prognosis and to predict which treatments patients may require. Many of the tests used to provide this information are based on an understanding of pathology at a molecular level. In future, this will depend largely on 'omic' technologies, including those enabled by new rapid, affordable nucleic acid sequencing, as well as proteomic methods such as mass spectroscopy and immunohistochemistry. Deciding when to use these tests and how to interpret the results to guide management will become important parts of medical practice and will be an important role for pathologists (see Example 1).

Rare genetic diseases

The extent to which a disease is influenced by genetic versus environmental factors varies from disease to disease. In some, genetic factors are the predominant influence (*e.g.* inherited disorders of metabolism such as phenylketonuria). Rare diseases, 80% of which are genetic in origin, collectively affect 1 in 17 people in the UK population and therefore make up a proportion of the clinical caseload in all specialties. Although a single gene mutation may be responsible for disease in an individual patient, the causal mutations in any particular inherited disease may be found in one of several different genes (*e.g.* familial hypercholesterolaemia (FH) may be caused by four different genes involved in cholesterol metabolism). These diseases usually display a clear inheritance pattern if there are multiple cases within one family (*e.g.* autosomal dominant inheritance).



Example 1

Molecular pathways in cancer are now targetable by an increasing range of drugs, most of which need companion diagnostics to guide their use. However, there are disease-specific differences: small molecule inhibitors such as gefitinib, erlotinib, and afatinib work well in lung cancer, but are ineffective in colorectal cancer which does not have activating mutations of their target, the epidermal growth factor receptor (EGFR). Equally, some EGFR mutations are more susceptible to these drugs than others.

Advances in genetic knowledge and sequencing have led to the development of new genetic tests for rare monogenic diseases. In the past, 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 expense. Eventually, whole genome sequencing (WGS) may allow all such tests to be done at once, and it is likely that clinicians across multiple specialties will have access to the results.

Use of genetic testing will be supported by clinical guidelines, published testing criteria, and educational resources. However, it is recognised that expert support from clinicians and pathologists will still be required to help with interpreting the results from larger panels or WGS, as there is a greater risk of finding changes in the genome that are of uncertain significance. Ethical issues involving family members may also need to be addressed.



Mycobacterium tuberculosis (MTB)

Example 2

Tuberculosis is known to be associated with environmental factors and co-existing immunosuppression, but is up to 50% associated with genetic predisposition.

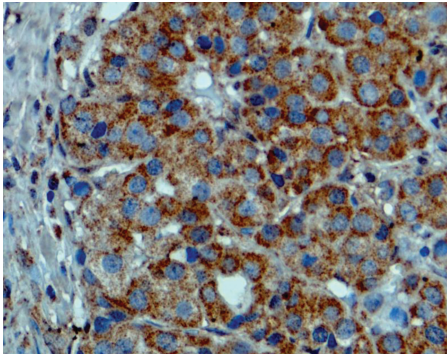
Genetics of common complex diseases

Most common diseases including autoimmune disorders, cancer, and infectious disease are complex in aetiology, caused by a combination of environmental risk factors and an underlying genetic susceptibility (see Example 2). Recent advances in medical genetics have led to a more comprehensive understanding of the contribution to different diseases of genetic factors and normal genetic variation between individuals. As well as contributing to a greater understanding of pathways involved in disease mechanisms (which are potential targets for drug development), investigation of rare cases of 'genetic' disease has been important for understanding the more common forms of a disease.

Pharmacogenetics and treatment

In addition to providing detailed diagnostic support, pathologists may also be involved in the provision of laboratory tests that help to guide treatment by understanding the variability in individual responses to medicines. This can be due to differences in the way a drug is handled in the body (pharmacokinetics) and/or variation in the drug targets (*e.g.* receptors, enzymes, ion channels *etc.*).

Knowledge of the genomic influences in these processes, when combined with clinical risk factors can provide insights into how a patient will respond in terms of efficacy to a given drug which may alter drug choice and/or dose. This information can also predict susceptibility to adverse drug reactions, including those at the more severe end of the spectrum, such as warfarin toxicity. With the development of WGS 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.



BRAF V600E immunohistochemical staining, image reproduced with kind permission from RevMab Biosciences USA, Inc

Example 3

BRAF mutation in melanoma shown by immunohistochemistry for the abnormal protein.

Cancer

With over 330,000 new cases in the UK each year, cancer patients are diagnosed and cared for across all specialties within the healthcare service. Again, genomics is transforming care in this area. The detection of a tumour's genetic signature may be used to provide a more accurate prognosis and better tailored treatment for individual patients. 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 (see Example 3). Examination of free tumour DNA in body fluids in cancers may also be used to identify mutations, avoiding the need for biopsy.

A small proportion of cancers (around 5-10%) are due to inherited cancer syndromes (e.g. breast cancer with *BRCA1* or *BRCA2* mutation). These usually occur in families where multiple individuals have had cancer of one or more specific types. Demand for testing for these has increased thanks to greater awareness of these conditions amongst clinicians and patients. *BRCA* mutation testing of breast and ovarian tumours is also relevant in sporadic cases, as these patients respond well to platinum-based chemotherapy.

Personalised prevention using genomics

Personalised prevention recognises that people differ in their risk of disease and in their likely response to preventive interventions. Genetic differences account for some of this variation. Testing may be used to identify individuals with rare mutations associated with a high risk of disease (such as FH or breast cancer) to whom different preventive measures may be offered. It is also anticipated that testing for a range of genetic susceptibility variants for common diseases such as cardiovascular disease or colorectal cancer will become routinely feasible and such data could be incorporated into risk assessment tools, allowing individuals to be more accurately placed into different risk groups and preventive programmes offered accordingly.

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
- Implications of significant results for other family members
- Bioinformatics provision and secure genomic data storage and access within the health service

Further information and resources

RCPATH Molecular Pathology Guidance
jcp.bmj.com/content/early/2014/07/10/jclinpath-2014-202404

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 (UKGTN)
0203 350 4999
SECSU.UKGTN@nhs.net
ukgtn.nhs.uk

UK Pharmacogenetics and Stratified Medicine network.
www.uk-pgx-stratmed.co.uk

Normanno N, Cree IA. Genomics-driven oncology: challenges and perspectives, BMC Cancer 2015; 23 (15): 141.

Cree IA, Deans Z, Ligtenberg ML et al. Guidance for laboratories performing molecular pathology for cancer patients. J Clin Pathol. 2014; 67 (11): 923-31.

- 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, and pathologists of all specialties are likely to be at the forefront of this revolution in medical practice.

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