Gastroenterology and genomics

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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 needs to be empowered to identify the opportunities for genomic medicine and feel confident in their skills to deliver personalised care effectively and compassionately.

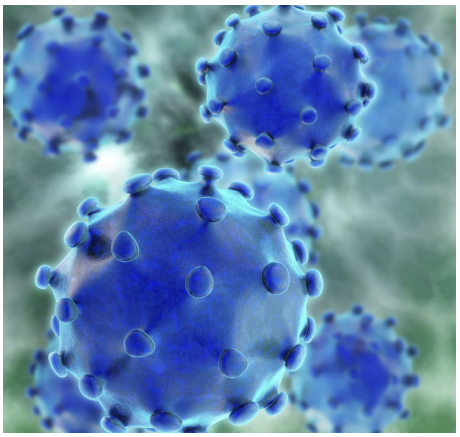
Making a detailed diagnosis

Precision of diagnosis including the identification of disease subtypes directly influences optimum care and treatment. 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 (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.* familial adenomatous polyposis). 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.* Hirschprung disease). These diseases usually display a clear inheritance pattern if there are multiple cases within one family (*e.g.* autosomal dominant inheritance).

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 wereusually 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. It is likely that clinicians across multiple specialties will have



Example 1: Hepatitis C Virus (HCV) Genotyping

The HCV genome displays a large amount of genetic diversity, with at least six different genotypes and numerous subtypes known. Determination of the HCV genotype is essential for making decisions about treatment, as the regimens, dosing, and duration of therapy, as well as the likelihood of response to treatment, vary across the genotypes. As sequencing costs fall, it will become possible to routinely sequence the critical areas of the HCV genome that determine the genotype and subtype, allowing better tailoring of treatment to eradicate infection.

Example 2: The Role of *NOD2* in Inflammatory Bowel Disease

Rare families with a history of Crohn's disease in multiple related individuals have been extensively investigated to identify any predisposing genes that may increase the risk of developing the condition. One candidate gene identified via this route was NOD2, located on chromosome 16. Further research showed that the protein encoded by this gene activates nuclear factor kappa B in response to muramyl dipeptide, a fragment of bacterial peptidoglycan. This process is deficient in patients with the mutant form of NOD2, and is thought that this leads to failure of early immune pathogen clearance and an increased susceptibility to bacteria-induced intestinal inflammation.

Example 3:Thiopurine Methyltransferase (TPMT) Testing

Azathioprine (AZA) is an important immunomodulatory drug, used for example to treat inflammatory bowel disease. AZA is converted to its active metabolites by several enzymes, the most critical of which is TPMT. Low levels of TPMT activity results in the overproduction of AZA metabolites that are toxic to bone marrow, leading to bone marrow suppression and potentially life-threatening side effects. TPMT activity is influenced by polymorphisms in the TPMT gene, some of which lead to higher risk of adverse side effects from AZA treatment. Genotyping of the TPMT gene using sequencing (as well as assays directly measuring TPMT activity) can predict patients at higher risk of AZA toxicity, and help in personalising the dose and choice of immunosuppressant.

access to these tests, and eventually to tests for all genes or even the whole genome. The UKGTN website provides information on genetic tests that are currently listed on the NHS directory of genetic tests. NHS test development is now focusing on panel tests, enabling diagnosis at an earlier stage of investigation.

Use of genetic testing will be supported by clinical guidelines, published testing criteria and educational resources (useful contact details for support are provided at the end of this document). However, it is recognised that expert support will still be required to help with interpreting the results from larger panels, as there is a greater risk of finding changes in the genome that are of uncertain significance. Complex ethical issues involving family members may also need to be addressed.

Genetics of common complex diseases

Most common diseases (*e.g.* inflammatory bowel disease) are complex in aetiology, caused by a combination of environmental risk factors and an underlying genetic susceptibility. 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 (see Example 2).

Pharmacogenomics and treatment

Even after taking into account disease subphenotypes, there is considerable variability in individual responses to medicines which can be due to differences in the way a drug is handled in the body (pharmacokinetics) and / or variation in the drug targets (for example, 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 (see Example 3). 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. 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 and the FDA.

Example 4 : Tumour Testing For RAS Mutations

The chemotherapy drugs cetuximab and panitumumab, used for treating metastatic bowel cancer, target the epidermal growth factor receptor (EGFR) signalling pathway to inhibit tumour growth. Their efficacy relies on the tumour cells retaining normal KRAS and NRAS proteins; those tumour cells that have a mutated, overactive KRAS will be resistant to anti-EGFR therapy. NRAS mutations can also impair responsiveness to anti-EGFR therapy and it is important to assess both KRAS and NRAS (collectively known as RAS) status to identify which patients will respond to anti-EFGR therapy. Testing of bowel tumour samples for activating RAS mutations is now used to determine which patients are most likely to benefit from anti-EGFR therapy. This has the potential to improve survival by identifying responders and to generate cost savings by identifying non-responders.

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 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 (see Example 4). Examination of free tumour DNA in body fluids may also be used to monitor treatment response and early relapse.

A small proportion of cancers (around 5-10%) are due to inherited cancer syndromes (*e.g.* Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer or HNPCC). 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, and might be incorporated into regular oncological care in the near future.

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 (*e.g.* Lynch syndrome), for which different preventive measures may be offered (*e.g.* screening colonoscopies).

Currently, such individuals are usually identified through clinical diagnosis or cascade testing within families. However, the wider availability of genome-wide testing may soon mean that patients learn about these risks unexpectedly when tested for other clinical reasons.

It is also anticipated that testing for a range of genetic susceptibility variants for common diseases (*e.g.* coeliac disease) will become feasibleand such data could be incorporated into risk assessment tools, allowing individuals to be more accurately placed into different risk groups within the population.

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)

Further information and resources

British Society of Gastroenterology,
3 St Andrews Place, Regent's Park,
London, NW1 4LB
020 7935 3150
www.bsg.org.uk

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@nwlcsu
ukgtn.nhs.uk

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

Beyond gene discovery in inflammatory bowel disease: the emerging role of epigenetics. Ventham NT, Kennedy NA, Nimmo ER, Satsangi J.Gastroenterology. 2013 Aug;145(2):293-308. doi: 10.1053/j.gastro.2013.05.050.

Advances in IBD genetics. Van Limbergen J, Radford-Smith G, Satsangi J. Nat Rev Gastroenterol Hepatol. 2014 Jun;11(6):372-85. doi: 10.1038/nrgastro.2014.27

- 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
- 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.

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