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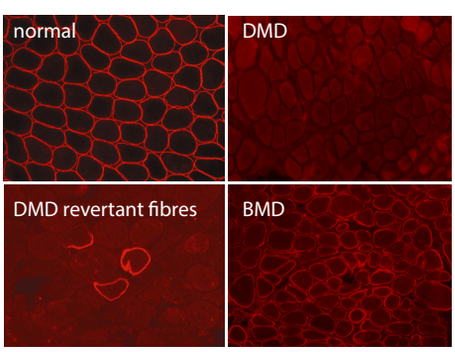
Neurology and genomics

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, are 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.



Example 1:

Dystrophin immuno-staining in normal muscle, Duchenne muscular dystrophy, Becker muscular dystrophy and "revertant" fibres relating to somatic variation in the Dystrophin gene (courtesy of Prof Caroline Sewry)

There are many types of muscular dystrophy which differ in inheritance, phenotype, prognosis and associated systemic features. The mainstay of the diagnosis of Duchenne muscular dystrophy has been muscle biopsy with immuno-histochemical identification of dystrophin deficiency. Genetic testing may now provide a more direct route to the disease subtype enabling more precise counselling, treatment and support, possibly even eventually replacing the need to biopsy.

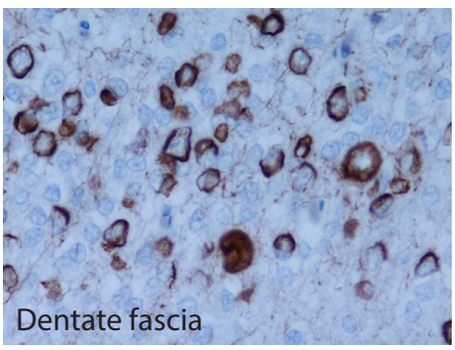
Making a detailed diagnosis

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). In some cases, genetic testing can avoid the need for an invasive procedure such as a nerve, muscle or brain biopsy.

Rare genetic diseases

The extent to which a disease is influenced by genetic versus environmental factors varies from disease to disease. In some diseases, for example Huntington's disease, genetic factors are the predominant influence. 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.* ataxia or Hereditary Spastic Paraparesis. 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 were usually offered as single-gene tests. Increasingly, new technologies allow for these single genes related to the suspected condition to be tested in parallel as 'panels' of genes, most recently using whole genome sequencing, and such approaches are increasingly cost effective. It is


Dentate fascia

Example 2:

Locus coeruleus neuronal alpha-synuclein inclusions in a family carrying a G51D alpha-synuclein mutation (courtesy of Dr Aoife Kiely and Prof Janice Holton)

Less than 5 % of Parkinson's cases are familial in nature. Study of the Contursi kindred, where the disease was known to be inherited, identified mutations in the alpha-synuclein gene responsible for a protein that aggregated into forms that deposited in Lewy bodies in Parkinson's Disease and other forms of brain atrophy. This has led to wider insights into disease pathogenesis in these conditions and potential therapies.

likely that clinicians across multiple specialties will have 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 such as Alzheimer's, Parkinson's, stroke and motor neurone disease are complex in aetiology, likely to be 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. Genome wide association studies have also increased understanding of disease pathways (*e.g.* genes implicated in multiple sclerosis are mostly concerned with inflammatory response and autoimmunity) and investigation of rare cases of 'genetic' forms of Parkinson's Disease have revealed pathological mechanisms likely to be implicated in the more common forms of disease (see Example 2).

Pharmacogenetics and treatment

Even after taking into account disease sub-phenotypes, 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.

Example 3:

Stevens-Johnson syndrome associated with carbamazepine

The risk of a serious cutaneous syndrome in patients taking carbamazepine for epilepsy or neuropathic pain is estimated at 1-4/10,000 users. In some cases, this can take the form of the serious and potentially fatal Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis (TEN). There is a strong association between the *HLA-B*1502* allele and susceptibility to SJS/TEN in the Han Chinese population. The FDA now recommends that Asian patients (including South Asian Indians) should be tested for *HLA-B*1502* and that Asian patients carrying this allele should not be prescribed carbamazepine unless the benefits clearly outweigh the risks.

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.

Cancer

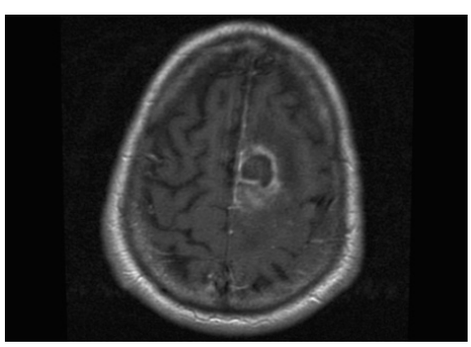
With over 330,000 new cases in the UK each year, cancer patients are diagnosed and cared for across all specialties within the healthcare service. Again, genomics is transforming care in this area. The detection of a tumour's genetic signature may be used to make a precise diagnosis, enabling a more 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. Furthermore, genetic analysis may be useful in determining response to treatment (Example 4).

A small proportion of cancers (around 5-10%) are due to inherited cancer syndromes, including neurological-cancer/tumour overlap syndromes such as Ataxia Telangiectasia, Neurofibromatosis Types 1 and 2 and Von-Hippel-Lindau disease. These usually occur in families where multiple individuals have had tumours of one or more specific types.

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 to whom different preventive and screening measures may be offered, for example Von-Hippel-Lindau disease. 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, such as *ApoE* ε4 and *TREM2* rare variants for Alzheimer's and GBA-Gaucher's risk alleles for Parkinson's, 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 within the population. This information could be combined with genetic risk profiles based on common risk variants identified in genome wide association studies. Currently we do not have preventative treatments for individuals in high risk groups and so the development of individual risk prediction is of uncertain value. However, there is intense activity in the development of potential new treatments and this area is likely to rapidly evolve.



Example 4:

Glioblastoma multiforme: Enhanced T1 weighted MRI showing left para-sagittal glioma (courtesy of Dr Jeremy Rees)

In the treatment of glioma, the DNA repair gene *O^6-methylguanine-DNA methyl-transferase* (*MGMT*) methylation status predicts the response to the chemotherapeutic agent temozolomide. Tumours with a methylated *MGMT* promoter are chemosensitive whereas unmethylated *MGMT* gene promoter tumours do not respond.

Further Information and Resources

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

Warner TT and Hammans SR. Practical Guide to Neurogenetics. 1st ed. Saunders; 2008. ISBN: 978-0-7506-5410-4.

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
- 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

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.

NHS
Health Education England

Royal College of Physicians

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