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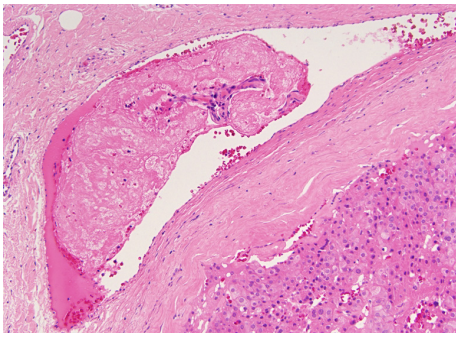
Endocrinology, diabetes and genomics

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.



Example 1

Familial hypocalciuric hypercalcaemia (FHH) is a rare autosomal dominant cause of hypercalcaemia that biochemically can be difficult to distinguish from primary hyperparathyroidism. Inactivating mutations within the calcium sensing receptor gene (*CASR*) cause decreased sensitivity to elevations in serum calcium and usually no active treatment is required. Identification of mutations in the *CASR* gene allows unnecessary additional investigations and inappropriate parathyroid surgery to be averted within the proband and within extended family members.

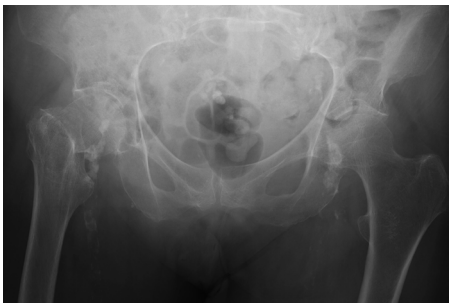
Advances in genetic technology and understanding, coupled with an increasing patient demand for genetic and genomic investigation, is driving this momentum. The healthcare workforce needs to be empowered to identify the opportunities for genomic medicine and feel confident in their skills to deliver 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.* Multiple Endocrine Neoplasia Syndrome Types 1 and 2). Rare diseases, 80% of which are genetic in origin collectively affect 1 in 17 people in the UK population, are typically life-long and therefore make up a significant proportion of the clinical caseload in all specialties. Although a single gene mutation may be responsible for a disease in an individual patient, the causal mutations in any particular inherited disease may be found in one of several different mendelian inherited genes, *e.g.* Congenital adrenal hyperplasia (CAH). 90-95% of CAH is as a result of a mutation in the *CYP21A2* gene, resulting in deficiency of the enzyme 21 hydroxylase within the steroid pathway. The remaining 5-10% is a result of mutations leading to deficiencies in other enzymes within the steroid pathway. Therefore identifying the correct gene to test is important in obtaining an informative genetic result but also identifies the different clinical presentations associated with the different enzyme deficiencies. These diseases usually display a clear inheritance pattern if there are multiple cases within one family. For isolated cases with multiple candidate genes, the inheritance pattern may vary and correct genetic advice is dependent on identifying the correct genetic cause.



Example 2

Osteoporosis is the commonest metabolic bone disorder, which due to our worldwide ageing population, is increasing in prevalence. Osteoporotic fractures cause significant morbidity and mortality as well as conferring a societal and financial burden.

Individual genome-wide association studies (GWAS) in the last decade have identified over 60 genome-wide-significant loci associated with low bone mineral density and a further 20 loci associated with increased risk of osteoporotic fracture.

Pathways and proteins that have been identified provide information on bone architecture and the pathophysiology behind osteoporosis. Greater insight into heritability and a better understanding of the pathogenesis provide hope in the future for genetically targeted drug therapies.

Until recently if several candidate genes existed for the same clinical presentation (heterogeneity) then each gene had to be tested sequentially. 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 access to these tests, and eventually to test for all genes or even the whole genome. One clear illustration of the benefit of 'panel' testing is in cases of phaeochromocytoma where it has been shown by utilising a panel of up to 10 candidate genes, a genetic cause is likely in almost 30% of cases rather than the figure of 10% quoted in older literature. Depending on the gene involved, there are significant implications for management of the proband's contra-lateral adrenal gland and also distant tumour and extended hormone monitoring. The follow up instigated for a causative *VHL*, *SDHB* or *RET* proto-oncogene would each be very different, both for the proband and extended family members. 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.* osteoporosis] 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 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 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. Knowledge of the genomic influences in these processes 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. With the development of rapid sequencing assays, and multiple gene panels, it is

Example 3

Hepatocyte Nuclear Factor 1-alpha **(***HNF1A***)** is the most common cause of maturity onset diabetes of the young (MODY) in the UK. A mutation in the *HNF1A* gene on chromosome 12q results in reduced insulin production and in particular post prandial hyperglycaemia after high carbohydrate meals.

Identification of this mutation has had significant impact on patient management as this patient group is highly sensitive to sulphonylureas; even at small doses *e.g.* 20-40mg gliclazide.

There is substantial evidence of patients initially diagnosed with type 1 diabetes being commenced on insulin that can be successfully converted to sulphonylureas after HNF1A-MODY diagnosis. Identification of MODY due to other causative genes can also substantially modify the proband's management and allow for early identification of at risk relatives.

Example 4

Mutations within the *RET* proto-oncogene have been identified in both inherited and sporadic forms of medullary thyroid cancer (MTC). *RET* is a receptor tyrosine kinase and molecular therapies targeted at *RET* and other kinases have shown great promise in the treatment of MTC. There is considerable variation in treatment response to tyrosine kinase inhibitors (TKIs) but further genetic and molecular stratification of tumours may have great potential to improve targeting of TKI therapies.

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 the guidance provided by the European Medicines Agency and 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 (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 most different cancer types (around 5-10%) are due to inherited cancer susceptibility. There are however, some cancer types where the proportion is higher, for example phaeochromocytoma and medullary thyroid cancers where up to 30% are due to an identifiable genetic cause or where endocrine tumours are part of a recognisable cancer syndrome, for example MEN1 and 2. Identification of the genetic basis allows appropriate management of the proband and accurate pre-symptomatic testing and appropriate management of the extended family. These options are only possible with knowledge of the genetic basis of these cancers. While these disorders are usually recognised in families where multiple individuals have had cancer of one or more specific types, alertness to the possibility of a de novo mutation in a sporadic cancer is important.

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.* Inherited medullary thyroid carcinoma (MTC) related to *MEN2A*, *MEN2B* or familial MTC, who require a prophylactic thyroidectomy. The age for this surgery is dependent on the specific identified *RET* mutation. 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.* type 2 diabetes and osteoporosis] may 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.

Further information and resources

Society for Endocrinology
www.endocrinology.org

Endocrine Society
www.endocrine.org

Diabetes UK
www.diabetes.org.uk

Diabetes Genes
www.diabetesgenes.org

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

Forlenza GP, Calhoun A, Beckman KB *et al.* Next Generation Sequencing in Endocrine Practice. Molecular Genetics and Metabolism. 2015: 115(2-3): 61-71.

Ethical, legal, social and organisational implications

- The following challenges will influence the use of genomic medicine
- 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

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

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