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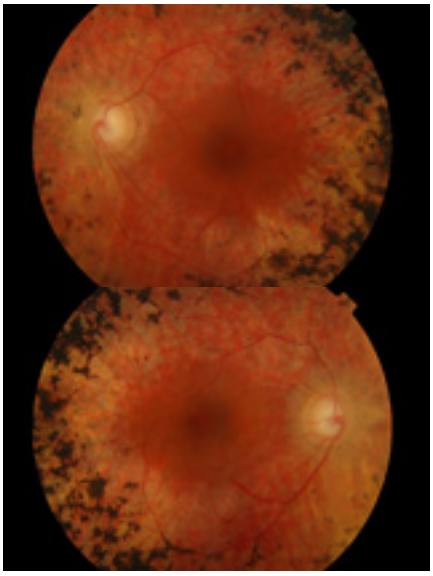
Audiovestibular medicine and genomics

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

Usher syndrome is an autosomal recessive condition in which hearing loss, usually from birth, is associated with progressive loss of vision due to a retinal dystrophy (retinitis pigmentosa). Early diagnosis is important, especially in the most severe type of Usher syndrome (type 1), in order to be able to offer early cochlear implant so that the child does not come to rely on visual means (sign language) as their only form of communication. Knowledge of which gene and what sort of mutation causes the Usher syndrome in an individual will become more important now that therapy trials are beginning for some forms of Usher syndrome.

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.

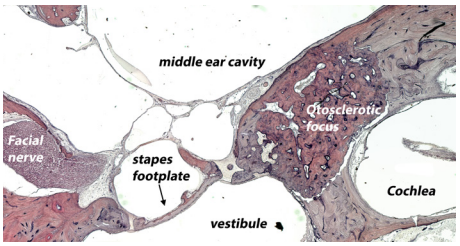
Making a detailed diagnosis

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 Example1).

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.* Pendred syndrome). 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.* Waardenburg syndrome). 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 as determined by genetics specialists. Increasingly, new technologies allow for these single genes related to the suspected condition to be gathered together into multiple



Temporal Bone Collection, UCL Ear Institute: Otosclerotic focus in the otic capsule, anterior to the stapes footplate.

Example 2

Otosclerosis is a frequent cause of hearing loss as a result of abnormal resorption and deposition of bone in the otic capsule. It has a complex aetiology with most cases likely to be due to an interaction between both genetic and environmental factors. Rare families in whom the condition is inherited as an autosomal dominant condition have indicated *TGFB1* as a possible genetic cause. The same gene has also been implicated as a factor in more common forms of the condition along with *COL1A1, BMP2, BMP4, AGT,* and *RELN*.

'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 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.

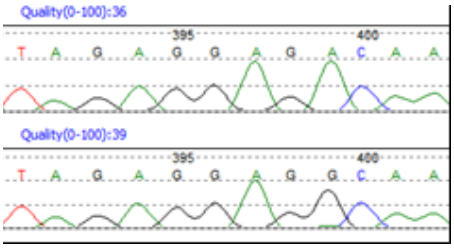
Genetics of common complex diseases

Most common diseases (*e.g.* age-related hearing loss) 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 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 Figure 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 3

One in 500 individuals with the mitochondrial mutation *m.1555A>G* are known to be exquisitely sensitive to the ototoxic effects of aminoglycoside antibiotics. People with the mutation may lose their hearing even if drug levels are maintained within normal limits. Anyone who has experienced hearing loss after aminoglycosides should be offered testing for the mutation. Maternally related family members should also be tested and counselled to avoid these drugs whenever possible. Other rarer mutations may also have a similar effect and testing is likely to become available in the future.

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. 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.* Neurofibromatosis type 2). 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 (for example it has been shown that rare genetic variants in genes which cause inherited Long QT syndrome, with or without deafness, may be enriched in people who have suffered from drug-induced Long QT syndrome). Alternative therapies may be offered to those with potassium channel gene variants. 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 noise-induced hearing loss) 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.

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

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

Parker M, Bitner-Glindzicz M. Genetic investigations in childhood deafness. Arch Dis Child. 2015 Mar;100(3):271-8. doi: 10.1136/archdischild-2014-306099. Epub 2014 Oct 16. Review. PubMed PMID: 25324569.

- 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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