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Rheumatology 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, 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. periodic fever syndromes). 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. classic Ehlers Danlos 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 '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

HLA-B27 genotyping in juvenile idiopathic arthritis: Testing for the presence of *HLA-B27* is used to confirm the diagnosis of the enthesitis-related subgroup of juvenile idiopathic arthritis. The arrow on the MRI scan shows inflammation at the enthesis of the Achilles tendon. Children who are *HLA-B27* negative have a better prognosis with a better response to treatment.



Example 2

Rheumatoid Arthritis: 101 genes are known to increase the risk of rheumatoid arthritis. Among them are the *CTLA-4*, *IL6R* and *TYK2* genes, which are the targets of biological therapies used to treat RA (abatacept, tocilizumab and tofacitinib, respectively).

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.

Genetic of common complex diseases

Most common diseases (*e.g.* rheumatoid arthritis) are complex in aetiology, caused by a combination of environmental risk factors and an underlying genetic susceptibility. Recent advances in genetics have led to a more comprehensive understanding of the contribution to different diseases of genetic factors and normal genetic variation between individuals. A greater understanding of pathways involved in disease mechanisms can identify potential targets for drug development; for example, the genes that predispose to the risk of rheumatoid arthritis are enriched for drug targets for medications already used to treat other conditions (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. 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 Food and Drug Administration (FDA).

Example 3

Thiopurine methyltransferase (TPMT)

Testing : Azathioprine (AZA) is an important immunomodulatory drug, used for example to treat systemic lupus erythematosus. 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 effects from AZA treatment. Genotyping of the *TPMT* gene using genotyping (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.

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. familial Mediterranean fever), to whom different preventive measures may be offered (e.g. colchicine). 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. risk of psoriatic arthritis in patients with psoriasis) 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
- 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

Further information and resources

British Society of Rheumatology
Bride House
18-20 Bride Lane
London
EC4Y 4EE
bsr@rheumatology.org.uk
www.rheumatology.org.uk

British Society for Paediatric and Adolescent Rheumatology
105 St Peter's Street
St Albans
Herts
AL1 3EJ
enquiries@bspar.org.uk
www.bspar.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@nwlcslu
ukgtn.nhs.uk

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

Okada Y, Wu D, Trynka G *et al.* Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014; 506(7488): 376-81.

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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