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Paediatrics 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).

Early genomic diagnosis and treatment in paediatric services will have a significant impact over the lifetime course of disease, alleviate some of the symptoms and could prevent secondary complications.

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. myotonic dystrophy type 1-DM1*]. 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 (see Example 2). These diseases usually display a clear inheritance pattern if there are multiple cases within one family (*e.g.* autosomal dominant inheritance).

A diagnosis made in timely manner, especially in childhood, will allow families to access appropriate reproductive health counselling.

Example 1: Monogenic diabetes of children and neonates

The prevalence of monogenic diabetes in the UK paediatric population is 2.5%. It is often not recognised, misdiagnosed as Type 1 and incorrectly managed. About 50% patients with monogenic diabetes are not diagnosed. Genetic characterisation of the commonest subtypes (8 GCK, 5 HNF1A, 4 HNF4A, 1 HNF1B, 1 ABCC8, 1 INSR) can prevent unnecessary insulin treatment, diagnostic delay and inappropriately estimated risk for family counselling. Neonates with monogenic diabetes (mostly with 6q24 abnormalities or *GATA6* mutations) can be born preterm. Moreover, 37% of preterm neonates with hyperglycaemia have a potassium channel mutation and improve by replacing insulin with sulphonylurea therapy.
Non-invasive prenatal testing in families would be beneficial for the clinical management of neonates.

Example 2: Congenital Myasthenic Syndrome (CMS)

CMS are inherited disorders of impaired neuromuscular transmission at the motor endplate. Different genetic mutations lead to diverse clinical phenotypes and prognosis, requiring different therapeutic options. The mainstay of diagnosis includes a thorough clinical evaluation with blood tests for circulating antibodies directed against AChR, MuSK; the voltage-gated P/Q type calcium channel tests for botulism in some infants, neurophysiological tests (EMG, RNS) and a muscle biopsy with electron microscopy (morphometric analyses). In some CMS there are no clinical clues to the genetic diagnosis. Here genomic sequencing offers a powerful alternative to costly and time-consuming analyses, as multiple genes can be screened for mutations in one test. This enables more rapid diagnosis of CMS and guides individualised therapy.

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 access to these tests, and eventually to tests for all genes or even the whole genome. The UK Genetic Testing Network (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, especially pre-symptomatic carrier testing and expanding neonatal screening for a variety of conditions.

Genetics of common complex diseases

Most common diseases 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 normal genetic variation between individuals and the contribution of genetic factors to different diseases. As well as adding 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 3).

Example 3: Early Infantile Epileptic Encephalopathies (EIEE)

These are progressive genetic epilepsies associated with cognitive and motor impairment and severe intellectual disability. EIEE are age-dependent, often refractory to antiepileptic medications with clinical and electro-encephalographic features that change as the central nervous system evolves. In recent years, next generation sequencing has revealed mutations in approximately 97 genes. This has helped the understanding of disease mechanisms and stratification of treatment such as prescribing a ketogenic diet for GLUT-1 (SLC2A1) deficiency and potential use of Fenfluramine for SCN1A or Retigabine for KCNQ2.

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 (*e.g.* 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 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 4). 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: Drug reaction with Eosiniophilia and Systematic Symptoms (DRESS)

DRESS is a hypersensitivity syndrome most commonly associated with antiepileptic drugs, allopurinol, and sulfonamides. Severe drug reactions lead to 1 in every 15 hospital admissions. Specific alleles of the human leukocyte antigens (HLA) interact with certain drugs, causing adverse reactions by triggering immune responses in exposed tissues. This has been demonstrated for antiepileptic drugs such as carbamazepine, oxcarbazepine and phenytoin (HLA B*15:02).

Cancer

There are over 330,000 new cases in the UK each year (including 1,600 in children under 15) and 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 personalised 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 5). 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. familial neuroblastoma*]. 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 families, and might be incorporated into regular oncological care in the near future.

Example 5: Childhood Cancers

Mutations in tumour-suppressor genes *RB1* and *TP53* can lead respectively to retinoblastoma (eye cancer) and osteosarcoma (bone cancer). Mutations in the *H3F3A* gene may cause glioblastoma, one of the commonest brain tumours in childhood. *CREBBP* mutations are found in relapsed acute lymphoblastic leukaemia (ALL). Mutations in the *ALK* and *PHOX2B* genes increase the risk of sporadic and familial neuroblastoma, a solid tumour of neuroblasts (immature nerve cells) in children <5 years.

In families with a history of childhood cancers (medullary thyroid carcinoma; RET gene mutations or Wilm's tumour; *WT1*, *CTNNB1*, *WTX* gene mutations) carriers can be identified with early genetic testing.

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 children with rare mutations associated with a high risk of disease (see Example 6), to whom different preventive measures may be offered [*e.g.* alternative antibiotic therapy]. In the UK the newborn blood spot screening already includes genetic tests for sickle cell disease and cystic fibrosis, whilst other conditions are usually identified through clinical diagnosis or cascade testing within families. However, the wider availability of genome-wide testing may soon mean that patients and parents/carers 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, heart disease or cancer] 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.

Example 6: Aminoglycoside-Induced toxicity in Mitochondria Mutations

Mitochondrial DNA mutations (T1095C, C1494T and A1555G in the *12SrRNA* gene) cause susceptibility to gentamicin toxicity, a commonly used antibiotic in neonates.

This commonly manifests as sensori neuronopathy or vestibulopathy depending on mutation penetrance. Knowledge of these mutations prior to antibiotic administration could prompt choice of alternative medications.

Further Information and Resources

Royal College of
Paediatrics and Child Health (RCPCH)
www.rcpch.ac.uk

HEE Genomics Education Programme
Health Education England
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

British Society for Genetic Medicine
www.bsgm.org.uk

Genetic Alliance UK
www.geneticalliance.org.uk

The 100 000 Genomes Project: What it means for paediatrics
Griffin BH, Chitty LS, Bitner-Glindzicz M. *Arch Dis Child Educ Pract Ed*, Published Online First: December 9, 2016.

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
- Handling uncertain, unexpected or incidental findings from genomic tests and managing parental expectations
- Implications of significant results, including on reproductive health, for other family members
- 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 in prescribing
- Educating the public about benefits and risks associated with using genomic tests for opportunistic or neonatal screening
- Facilitating an open debate about the potential use of novel techniques like mitochondrial donation or germ-line editing

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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