September 2015

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Respiratory 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. Here we address how this currently impacts on the practice of respiratory medicine, and what can be expected in the near future.

Advances in genetic technology and understanding, coupled with an increasing patient demand for genetic and genomic investigation, is driving the integration of genomic technologies into clinical care. Deciding when to use these powerful new tools, and how to interpret their results, will become important parts of medical practice.

For cystic fibrosis, advanced understanding of the genomic basis of this inherited disease is currently directing not only diagnostics, but also, targeted molecular therapies as discussed below.

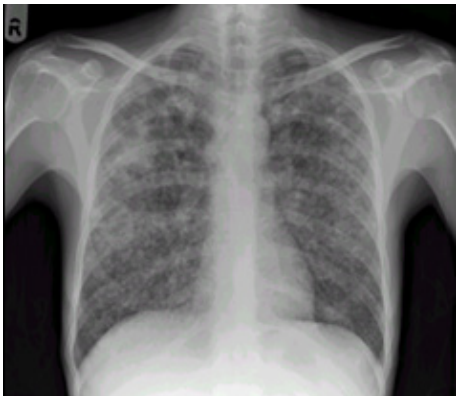
More generally, compared to other medical disciplines, the potential for genomics to enhance diagnostic precision remains in its infancy within respiratory medicine. Nevertheless, there are multiple settings in which it is already modifying the landscapes of disease treatment and prevention.

Pharmacogenomics and respiratory disease

Part of the considerable variability in individual responses to medicines is due to the way a drug is handled in the body (pharmacokinetics) and / or variation in the drug targets (for example, receptors, enzymes, or ion channels).

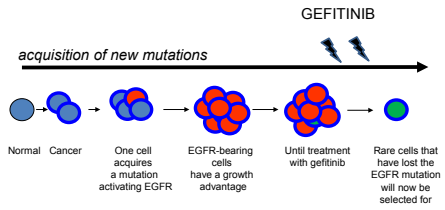
Genomic information can help predict susceptibility to adverse drug reactions, including those at the more severe end of the spectrum: For example, first line treatment of pulmonary tuberculosis (TB) still depends on the multi-drug combinations evaluated by MRC trials more than half a century ago. Genomics approaches provide a platform from which to improve prescribing patterns (see Example 1).

Similarly, Azathioprine is a prodrug of mercaptopurine, which is metabolised by thiopurine methyltransferase (TPMT). Genetic mutations leading to TPMT deficiency place people at high risk of potentially life-threatening bone marrow toxicity when treated with conventional doses of azathioprine. It is possible to test patients for TPMT activity before starting treatment. Once genomics platforms become established, testing for response to Azathioprine will be done more routinely.



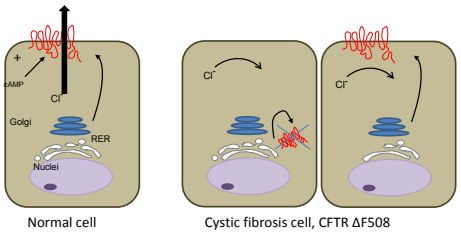
Example 1

Tuberculosis: Clinically unpredictable adverse drug reactions (ADRs) considerably impact on treatment completion rates, and hence drug resistance, and persistence of high TB rates. ADRs to anti-tuberculous therapies are seen more commonly in individuals with specific polymorphisms in the *NAT2*, *GSTM1*, *GSTT1*, and *CYP2E1* genes and HLA alleles. It is anticipated that within the next decade, more personalised genomics-based, tailored therapies will be adopted.



Example 2

Non small cell lung cancer: About 10 percent of patients with non small cell lung cancer have a rapid clinical response to the tyrosine kinase inhibitors gefitinib and erlotinib which target the epidermal growth factor receptor (EGFR). The molecular basis of this is the presence of a mutation in the *EGFR* gene within the cancer. A specific group of mutations in the *EGFR* gene lead to an overactive *EGFR*, and confer greater tumour susceptibility to gefitinib and erlotinib. Similarly, 3% of patients have anaplastic lymphoma kinase (ALK) mutations. In this group, unprecedented improvements in patient outcomes have been achieved with ALK inhibitors such as crizotinib.



Example 3

Cystic fibrosis (CF): CF is caused by inheritance of two mutant copies of the CFTR gene that encodes the cystic fibrosis transmembrane regulator, a cAMP-regulated chloride channel. In patients with mutations that alter chloride channel gating (*e.g.*G551D), patients' FEV1 and sweat chloride can be improved using Ivacaftor which restores chloride channel activity to mutant CFTRs.

Knowledge of genomic influences can provide insights into how efficacious a drug will be in a particular patient, knowledge that may further alter drug choice and / or dose. Over 40,000 new cases of lung cancer are diagnosed in the UK each year, and the detection of a tumour's genetic signature may be used to enable a more accurate prognosis and better tailored treatment. Cancers acquire somatic mutations during their development. Many mutations contribute to accelerated growth and metastases, but some can also lead to improved response to treatment.

In some cases, the gene mutation that directly caused a genetic disease can also inform the optimal drug treatment. For example, in cystic fibrosis, specific inherited molecular defects are being used to define which therapeutic approaches are most appropriate for the individual to improve production and / or function of the mutant cystic fibrosis transmembrane regulator (Example 2). In addition, up to 50% of the risk of developing TB is considered to be genetically determined.

Similarly, genome sequencing of respiratory pathogens (including TB) is likely to direct therapy in the future. For TB, the time taken to diagnose resistance patterns means that it can be challenging to plan a patient's treatment in places where drug resistance is highly prevalent. Using whole genome sequencing to both diagnose TB and determine its drug resistance profile results in quicker diagnosis at around two weeks compared to eight weeks or more using currently available methods. The information can then be used to plan the correct treatment, which is initiated more quickly.

Beyond these examples, it is anticipated that testing for genetic variants that influence both drug safety and drug efficacy 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.

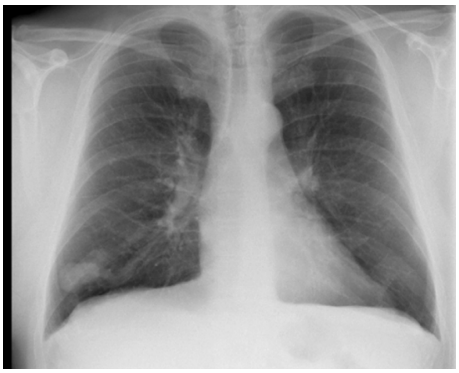
Current and future uses of genomics in respiratory diagnosis

Advances in genetic knowledge and sequencing have already led to the development of new genetic tests for rare monogenic diseases such as cystic fibrosis (Example 3). Antenatal testing can be offered to mothers who are thought to be at high risk of having a child with the disease.

Other rare respiratory conditions that already use genomics for diagnosis include primary ciliary dyskinesia; pulmonary arteriovenous malformations due to hereditary haemorrhagic telangiectasia (*HHT*, Example 4); and pulmonary arterial hypertension.

Genomic tests may also be used to identify individuals to whom different preventive measures may be offered, such as anorexigen avoidance for people at high risk of pulmonary arterial hypertension; smoking avoidance / cessation for patients with mutations in alpha1 protease inhibitor (A1P1, alpha-1 antitrypsin), and iron rich diets for people with hereditary haemorrhagic telangiectasia (HHT).

The more common F508del ("ΔF508") mutation also impairs CFTR processing to reach the cell surface, and is more difficult to correct: combination therapy using Lumacaftor (to correct CFTR misprocessing), plus Ivacaftor has shown clinical promise in Phase III trials. Nonsense mutations generating premature termination codons may be targeted by drugs such as Ataluren which allow stop codon "read through."



Example 4

Pulmonary arteriovenous malformations (PAVMs): Most cases were thought to be due to hereditary haemorrhagic telangiectasia (HHT), caused by mutations in the *ENG, ACVRL1*, or *SMAD4* genes. PAVMs are now thought to affect as many as 1 in 2,600 people, making them twice as common as HHT itself. Genomics approaches may illuminate the cause(s) of non HHT PAVMs, and clarify requirements for familial screening.

Additionally, it is anticipated that testing for a range of genetic susceptibility variants for common diseases such as asthma, COPD and idiopathic pulmonary fibrosis will become routinely feasible. Such data may allow individuals to be more accurately placed into different diagnostic sub-groups within the population.

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 across the whole genome. As a result, findings that were previously only identified following clinical diagnosis or family-based testing may be identified unexpectedly when patients are tested for other clinical reasons.

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
- Managing the 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
- Potential insurance issues, that differ between countries

Genomics can no longer be left to specialists and enthusiasts, but must be grasped by every clinician throughout the NHS. 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.

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

Wainwright CE *et al.* Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. New Engl J Med. 2015 Jul 16;373(3):220-31. doi: 10.1056/NEJMoa1409547. Epub 2015 May 17.

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.

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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Health Education England

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