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Dr Jemma Longley
Dr Salma Naheed
Dr Ellen Copson

Contact

Somers Cancer Sciences Building,
Southampton General Hospital,
Southampton
S016 6YD

Medical oncology 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.

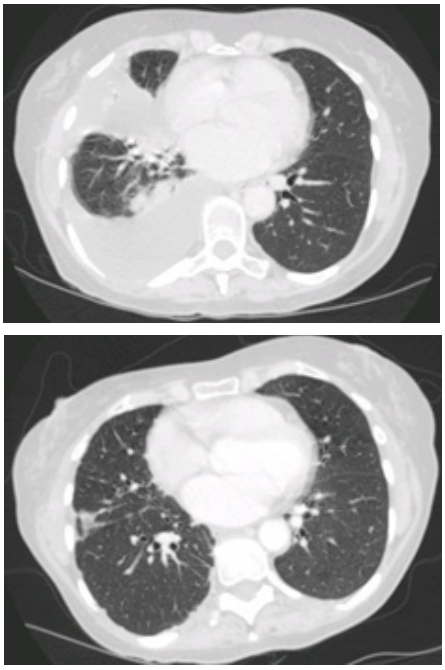
Cancer and genomics

With over 330,000 new cancers diagnosed in the UK each year, patients with cancer are cared for across all specialties within the healthcare service. Genomics has already transformed oncology by allowing the detection of a tumour's individual genetic signature. In doing so, it allows clinicians to make a precise diagnosis, offer a more accurate prognosis and tailor treatment with a view to reducing toxicity, when compared to traditional cytotoxic chemotherapy.

Thanks to the Human Genome Project, we know that between 1000 and 10000 somatic mutations are present in the genome of most adult cancer cells. The key 'driver mutations', which directly result in uncontrolled cell proliferation pathways have now been identified in some tumour types.

Making a detailed diagnosis

Precision diagnosis includes the identification of disease subtypes, which directly influences optimum care and treatment. Advances in cancer biology and sequencing have led to the development of new genomic tests on tumour tissue. With older technologies, these tests are usually offered as single-gene tests to look for a single specific tumour associated mutation. As actionable mutations in more genes are identified there is a need to start using panel tests. Next generation sequencing of tumours has been shown to be feasible by multiple programmes across the world including the Cancer Research UK Stratified Medicine Programme. The NHS 100,000 Genomes Project is now working to achieve whole genome sequencing of 50,000 tumours and matched germline sequences in a transformational project which aims to embed modern genomic pathways into NHS cancer care.



Example 1: Treating Non-small Lung Cancer with Erlotinib

Erlotinib is an endothelial growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) used as first line treatment for adenocarcinoma of the lung. Clinical trials have revealed that Erlotinib is most effective in tumours with EGFR activating mutations such as a deletion in exon 19 and a leucine to arginine substitution at codon 858 in exon 21. In tumours with these DNA variants EGFR is over-expressed on the surface of tumour cells leading to the activation of phosphorylation cascades within the cell, which promotes cell growth and proliferation, whilst also inhibiting apoptosis. By reversibly blocking this cascade, Erlotinib leads to tumour shrinkage.

Example 2: Predicting dangerous toxicity from 5-fluorouracil chemotherapy

5-fluorouracil (5FU) is used in the treatment of several common cancers. 5FU is metabolised by the DPD enzyme. Low levels or deficiency of the DPD enzyme can lead to accumulation of 5FU, resulting in life-threatening neutropenia, mucositis and diarrhoea. Approximately 6% of the population are estimated to have a variation (polymorphism) in the *DYPD* gene, leading to decreased enzyme activity and are therefore at risk of excessive toxicity from this drug. Pre-treatment identification of carriers of DPD variants is now possible using genomic testing. A programme to develop cost-effective test for use in the chemotherapy clinic is now underway.

Example 3: Predicting benefit from adjuvant chemotherapy in early breast cancer

Genomics is changing oncology through the utilization of gene expression profiling (GEP) to guide management decisions. By extracting RNA from a breast tumour and comparing the expression of genes associated with cell proliferation and metastatic potential with reference genes these tests provide information regarding the likelihood of breast cancer recurrence as well as the degree of benefit from chemotherapy. Oncotype DX has now been approved by NICE as a decision aid for selected patients with early breast cancer and this will reduce the number of patients undergoing adjuvant chemotherapy for minimal benefit.

With a greater understanding of the genetic diversity found within a single tumour, it is increasingly clear that a single biopsy only represents an isolated 'genetic snapshot' of a tumour, at a specific point in time. Examination of circulating tumour DNA within the peripheral blood of cancer patients may provide both an alternative to biopsies for companion diagnostic use and a method of monitoring for secondary resistance to systemic treatments. Deciding when to use such tests and how to interpret the results they generate will become important parts of future practice.

Targeted therapies

The discovery of key somatic mutations which drive oncogenesis has enabled the development of therapies that target the abnormal proteins produced by these oncogenes. A number of specific small molecules and monoclonal antibodies that block these mutant proteins and the biochemical pathways required for cell growth and survival have been developed in the last two decades. These include inhibitors of BRAF, EGFR and HER2 (see Example 1); treatments which allow for a more personalised, selective approach, with reduced toxicity when compared to traditional chemotherapy.

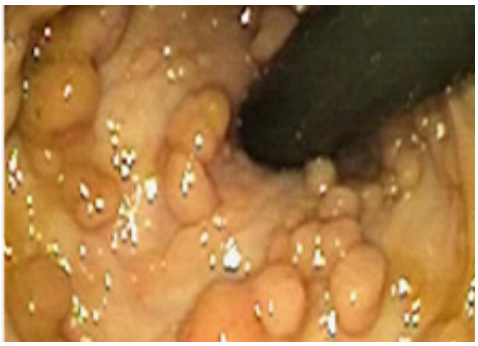
Pharmacogenomics

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 2). 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).

Genomics and cancer prognosis

Historically, oncologists have used information about a tumour's size, grade and extent of spread to decide whether a patient requires chemotherapy to reduce the risk of developing metastatic disease in the future in addition to surgical management of their primary cancer. Genomic analysis of tumours can now provide a far more detailed and individual assessment of cancer behaviour permitting oncologists to



Example 4: Familial Adenomatous Polyposis (FAP)

FAP is characterized by the development of hundreds of colonic adenomatous polyps at a young age with a risk of malignant transformation of almost 100%. Mutations within the *APC* tumour suppressor gene on chromosome 5q2 1 are found in >90% of FAP cases. Where the causative gene mutation in the family is known, genetic testing is recommended to establish a genetic diagnosis in children of an affected individual around the age of 10–12 years, with the aim of sparing children carrying the wild type *APC* gene from invasive colonoscopy surveillance.

Example 5: Preventing breast and ovarian cancer in carriers of *BRCA* gene mutations

Women carrying pathogenic mutations in the *BRCA1/2* genes have a lifetime risk of breast cancer of 40-85% and a 10-60% risk of ovarian cancer. Risk-reducing double mastectomy reduces the risk of breast cancer by up to 90%. More acceptable to many women is prophylactic bilateral oophorectomy which reduces ovarian cancer rates by 95% and also reduces breast cancer risk. Chemoprevention with tamoxifen or raloxifene is also now NICE approved. To facilitate early identification of malignancies annual breast MRI surveillance and / or mammography is recommended. *BRCA1/2* carriers should also be encouraged to be "breast aware" and adopt healthy lifestyle measures. Screening for ovarian cancer remains under investigation.

recommend chemotherapy only when there is clear evidence that the benefits of this will outweigh the inevitable side effects. Several commercial genomic tests are now available to aid decision making in breast cancer with tests for other tumour types in development.

Hereditary Cancer

A small proportion of cancers (around 5-10%) are due to germline mutations in a cancer predisposition gene (CPG) giving rise to familial cancer syndromes such as Hereditary Breast and Ovarian Cancer. These usually occur in families where multiple individuals have had cancer of one or more specific types, often with an unusually young age of onset. Some carriers of these germline mutations do not develop cancer, suggesting that these altered genes are 'incompletely penetrant'.

Over 100 CPGs have been identified. The most notorious example of a CPG is *BRCA*. Individuals with germline mutations in *BRCA1* or *BRCA2* have a significantly increased risk of developing breast and ovarian cancer. Hereditary non-polyposis colon cancer (HNPCC) (also known as Lynch syndrome), is an autosomal dominant disorder which accounts for 2-5% of all colorectal cancers. In this instance, the germline mutation resides in one of several DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2*) or the *EPCAM* gene.

Until recently, knowledge of a CPG mutation mainly benefited healthy relatives in better quantifying risk and considering options for targeted prevention. However, knowledge of CPG mutations is now starting to influence management of primary cancers. PARP inhibitors are a targeted therapy which exploits the underlying DNA repair deficiency in BRCA mutation carriers. These drugs are currently being evaluated in clinical trials in both the adjuvant and metastatic settings. Furthermore, there is emerging and increasing evidence that CPGs alter the effectiveness of some chemotherapy drugs. BRCA mutation carriers have enhanced sensitivity to platinums, whilst those with mismatch repair gene mutations have reduced efficacy of 5-FU.

Demand for testing for CPG mutations has increased thanks to greater awareness of familial cancer syndromes conditions amongst clinicians and patients, and is likely to become incorporated into regular oncological care in the near future. The UKGTN website provides information on genetic tests that are currently listed on the NHS directory of genetic tests. 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.

Further Information and Resources

Association of Cancer Physicians
www.cancerphysicians.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@nwlcsu
ukgtn.nhs.uk

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

Diagnosis and Treatment of Cancer Using Genomics. Vockley and Niederhuber. BMJ, 2015; 350:h1832.

Personalised prevention using genomics

Personalised prevention recognises that people differ in their risk of disease and in their likely response to preventative interventions. Genetic differences account for some of this variation and identifying individuals with mutations in cancer predisposition genes allows for preventive measures to be tailored to the individual (Example 5). 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 when 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
- 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

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

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