Scanning the human genome and the horizon:

the potential and pitfalls of pharmacogenetics and stratified medicine

Using genetic tests in treatment stratification has the potential to improve patient outcomes and cost-effectiveness when prescribing medicines. However there are pitfalls to consider; from the lack of translation of discovery science into useful biomarkers, to the practical and ethical problems of handling and interpreting data from whole human genomes.

This review is timely because a new initiative called Genomics England (<http://www.genomicsengland.co.uk/>) aims to sequence 100 000 genomes from patient volunteers treated within the NHS by 2017. The ultimate aim being the rapid translation of genomic findings into routine health care. Genomics England is, in turn, a response to unprecedented developments in our understanding of the genetic basis for disease.

Stratified medicine can be viewed as the ultimate goal of the human genome project (HGP); and technologies arising from this initial \$3 billion task may enable us to routinely analyse whole genome sequences for just a \$1000 per patient.^{1,2}

THE HUMAN GENOME, GENETIC VARIATION, AND COMPLEX TRAITS

Thanks to the efforts of the HGP, we have had access to a consensus DNA sequence for the human genome for more than a decade; this is used as a reference tool to interrogate the variation that is found between individual genomes. The data and tools from these projects have accelerated the progress of genome-wide association studies (GWAS); case control and cohort studies that examine the association between variants and significant disease phenotypes. As of April 2015, a curated catalogue of GWAS describes 2111 publications (analysing 15 396 variants) for many important traits.³ Associations between common variants and well-defined phenotypes have been identified and reproduced in large studies, but most individual effect sizes are very small and so have not generated biomarkers with clinical utility.

STRATIFIED MEDICINE AND PHARMACOGENETICS

In the future it is possible that we will each have our own personalised plans for detecting early signs of disease based on our

"We know that a 'one size fits all' dose is not appropriate for many commonly-prescribed drugs ..."

genetic profiles and associated biomarkers. The advantage of this approach over the use of public health strategies aimed at whole populations remains questionable, but is a component of a philosophy called P4 medicine that is predictive, preventive, personalised, and participatory. Mapping biochemical processes and networks of gene interactions is integral to P4 medicine and part of the emerging field of systems biology,⁴ which can capture molecular events within complex pathways, but its clinical utility is theoretical rather than imminent.

The area of genetic medicine that is certain to expand over the next decade is pharmacogenetics. Evaluation of translational genomics from discovery phase to health impacts for individuals or populations⁵ shows that most of the studies of clinical utility and the implementation of genomic medicine apply to pharmacogenetics; particularly for patients with cancer. However, it is also worth noting that most human genomics research may be lost in translation, with studies of healthcare applications comprising only 0.5% of this published literature during that time.⁶

We know that a 'one size fits all' dose is not appropriate for many commonly-prescribed drugs because genetic variations affect both how rapidly a drug is activated or cleared from our bodies and also, the amount that may be required to elicit the target response. It is estimated that, for appropriately prescribed medicines, fewer than one-half of the people treated gain benefit, yet they face a potential risk of morbidity and mortality associated with adverse events.⁷ Where medical treatment damages health, it violates the key ethical principle of non-maleficence, 'to do no harm'. Therefore it is an urgent ethical priority to understand adverse drug reactions so that harm can be avoided. It is also an economic imperative for health systems to avoid incurring costs of ineffective treatment or worse still, costs for treatment of side effects.

TAILORING TREATMENT FOR PATIENTS WITH CANCER

Cancer is viewed as a genetic disease and pharmacogenetics is already being applied to its management. Its pathogenesis is a multistep process associated with inherited risk factors but most importantly with the accumulation of somatic mutations that alter key signalling pathways. Much of the process is stochastic and so marked by heterogeneity between individuals; tumours of apparently similar histological classifications can differ markedly in genotype. The Cancer Genome Project (<https://www.sanger.ac.uk/research/projects/cancergenome/>) is underway, systematically identifying all mutated cancer genes and their associated biochemical pathways. This is leading to new paradigms of disease classification that are based on perturbed pathways, and for which rational drug design is leading to targeted therapeutics.⁸ It has been proposed that signatures of somatic oncogene mutations that cut across traditional tissue-specific classifications could result in personalised treatment regimens.⁸ The clinical utility of a genetic approach to stratify treatment protocols is yet to be determined through clinical trials but there is most scope for the application of pharmacogenetics to prevent adverse events when treatments have a narrow therapeutic index, which is a characteristic of most cancer therapy.

There are two distinct forms of treatment stratification that are already embedded within management protocols for the oncology clinic. First, through the use of 'companion diagnostics' for actionable driver mutations, before prescribing the targeted drug. The rationale being to use therapeutics only when there is proven clinical utility. The classic example is the detection of over-expression of the *ERBB2* oncogene in breast cancer before prescribing the monoclonal antibody therapy, trastuzumab. However, it must be recognised that stratifying the patient group could result in some patients, who could derive some benefit from an expensive drug, but would not benefit from

"Discovery science in human genetics has made unprecedented progress this century and this could herald the era of genetic medicine."

it as much as another group of patients, being refused access to it. Where a new drug is perceived by the public to be an effective and hence desirable treatment for cancer, denial of treatment might lead to individual distress and to adverse publicity, unless communication is managed extremely carefully. Another related risk is that people categorised as 'non-responders' or 'difficult to treat' may be stigmatised or discriminated against, for example in insurance-based healthcare systems.⁹

The second form of stratification is to avoid severe adverse events with tests for inherited variants of pharmacokinetics and pharmacodynamics. For example, the fluoropyrimidine 5-FU is an anti-metabolite that has been used as a chemotherapeutic agent for more than five decades for many common cancers. Rare variants for the rate-limiting enzyme of 5-FU catabolism, dihydropyrimidine dehydrogenase, have recently been recommended as pharmacogenetic markers to guide fluoropyrimidine dosing because carriers can have life-threatening adverse events with standard protocols.¹⁰

The rapid progress in the field of human genomics has been contingent on the emergence of key technologies exploiting the chemistry of DNA synthesis. The most relevant today being high-throughput DNA sequencing¹¹ referred to as next generation sequencing. If we scan the horizon it seems likely that further stratification will occur through the increasing use of sequencing to analyse cancer genomes, which is one of the aims for Genomics England. The advances in our understanding of cancer biology, coupled with rapid and cheap whole-genome sequencing is even permitting the non-invasive analysis of cancers as they evolve through treatment regimens, and so cancer management could become truly personalised and depend on fewer surgical investigations.¹²

THE CLINICIAN AS THE CUSTODIAN OF GENOME DATA AND THE PROBLEM OF 'TOO MUCH INFORMATION'

The most striking problem for clinicians may be engaging in discussions about genetic tests for which there is little or no evidence of clinical utility. The rapid and inexpensive

generation of whole genome sequencing data allows us to identify all of the markers of interest for a particular patient in a single episode (for example, a patient with cancer whose treatment protocol depends on information about somatic genetic markers and pharmacokinetics) but the corollary is that incidental findings will be inevitable and the custodian will have to grapple with variants of unknown clinical significance.

Other logistical challenges are manifold, including the use of genome data from unregulated as well as health service sources, the storage of data, and the interpretation of gene nomenclature; which is not an area of competence for many clinicians who are not genetic sub-specialists. The interpretation and communication of genomic data were addressed in a report summarising discussions from a European workshop that considered predictive screening and direct-to-consumer testing.¹³

CONCLUSION

Discovery science in human genetics has made unprecedented progress this century and this could herald the era of genetic medicine. However, the translation of our knowledge to interventions with clinical utility is in its infancy; with a few notable exceptions in the field of oncology and pharmacogenetics. The education of clinicians from all specialties about the interpretation and application of genomics data and biomarkers will be crucial to the timely and evidence-based development of stratified medicine.

Barbara A Jennings,

Senior Lecturer in Molecular Medicine, Norwich Medical School, University of East Anglia, Norwich.

Tom Shakespeare,

Medical Sociologist and Senior Lecturer, Norwich Medical School, University of East Anglia, Norwich.

Yoon K Loke,

Professor of Medicine and Pharmacology, Norwich Medical School, University of East Anglia, Norwich.

Provenance

Freely submitted; not externally peer reviewed.

DOI: 10.3399/bjgp15X685153

ADDRESS FOR CORRESPONDENCE

Barbara A Jennings

Norwich Medical School, Faculty of Medicine and Health Sciences University of East Anglia, Norwich NR4 7TJ, UK.

E-mail: b.jennings@uea.ac.uk

REFERENCES

1. Lander ES. Initial impact of the sequencing of the human genome. *Nature* 2011; **470(7333)**: 187–197.
2. Hayden EC. Technology: the \$1,000 genome. *Nature* 2014; **507(7492)**: 294–295.
3. Hindorf LA, MacArthur J (European Bioinformatics Institute), Morales J (European Bioinformatics Institute), *et al.* A catalog of published genome-wide association studies. www.genome.gov/gwastudies [accessed 29 Apr 2015].
4. Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. *N Biotechnol* 2012; **29(6)**: 613–624.
5. Schully SD, Benedicto CB, Khoury MJ. How can we stimulate translational research in cancer genomics beyond bench to bedside? *Genet Med* 2012; **14(1)**: 169–170.
6. Clyne M, Schully SD, Dotson WD, *et al.* Horizon scanning for translational genomic research beyond bench to bedside. *Genet Med* 2014; **16(7)**: 535–538.
7. Pirmohamed M, James S, Meakin S, *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329(7456)**: 15–19.
8. Ciriello G, Miller ML, Aksoy BA, *et al.* Emerging landscape of oncogenic signatures across human cancers. *Nat Genet* 2013; **45(10)**: 1127–1133.
9. Smart A, Martin P, Parker M. Tailored medicine: whom will it fit? The ethics of patient and disease stratification. *Bioethics* 2004; **18(4)**: 322–342.
10. Caudle KE, Thorn CF, Klein TE, *et al.* Clinical pharmacogenetics implementation consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clin Pharmacol Ther* 2013; **94(6)**: 640–645.
11. Bentley DR, Balasubramanian S, Swerdlow HP, *et al.* Accurate whole human genome sequencing using reversible terminator chemistry. *Nature* 2008; **456(7218)**: 53–59.
12. Murtaza M, Dawson SJ, Tsui DW, *et al.* Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature* 2013; **497(7447)**: 108–112.
13. Hastings R, de Wert G, Fowler B, *et al.* The changing landscape of genetic testing and its impact on clinical and laboratory services and research in Europe. *Eur J Hum Genet* 2012; **20(9)**: 911–916.