BUSTING THE NICHE:

THE FUTURE OF GENOMICS

The sequencing of patients' genes has opened the way for exciting new approaches to therapy. The challenge for the pharmaceutical and life sciences sectors is to adapt R&D, production and sales and marketing to become swift, agile developers of more specialised drugs with smaller target audiences

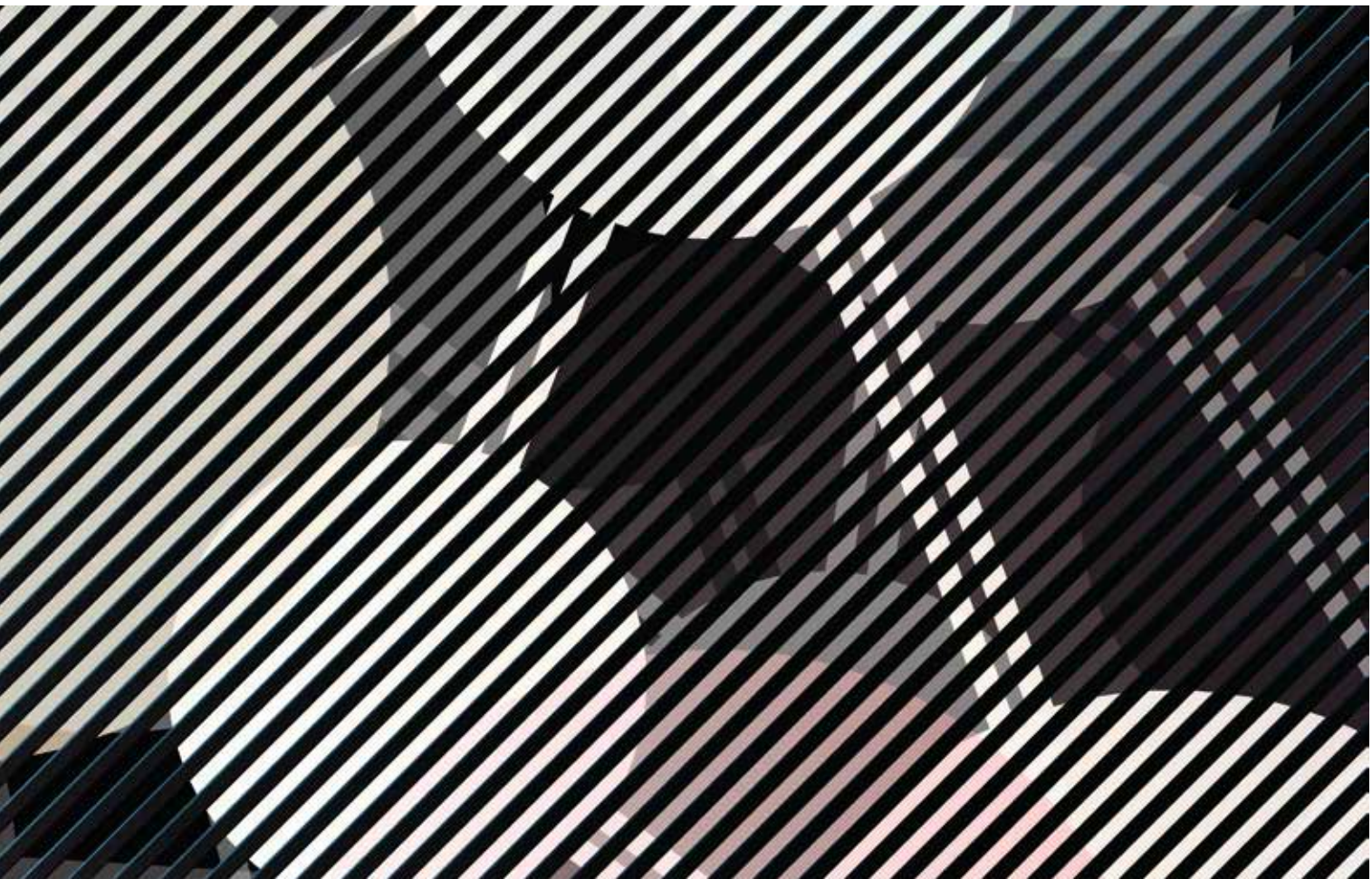
GUEST AUTHORS PROFESSOR HILARY THOMAS, DR LIZZIE TUCKEY AND DR MALIK MOLEDINA / EDITED BY CLAIRE BOWIE/JENNY HONE

BY the time the first human genome was sequenced in 2004, the total cost of reaching this goal had soared to £1.6 billion over 14 years. Fast-forward a decade, and Illumina's HiSeq X Ten sequencing platform can carry out the task in less than 24 hours for just £600.

These achievements have generated considerable excitement over the potential for genomics to herald a new era of personalised medicine, where customised information can be used for prevention, diagnosis and treatment. Consequently, genomics has become a high priority for biomedical research, with the pharmaceutical and life sciences sectors desperate for 'nichebuster' breakthroughs to compensate for the decline in blockbuster drugs.

Frustratingly, though, genomics has so far failed to yield much in the way of specific treatments, while health systems are still working out how best to share and use the vast amount of data accruing from sequencing and other research.

Genomics England – a company owned by the Department of Health – plans to sequence 100,000 whole genomes by 2017, while a host of similar initiatives are taking place around the world, creating an ever-expanding library of genetic information. But despite significant investment from governments, academic institutions and pharma companies, there have been few breakthroughs in genome-based therapeutic intervention.



This is considered to be the holy grail of genomics – a select group of treatments that actually modify the expression of genes to reduce the impact of disease – and what does exist is mainly restricted to certain forms of cancer. For example, trastuzumab is a monoclonal antibody that targets the HER2 gene in certain breast cancers, while another monoclonal antibody, cetuximab, is used to treat non-small cell lung cancer and metastatic colon cancer.

So although the number of genes proven to cause diseases rose from 53 in 1990 to 2,900 in 2013 – enabling scientists to screen patients and allow for early diagnosis and treatment – only nine out of 61 recent genomics articles from leading journals relate to trials that show effective treatment, with the majority focusing on pathogenesis and underlying genetic causes of disease.

It seems that scientists are struggling to overcome the complexity and excessive variables involved in linking genes to chronic disease, with only the largest organisations able to fund such high-risk research.

Genomics in practice

However, one common and growing use of genomics is in the field of pharmacogenomics – the technology that assesses the impact of genetic make-up on an individual's response to drugs, which helps to increase efficacy while minimising side effects.

More than a hundred drugs now carry pharmacogenomic medical information on their labels, providing a vital aid to doctors' therapeutic choices. For example, an established association between certain genes and side effects means patients are routinely genotyped before being prescribed the antiretroviral therapy abacavir, to avoid an unwanted response. And it's a similar story with the immunosuppressant azathioprine, with patients genotyped for the enzyme TMPT, which predicts their ability to deal with the drug's toxicity.

Its effectiveness is also being seen in clinical trials. For example, the efficacy of AstraZeneca's anti-lung cancer drug IRESSA was questioned after its early use showed a high failure rate. However, after the introduction of genetic testing the success rate increased significantly when the product was used only for patients with a specific EGFR mutation, leading to greater use by health providers and higher

'Genomic treatments are unlikely to achieve wider adoption without the clinical reassurance of improved patient outcomes, which is currently limited'

SIR JOHN CHISHOLM
EXECUTIVE CHAIRMAN, GENOMICS ENGLAND

"Columbus didn't achieve what he set out to do, but he did discover America," says Sir John. "It's a similar issue for genomics and the 100,000 Genomes Project announced by David Cameron in 2012 – which aims to complete 100,000 DNA sequences taken from NHS patients with cancer and rare disease over the next four years."

"The long awaited era of personalised medicine is now really on its way and the scale of the datasets available will become truly colossal," Sir John adds. "As health services become increasingly data driven, generalist provision will give way to precise diagnosis followed by treatment in specialist centres and patients will play a much greater part in their own treatment pathway. The era of blockbusters will end and be replaced by highly targeted molecules that can be recommended through digital screening based on a precise molecular diagnosis."

BARONESS SUSAN GREENFIELD
SENIOR RESEARCH FELLOW, UNIVERSITY OF OXFORD

"We shouldn't lose sight of the objectives in the white heat of excitement around new technologies," says Greenfield. "We need to put genes in their place and see the context in which they are working."

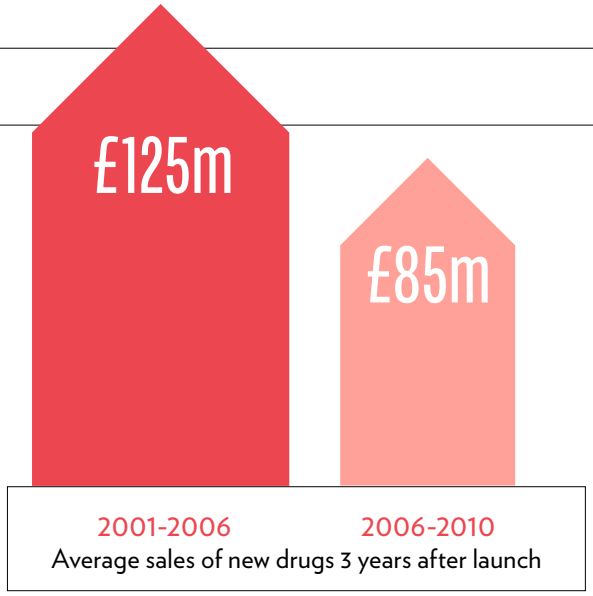
In terms of Alzheimer's disease, the 'dream' is to have a blood marker that will give an accurate early indication of the disease – to allow for more timely treatment intervention. "There has been no new drug for 10 years despite the massive muscle of pharma, because of the slavish dogma to the amyloid protein. While amyloid may play a part in the secondary or tertiary cascade – it is not the cause of Alzheimer's. We need to find the basic mechanism so that we can develop a genetic approach to combat this devastating disease. What we should be getting excited by is the potential for diagnosis and modelling – not new treatments."

PROF HILARY THOMAS
FORMER ONCOLOGIST AND BREAST CANCER PATIENT

"The huge incremental pace of progress has had a huge impact and it's no longer possible to be a generalist in oncology," says Thomas. Eight years ago, when working as a clinician, she was diagnosed with triple negative breast cancer – but the huge generalisations made then about disease pathology defined Hilary as a young, Afro-Caribbean woman with a poor prognosis! Since this time, treatment has been personalised to a greater extent than could ever have been imagined – unlike the earlier blunderbuss approach – with the patient group Breakthrough Breast Cancer now conducting trials in triple-negative breast cancer.

sales. Indeed, other underperforming blockbusters have been similarly revitalised thanks to sequencing of the target audience.

Yet genomic treatments are unlikely to achieve wider adoption without the clinical reassurance of improved patient outcomes, which is currently limited. Although there are some examples of successful treatments, genomics arguably does not fit into traditional trial methodology, which calls for large sample sizes. By definition, genomic therapies only apply to small groups, so a wider range of analyses should be used as part of an adaptive approach combining retrospective, prospective and comparative studies. There is also a growing body of opinion in favour of making genomic treatments available to patients far earlier than is usually permitted, to hasten the move to more flexible trials.



Making sense of the data

Ultimately, genomics is a data-rich form of research and requires appropriately robust electronic medical health records systems that can adapt over a patient's lifespan. The NHS has some way to go before its own IT systems are best in class, which could hinder the full integration of genetic information into patient records. And the failure of the ill-fated National Programme for IT illustrated the challenge of creating a modern, streamlined infrastructure so, for now at least, any attempts to introduce genomic data will have to fit in with existing records.

The journey towards personalised healthcare could be accelerated by reporting the patient's full family history – along with functionality such as clinical decision support and a patient portal for entering and viewing data – all of which takes time and resources.

Patient confidentiality is a further concern, especially where genotyping reveals 'incidental findings' that could indicate susceptibility to conditions beyond the scope of the initial test. As a result, doctors face an ethical dilemma over whether to let a patient know they have a chance of developing a serious disease. Moreover, any investigations can add substantial costs for cash-strapped health systems.

From an R&D perspective, scientists need appropriate data management and modelling support to make sense of the vast amount of sequencing information. While open source platforms can aid interoperability and make use of the latest clinical applications and services across the patient lifecycle, the ultimate aim is, of course, to have a global database that researchers can tap into to share and advance learning.

Paving the way for nichebusters

So with a rising number of drugs approaching the patent cliff, a lack of new, replacement blockbusters, and government cutbacks on health spending, more and more pharmaceutical and life sciences companies recognise the need to embrace personalised products aimed at smaller audiences, but with (hopefully) better outcomes.

New drugs launched between 2006-2010 in the USA had average sales of £85 million three years after launch, compared with £125 million from 2001-2006, whereas drugs targeting niche therapeutic areas

'The transition to nichebusters will affect every aspect of a pharmaceutical company's operations'

typically enjoy stronger support from regulators and governments, with tax breaks and longer market exclusivity licences. These medicines also often command much higher prices, with gross margins up to five times the industry average. Kalydeco, the first drug to treat cystic fibrosis in patients with a G551D mutation, can cost as much as £180,000 a year, with margins further protected by high entry barriers in the form of complex and sensitive manufacturing processes that deter competitors.

As Chris Stirling, global head of life sciences at KPMG says: "The transition to nichebusters will affect every aspect of a pharmaceutical company's operations." R&D is likely to be carried out by a series of smaller scale, autonomous teams able to work swiftly and flexibly to react to changes in adaptive trial results. "Sales and marketing models should also change dramatically, with the old model of huge fieldforces selling one or two drugs becoming redundant, to be replaced by compact teams detailing very specific treatments to a specialised target group of physicians."

But Stirling believes: "Such a revolutionary change can only succeed with the permission of regulatory authorities, and pharma firms must work in partnership to agree a new, accelerated and adaptive approach to trials, and a suitable payment model based on outcomes and quality of life." The industry can also play a part in educating physicians on the concepts and benefits of genomics. Finally, the return on investment in R&D may have to be reappraised, with a regular stream of new compounds that have shorter lifecycles, rather than expecting a decade or more of patent-protected blockbuster revenue.

So near and yet so far

When the Human Genome Project began in 1990, no-one involved could have predicted the potential for genomics to tackle rare or complicated conditions. Despite considerable progress, the healthcare sector as a whole is only now beginning to truly understand the link between therapeutic effectiveness and genetic makeup.

As the costs of sequencing continue to fall, every citizen will eventually have a recorded genetic profile that can be used by providers and researchers to predict the likelihood of disease, and treat known conditions more effectively. The challenge is to capture, process and use this information in a way that improves the targeting of existing drugs and stimulates the development of new drugs that attack specific conditions. ◘

Professor Hilary Thomas is a partner in chief medical adviser at KPMG, Dr Lizzie Tuckey is the sector COO for life sciences. Malik Moledina is a qualified doctor at Imperial College London

This feature stems from a meeting organised by +91 Europe, hosted by KPMG in partnership with PharmaTimes Media.

Photo: Paul Wilkinson

PROF ALISON WOOLLARD
UNIVERSITY OF OXFORD

There is still a lot of basic biology to get to grips with before we will understand how best to utilise genomic information to develop new therapeutic strategies. For example, how do we become a complex being of 40 trillion cells from one single cell? How do they all know how to work together? What is the molecular signature of each type of cell, and how can we best exploit this knowledge to reprogramme them?

To understand these processes we need to understand more about the functions of our genes, and studying a simple organism like the nematode worm can tell you an awful lot about complex organisms. In fact four out of five species on earth are nematodes – they're fast, they're cheap, and you can screen for drugs. And model organisms are also a fantastic test bed for the development of new disruptive technologies, such as genome editing – paving the way for the possible "cure" of genetic diseases by targeting the genetic mutation itself.

ALASTAIR KENT OBE
DIRECTOR OF GENETIC ALLIANCE UK

For patients, advances in genomics mean a precise diagnosis at the molecular level, insights into flaws in basic biology and access to personalised/stratified medicines.

"We are generating genomic data in unimaginable quantities – how do we make sense of it and what do we do with it?" Kent asks.

To avoid another care.data fiasco, patients and clinicians need access to clear and trustworthy information. And we need to get the societal engagement right – it's not all about generating the money to fund research. Pharma and the research community need to better harness the expertise of patients and families in changing its model: not only do they bring valuable insight but samples, data, advocacy and, critically, public legitimisation.

JEREMY HAIGH
EUROPEAN COO R&D, AMGEN

"If we're going to make sure patients' needs are met we have to radically change the traditional model of drug development that takes on average 14 years, costs more than a billion dollars, and might result in a product that has very little added benefit," says Haigh. "Genomics will provide a much needed impetus for this change."

"As diseases fragment, every condition could become an orphan disease – and diseases with common molecular faults will have common therapies," Haigh adds. "Diagnostic tests will determine who is right for a new treatment and patients will be segmented into smaller subsets based on outcomes."

"For the first time I can recall, everyone is aligned with the need to be disruptive – to engage multiple stakeholders, enable collaboration, to revise the regulatory and reimbursement pathways and to ensure that, ultimately, patients receive earlier access to innovative stratified medicines."