# Editorials

# Genomics in routine clinical care:

## what does this mean for primary care?

*'The NHS will need to be ready to use genomics as part of its routine care.*[1]

But how will genomics impact on primary care and what is needed for primary care to be genomics-ready?

While genetics focuses on DNA coding for single functional genes, genomics is the study of the entirety of our DNA, recognising the crucial regulatory role of non-coding DNA and the complex interactions between multiple genes and the environment. Genomics and variation is fundamental to precision medicine which, through its four components of predictive, preventive, personalised, and participatory medicine, aims to promote wellness as well as to more precisely treat disease. The transformational 100 000 Genomes Project funded by the Department of Health aspires to kick-start a UK genomics industry and set up a genomics medicine service within the NHS.[1] GPs will play an important role within a genomics medicine service both in supporting patients through diagnostic and treatment processes and in using knowledge of genomics for disease prevention.

### CANCER

There are 356 000 new cancer cases diagnosed in the UK each year.[2] Testing of both the patient's own genetic makeup ('germline' DNA) and the tumour DNA ('somatic' testing) are important here.

A tumour's genomic signature may be used to make a precise diagnosis, enabling more accurate prognosis and better tailored treatment. Examples include Herceptin® (trastuzumab) in breast cancer treatment and BRAF inhibitors in malignant melanoma. Treatment can also be based on germline genomic information; PARP inhibitors are more efficacious in the treatment of ovarian cancer in individuals who carry a *BRCA* gene mutation.

Cancer follows the principle of complex disease: a proportion of disease risk is determined by a combination of genomic variation and gene–environment interactions, with around 5% attributable to single gene highly penetrant variants which underlie familial cancer syndromes. Perhaps the most well-known of these is breast or ovarian cancer associated with mutations ('pathogenic variants' in current nomenclature) in the *BRCA1* or *BRCA2* genes. Identification of these in affected patients and their relatives is important in order to offer targeted prevention such as increased screening (for example magnetic resonance imaging [MRI]) or risk-reducing treatment (for example, chemoprevention or risk-reducing mastectomy).[3] Primary care already plays a key role in assessing family history to identify these patients; however a sub-set of patients will present with a pathogenic variant identified through a research programme, or direct-to-consumer testing with no relevant family history.

> *"The NHS will need to be ready to use genomics as part of its routine care"*

Genomic variation could also enable tailoring of cancer screening programmes, such as breast, prostate or colorectal, through risk stratification at population level. Proof of principle has been provided by the European Commission funded multicentre Collaborative Oncological Gene-environment Study (COGS) on genetic variation and breast cancer risk;[4] however implementation of such strategies is not feasible as yet.

### RARE DISEASE

Rare diseases are defined as affecting <5 cases per 10 000 (for example cystic fibrosis), and at least 80% are genetic in origin. As a group they affect 1 in 17 of the population and therefore make up a proportion of the primary care caseload. Genomic testing will improve the likelihood of making a molecular and in some cases a clinical diagnosis, thereby avoiding protracted diagnostic journeys with huge emotional cost (the 'diagnostic odyssey'), and giving a greater understanding of underlying pathology, likely natural history, and responsiveness to various treatments.[5] Another important dimension is the familial element; relatives will access primary care for advice regarding risk and reproductive issues.

### OTHER COMMON COMPLEX DISEASE AND PHARMACOGENOMICS

Like cancer, common disorders such as diabetes and heart disease are influenced by underlying genetic susceptibility as well as environmental and lifestyle factors. Genomic variants are anticipated to play an increasing role in risk stratification through risk assessment tools alongside phenotypic and sociodemographic data.[6]

Testing for relevant genetic variants that influence both drug efficacy and drug safety will increasingly be used to aid choice of both drug and dosage. An exemplar is testing for variants in the *SCLO1B1* gene which increase the likelihood of simvastatin-induced myopathy, and guidelines informing dosage and statin choice in such patients.[7]

The implementation of pharmacogenomic testing has been limited by the need for evidence of clinical utility at population level and cost-effectiveness. However cost-effectiveness will improve as technologies allow parallel testing for 'panels' of genes at vastly reduced time and cost, with near-patient testing not far away. Development of decision support systems that allow the proven integration of genomic and clinical information to aid prescribing will be of value in the future.

### PRACTICAL AND ETHICAL CONSIDERATIONS

Nationally a need for service delivery redesign has been identified.[8,9] Consider familial hypercholesterolaemia; guidance recommends genotyping to confirm diagnosis,[10] yet only a few centres offer this test and it is funded nationally by specialist commissioning. The vast majority of patients are currently managed within primary or secondary care with no direct access or referral pathway to genotyping. As the drive to mainstream genomics testing continues there will be a need to develop clinical pathways with supporting resources such as detailed reports, guidelines, or provision of remote or virtual specialist advice for an increasing number of conditions.

Challenges for development of informatics are also considerable: the integration of genomic data into risk assessment and decision-support tools, embedding of these into primary care

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systems, and recording and data-handling within primary care records to name just a few. Read Codes are scheduled to be retired with full adoption of SNOMED CT codes (http://www.snomedbrowser.com) into primary care by December 2016; both include diagnostic and carrier status codes for only some inherited conditions, or codes for specific tests but not results. Expansion of the list of conditions with specific codes, inclusion of codes describing genomic test results, and cross-specialty consistency is essential.

It is conceivable in the near future that all of a patient's genome sequence data could be centralised, enabling access to all professionals involved in their care. IT systems could interrogate a database in order to capture relevant data within the primary care record for specific purposes such as integration into risk tools for common complex disease or personalised prescribing. This raises questions such as who should have access to this information, and where would consent be recorded?

## EDUCATION AND TRAINING

The RCGP Curriculum statement 'Genetics in primary care' identifies three main roles for primary care: identifying patients with, or at risk of, a genetic condition; clinical management of genetic conditions; and communicating genetic information. It encapsulates knowledge and skills which are transferable to genomics.[11] It is not anticipated that GPs will require substantial additional expertise or an in-depth knowledge of genomic variants.[6] However they will require an understanding of terminology, principles underpinning the use of genomics in clinical care and ethical issues in order to communicate effectively, support patients, and institute appropriate management. Alongside, it is anticipated that development of 'just-in-time' resources for use within the consultation will be crucial; these could include decision-support tools, guidelines, disease summaries, and routes to 'virtual' advice from genomics specialists. Health Education England's (HEE) Genomics Education Programme has outlined its strategy 'Engaging Primary Care', launching with an educational needs assessment specific to genomics that aims to inform development of curricula and resources.[12]

## SUMMARY

The 100 000 Genomes Project has accelerated the pace of scientific discovery within genomic medicine which, as a whole, has the potential for wide-ranging effects on health and disease with substantial patient benefit. In order to realise the contribution of genomics to true precision medicine there is still considerable distance to go in mainstreaming and implementation at primary care level. A firm foundation to deliver on this already exists within primary care, in the form of a long-established skill-base in risk communication and shared decision making, and the ability to rapidly incorporate novel management strategies into routine clinical care in the context of the consultation. However, implementation also demands a wider awareness and responsiveness from those responsible for commissioning, informatics and education at all levels in order for primary care to become truly 'genomics-ready'.

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