Editorials

Personalised medicine in general practice:

the example of raised cholesterol

With the rollout of the 100 000 Genomes Project,[1] NHS policymakers are working to maximise the benefits to patients of personalised medicine. In the US, this is also termed 'precision medicine'. Many GPs consider they already offer 'personalised medicine', recognising that 'one size does not fit all' and that management requires patients' medical histories and psychosocial issues are taken into account. While the field of genomics has been developing for many years its clinical value has, to date, largely been in the diagnosis of rare, inherited diseases. However, genomic information is increasingly offering the potential for transformed healthcare, including better prediction of potential disease, earlier and more accurate diagnosis, and prescribing tailored to an individual's likelihood of seeing benefit.

STRATIFIED MEDICINE

Better interrogation of electronic healthcare records in primary care offers an opportunity to stratify patients into subgroups for targeted management and this is expected to lead to improved efficiency in the NHS.[2] An alternative way of describing this new approach is 'stratified medicine', and this is already recognised in general practice, as demonstrated by the asthma and COPD clinical care pathways.[3]

In particular, genomic analysis, taken with the better interpretation of information in electronic health records, has the potential to improve the detection and management of common conditions earlier in life. This will allow interventions that may prolong healthy life to be started earlier than by using the current approach, which is largely dependent on a clinical event occurring before a diagnosis is made and an intervention offered.

HYPERCHOLESTEROLAEMIA

A good example of stratified medicine is the identification of hypercholesterolaemia in an individual, which is recognised to cause a higher lifetime risk of coronary heart disease (CHD). Causes of raised blood cholesterol may be stratified into those due to environmental and/or polygenic factors, with a small proportion of individuals having a single genetic defect (that is, a monogenic cause), most commonly, a disease called familial hypercholesterolaemia (FH). FH is an autosomal dominant condition, meaning that on average, 50% of the children and siblings of an affected individual will have inherited the same gene mutation. It is estimated that around 1:250 of the general population have FH, with a possible 240 000 patients with FH in the UK, making it one of the most common monogenic disorders and much more common than type 1 diabetes. Compared to those who have a multifactorial cause for elevation of cholesterol levels, those with monogenic FH have over a three-fold higher risk of premature CHD and would be expected to lose roughly 10 years of healthy life as a consequence. If treatment (usually with statins) is started early enough and cholesterol is well controlled, those with FH can expect to have the same life expectancy as their unaffected siblings.[4] It is advised that this initial management takes place under specialist care rather than general practice. In a small proportion of patients with FH, where on-treatment cholesterol levels remain above recommended targets, treatment with more powerful lipid-lowering PCSK9 monoclonal antibodies may also be considered. Compared to early and intensive lipid-lowering statin therapy for monogenic causes of raised cholesterol, those with polygenic and multifactorial causes can be managed using standard statin therapy in general practice. This is a clear example of how knowing the underlying genetic aetiology of an individual's hypecholesterolaemia will lead to a 'stratified' medicine approach, which will also focus NHS resources on those at highest risk where benefit of intensive lipid lowering therapy will be greatest.

"Better interrogation of electronic healthcare records in primary care offers an opportunity to stratify patients into subgroups for targeted management ..."

In the recently revised FH NICE guidelines,[5] the recommendations relevant to primary care are summarised in Box 1, highlighting those that have been amended since the 2008 guidelines.[5,6] Taking into account the 99.5th percentile of total cholesterol in the UK general population, it is recommended that all individuals in a general practice database aged between 16–29 years with a total cholesterol >7.5mmol/l and all individuals aged ≥30 years with a total cholesterol >9.0mmol/l should be assessed for FH. Also, a premature history of CHD may indicate the possibility of FH, and GPs are recommended to suspect this possible diagnosis if an individual has a first-degree relative with evidence of CHD before the age of 60 years. Building on the NICE recommendations in the era of 'personalised stratified medicine', more sophisticated 'big data' analysis of patient records in general practice computer systems will help predict those individuals who are likely to have monogenic FH.[7]

Further, the current NICE guidelines recognise the critical importance of confirming the diagnosis of (monogenic) FH using a genetic (DNA) test and only those found to carry an FH-causing gene mutation, on testing, will then be given the diagnosis of FH, while those with the clinical features of FH but no mutation are best designated as 'polygenic hypercholesterolaemia'.[8] Only those relatives of patients with genetic test-confirmed FH should then be 'cascade tested' using the genetic test for the specific family FH-causing gene mutation, together with lipid measures to determine appropriate advice and therapy options. Recent economic analysis has confirmed that this approach is a highly cost effective strategy,[9] since 50% of first-degree relatives will also have the condition. Of course this will result in many children with FH being identified and the guideline recommends that children at risk of FH because of one affected parent, should be offered a genetic test at the earliest opportunity, and certainly by the age of 10 years, when treatment with statins should be initiated by a healthcare professional with expertise in treating children and young people with FH.

The updated guideline reinforces the 2008 recommendation that CHD risk estimation tools, such as 10-year QRISK2 and those based on the Framingham algorithm, should not be used to estimate risk in patients with FH because such people are already at a high lifetime risk of premature CHD. However, as a result of the on-going NHS Health Check programme, many individuals will be identified with raised cholesterol. These represent a hitherto unrecognised pool of at-risk subjects, a significant proportion of whom are likely to carry an FH-causing gene mutation. Further,

Box 1: Key recommendations from the 2017 NICE guidelines[4] to identify familial hypercholesterolemia relevant to general practice

1. Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:
   - a total cholesterol level >7.5 mmol/l, and/or
   - a personal or family history of premature coronary heart disease (coronary event before 60 years in an index individual or first-degree relative) (NICE, 2008, amended 2017).
2. Systematically search primary care records for people:
   - <30 years old, with a total cholesterol concentration >7.5 mmol/l and
   - ≥30 years or older, with a total cholesterol concentration >9.0 mmol/l as these are the people who are at highest risk of FH (new NICE, 2017).
3. Healthcare professionals should exclude secondary causes of hypercholesterolaemia before a diagnosis of FH is considered (NICE, 2008).
4. To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-Cholesterol (C) concentration because biological and analytical variability occurs (NICE, 2008).
5. For people with a personal or family history of premature coronary heart disease offer to measure their total cholesterol if not already known (new NICE, 2017).
6. Coronary heart disease risk estimation tools should not be used because people with FH are already at a high coronary heart disease risk (NICE, 2008, amended 2017).
7. Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings (NICE, 2008, amended 2017).
8. Refer the person to an FH specialist service for genetic testing if they meet the diagnosis criteria (see recommendation 7) (new NICE, 2017).
9. Inform all people who have an identified gene mutation diagnostic of FH that they have the diagnosis irrespective of cholesterol level (NICE, 2008, amended 2017).
10. Offer a high-intensity statin as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement (new NICE, 2017).

the risk of premature cardiovascular events for those with both monogenic and polygenic FH will be exacerbated by traditional risk factors such as smoking and obesity, and the effect of combining these risk factors is much greater than the simple sum of their individual contributions. Individuals identified with FH should be offered similar lifestyle advice and support (for example, smoking cessation measures) as non-FH subjects to manage these factors.

The choice of lipid lowering therapy for raised cholesterol levels also falls within the domain of (personalised) stratified medicine, more commonly described as pharmacogenomics. A key issue in primary care is poor compliance with statin therapy due to perceived musculoskeletal problems. Genomic information can indicate those at greatest risk of statin-induced myopathy with specific statins, such as simvastatin and rosuvastatin.[10] The evidence base for the impact of genomics on therapeutic options in cholesterol management is still emerging.

WHERE NEXT?

In the future, to stratify risk and management of patients with raised cholesterol will require incorporation of genomic data in primary care electronic health records on both monogenic disorders conditions and predisposition to more common polygenic variations, combined with better access to information on other risk factors for familial hypercholesterolemia and cardiovascular disease. The latter will require application of novel data analytic methods, such as advanced statistical analysis and machine learning approaches. Further, effective personalised stratified strategies for identification of causes and management of raised cholesterol requires evidence-based clinical pathways from primary to secondary to tertiary care. To improve this referral process requires increased awareness of this new taxonomy by both GPs and patients. This includes embedding these concepts in continuous medical education and revisiting knowledge transfer strategies. An added benefit of systematic interrogation of electronic health records and genomic data is equity of access to the appropriate health care, rather than those with the greatest health literacy at the forefront of accessing health services. This may help break Tudor Hart's inverse care law — better care for all rather than the few.

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Conflict of Interest
Nadeem Qureshi and Steve E Humphries were members of the NICE Familial Hypercholesterolaemia Guideline Development group (2016–2017). Steve E Humphries was funded by the British Heart Foundation (BHF PG08/008) and by the NIHR UCLH BRC and he is the Medical Director and minority shareholder of a UCL spin-out company called StoreGene, which uses a 20 SNP genetic test, in combination with the classical risk factor profile, for estimating an individual's future risk of CVD.

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