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Genomic Testing and Genomic Care: Are They Talking to Each Other?

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Introduction

In an economic climate of limited resources alongside technological advances and rising patient expectations, there are new challenges to the implementation of preventative medicine. This paper debates the dawn of personalised health care through genomic medicine, the challenges this creates when applied to existing health systems and straight-to-consumer testing.

The vision of genomic medicine is that screening, preventative health care and prescribing choices and initial dosage decision making will be based on information stored in a personal genomic and integrated electronic health record system. Health care would then be based on an individual's calculated risk rather than empirical evidence [1].

The principle of basing medical decisions on the concept of risk is not new. Table 1 shows comparative information on medical management guidance in a number of relatively common scenarios such as the use of statins in hypercholesterolaemia, treatment of hypertension, prevention of sudden death in hypertrophic cardiomyopathy, prevention of berry aneurysm rupture in autosomal dominant polycystic kidney disease, screening for Down Syndrome in pregnancy and the management of familial breast cancer susceptibility (Table 1).

Condition	Genetic testing offered		Screening offered		Intervention offered	
	Annual risk (%/yr)	Comment	Annual risk (%/yr)	Comment	Annual risk (%/yr)	Comment
MI/Ischaemic stroke in Hypercholesterolaemia [2]	>1	Offer risk assessment	>1	Offer risk assessment	>1	Offer 20 mg atorvastatin
MI/Ischaemic stroke in Hypertension [3,4]	-	Risk assessment offered to all	-	Offer to all to check BP at least every 5 years	>2	Offer anti-hypertensive
Sudden death in Hypertrophic cardiomyopathy [5-7]	-	Supplements clinical diagnosis	-	Not recommended	>3	ICD/Pacemaker
Berry aneurysm presence in polycystic kidney disease [8-10]	-	Not offered, clinical diagnosis	>1.1	Screen for presence	0.9-9.6	Repair when procedure mortality < rupture mortality
Down's syndrome in Pregnancy [11,12]	-	Integrated test offered to all	-	Ultrasound scan offered to all	1/150	Screen positive result for amniocentesis
Familial breast cancer [13,14]	10	Combined BRCA1/BRCA2 mutation probability	>1.2	MRI surveillance offered to patients at high risk of breast cancer	>1.2	Offer risk reducing mastectomy to high risk patients

Table 1: Annual risks above which genetic testing, screening or inventions are offered in six common scenarios.

Healthcare economics and decision making on value for money treatments are often encapsulated in NICE guidance based on Quality Adjusted Life Years (QALYS). These take into consideration how common, serious and treatable a disease is, the cost and effectiveness of the intervention and the potential long term benefit to the patient. An example is in the NICE guidance for the management in primary care of suspected cancer [15], where although the guidance 'recommends urgent investigation in adults with a 3% or higher cancer risk', it appreciates that the risk threshold would be less in children and teenagers, where early treatment would provide longer-term benefit to the patient.

What is striking about the conditions in (Table 1) is the remarkable consistency in the resulting risk required to consider the minimum intervention quotient tends to be close to 1% per year. In other words it is often felt that an intervention is indicated, such as preventative breast surgery or starting a statin, if the likelihood of an adverse outcome has been calculated to be in the region of 1% per year.

This creates complex challenges when direct to consumer genetic testing, wider gene panel, SNP arrays or whole genome testing is introduced. This is largely due to three reasons: Firstly we all have a number of potentially disease causing genomic variants, the significance of which can be difficult to interpret. Secondly, we do not have experience in interpreting the significance of genomic variation in individuals without a disease or a family history of the disease. For example we manage individuals with BRCA mutations in families with a strong family history but are less able to advise individuals where a mutation has been identified in another context where there have been no affected relatives. This is because risks of disease in even so called relatively straightforward inherited Mendelian conditions such as this may be affected by other lower risk modifier genes.

Finally and crucially the genetic traits identified by the new wave of technologies are likely to identify risks which are either small, hard to quantify in a setting of other inherited traits and environmental risk factors or unable to easily influence. Risks identified often fall under the 1% per year threshold making medical intervention less likely to be indicated or available. A prime example is seen when looking at APOE variants as a predictor for developing Alzheimer's disease by 85 years of age (Table 2). While the risk of developing Alzheimer's disease is markedly increased with each copy of the ε4 allele, the maximum possible risk is 0.8, the lowest value for intervention seen in Table 1. In contrast, any of the bottom three results (with an ε4 allele) would be reported as conferring a noticeable increased risk of Alzheimer's disease by the test (Table 2).

Alzheimer's disease APOE genotype	Men (% risk/year)	Women (% risk/year)
All genotypes	0.12-0.13	0.16-0.2
ε2/ε2 or ε2/ε3	0.05-0.06	0.07-0.09
ε3/ε3	0.08-0.09	0.12-0.14
ε2/ε4	0.21-0.24	0.32-0.36
ε3/ε4	0.26-0.27	0.35-0.41
ε4/ε4	0.6-0.61	0.71-0.8

Table 2: Annual risk of developing Alzheimer's disease by APOE genotype [16].

Additionally, there is only limited evidence regarding the ability to slow disease progression [17]. Raising anxiety could compromise the ethical principles of doing no harm and protecting patient autonomy during the consent process. In other words it is important to discuss with patients the potential consequences of identifying genomic variation and any ensuing treatment that would be offered in advance of the test taking place.

Such concerns have been previously reported. In 2013, the US Food and Drug Administration (FDA) requested a review of personal genome services (PGS) [18]. They cited concerns regarding the accuracy of, and interpretation, of results given to patients. Given the number of tests offered, it is very difficult to counsel and consent patients on the specific risks, benefits and further action surrounding each potential result that might be received. Doctors will need training on how to interpret genetic variation and the difference between a variant of unknown significance and definitively pathogenic, disease causing traits.

However, there is a role for consumer genetic testing in modern society. The FDA gave its first authorization to market a direct-to-consumer genetic test in February 2015 for Bloom syndrome carrier status [19]. The test involves genetic analysis for mutations in the BLM gene, which is associated with the disorder [20]. This suggests that at the moment, consumer testing can work well for testing for conditions caused by mutations conferring a known risk and in the past month the FDA have re-issued a direct to consumer more limited licence on the 21st October 2015 [21].

This debate leads to a classical dilemma of the need to continually work at the boundaries of medical knowledge to progress the field whilst managing realistic patient and doctor expectations. For example, should patients understand the degree of risk associated with the conditions they are being tested for and whether this could warrant any medical intervention before they are offered testing? Should such testing be advertised as an adjunct to medical management, and go hand-in-hand with genetic counselling?

Doctors, medical managers and patient groups will need educational support to be able to debate these issues and develop a clear way forward. Wider genetic testing and the identification of difficult to interpret, and act upon, genetic variants is coming. Are we ready to deal with what it may find?

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