



Predictive genetic testing for type 2 diabetes

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greater benefit for older people by virtue of their higher absolute risk for future stroke.⁸ Stroke specialists have a responsibility to disseminate these principles of good practice actively in their local healthcare communities. One way is to redesign stroke services and to integrate specialist and primary care responses to the management of transient ischaemic attacks in a similar manner to the approaches developed for coronary heart disease, which have led to a welcome reduction in the degree of related ageism.⁹

Ageism will always prosper when resources are inadequate for the target population. The UK government has recently been embarrassed into action by a damning report from the National Audit Office that highlighted deficiencies in specialist stroke services nationally, including the underprovision of clinics for patients with transient ischaemic attacks.¹⁰

Tackling institutionalised age discrimination more broadly in health services will require national leadership, with governments and health services openly acknowledging the presence of ageism. In England some early progress has been made, almost certainly due in part to a policy initiative delivered through the National Service Framework for Older People since 2001.¹¹ Mortality from coronary heart disease and cancer declined between 1993 and 2003, and access to elective surgery increased between 2000 and 2003.¹²

Some will argue, however, that ageism is so deeply embedded in our health service that policy initiatives will never represent more than a tinkering round the edges. Don't be surprised if older people lose trust in

their health service and lobby for protection through anti-discrimination legislation. The result would indeed be a patient led health service.

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May raise unrealistic expectations

The discovery earlier this year that a variant of the TCF7L2 (transcription factor 7-like 2) gene is associated with type 2 diabetes was reported in a front page story in the *New York Times*.^{1,2} The principal investigator, Kari Stefansson, told the newspaper that the discovery could lead to a diagnostic test to identify people who carry the variant gene. People who knew of their extra risk, he said, would be motivated to avoid the lifestyle habits that lead to diabetes. A Scottish scientist headed the research team, which led the Glasgow Herald to report, "Discovery of holy grail will help scientists treat diabetes."³

Undeniably this discovery is noteworthy. Type 2 diabetes is a leading cause of morbidity and mortality in the developed world and is increasing in prevalence worldwide. The association is robust—the finding has been replicated in three large independent study populations and offers potential new insight into the pathobiology of diabetes. Yet the claim that this knowledge will lead to a diagnostic test and hence to disease prevention—now routine for such genetic discoveries—may not be true. We believe that this syllogism (a logical argument in which one proposition (the conclusion) is inferred from two others (the premises))

oversimplifies the research findings and the challenge of translation and, above all, misleads the public.

The investigators estimated a 21% population attributable risk for the risk genotypes. This means that 21% of cases of the disease can be prevented when the negative effects of the genetic "exposure" are eliminated. However, by itself, a large population attributable risk does not indicate what efforts are needed to reduce the prevalence of diabetes in terms of the number who need intervention or the effectiveness of the preventive strategy. If this discovery led to a 100% effective intervention that specifically targeted the effects of the genetic variant, 45% of the general population would need to receive this intervention to prevent 21% of diabetes cases. If we assume an overall lifetime risk of diabetes of 33%,⁴ 88% of heterozygous carriers and 63% of homozygotes might not benefit from this intervention because they would not develop diabetes despite their TCF7L2 carrier status or they would develop diabetes from other causes. An intervention that specifically targets the effects of TCF7L2 variants would need to be cheap, harmless, and burdensome to warrant such substantial overtreatment.

Alternatively, as Kari Stefansson suggested, the genetic test could identify people at high risk who would benefit from appropriate advice on diet and physical activity (although this advice is applicable to all). The risk of diabetes is increased from 33% to 63% in homozygous TCF7L2 carriers (7% of the population), but the risk is increased from 33% to only 38% in heterozygous carriers (38% of the population). Would these figures provide enough incentive for carriers to change their lifestyles?⁵

Only a month before online publication of the discovery of TCF7L2, another study evaluated the simultaneous testing of PPARG (peroxisome proliferative activated receptor γ) and CAPN10 (calpain 10) SNP43/44 (single nuclear protein 43/44) genotypes and claimed that “genetic testing might become a future approach to identify people at risk of developing type 2 diabetes.”⁶ This conclusion was based on the finding that carriers of the PPARG PP and CAPN10 SNP43/44 GG/TT genotypes who were obese and had raised fasting plasma glucose values, had a 21.2-fold increased risk for type 2 diabetes compared with non-obese non-carriers with normal fasting plasma glucose. We showed that testing for these genetic variants would not improve the prediction of type 2 diabetes over body mass index and fasting plasma glucose concentration.⁷

Inferences about the public health applications of genetic testing are often based on single measures of association or indicators of test performance, such as the risk ratio or population attributable risk. Predictive genetic testing is useful when the value it adds to existing interventions outweighs the additional personal and social costs. This requires a complete evaluation of the test's performance characteristics, including sensitivity and specificity; its positive and negative predictive value in the population to be tested; the likelihood ratio of positive and negative test results; and the rates of false positive and false negative test results. These data are only part of the evidence base needed to recommend a test, which also includes information about effectiveness relative to existing alternatives, side effects, and costs.⁸ A risk ratio or population attributable risk alone cannot predict the potential usefulness of genetic testing.

News about genetic associations with type 2 diabetes and the potential for predictive testing was quickly picked up by patient organisations.⁹⁻¹² Ultimately, genetic discoveries may lead to better under-

standing of the disease process and to better therapeutic and preventive interventions. In the meantime, scientists and the media are responsible for accurately and carefully interpreting the implications of studies of genetic associations for the benefit of the general public. Raising unrealistic expectations—even inadvertently—could distract attention from what can be done by applying what we already know to prevent diabetes and its complications.¹³

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Tackling alcohol misuse at the front line

Training staff where patients usually present should improve detection and advice

The UK government announced at the end of last year that £3.2m (€4.8m; \$6m) was to be made available “for new initiatives which will help identify and intervene early with” people who may be damaging themselves with alcohol.¹ In 2004 in England 38% of men and 16% of women aged 16-64 had an alcohol use disorder (26% overall), equivalent to around 8.2 million people.²

About £217m is currently spent on specialist alcohol treatment, but compare that with the £20bn

estimated cost of alcohol misuse. We hope that some of the new money will be used to support those clinical settings in which alcohol misuse is common and detection and intervention are most likely to be rewarding—for example, in hospital emergency departments, general practices, and hospital wards.

Most conurbations in England have one or more specialist alcohol units, which are usually headed by psychiatrists and largely deal with complex problems such as dependence, psychiatric comorbidity, and

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