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Can genetic information change patient behavior to reduce Type 2 diabetes risk?

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As technology has improved and costs have decreased, the increasing availability of genomic testing promises genotype-tailored medical care. In this vision of the future, one's genotype can guide disease treatment decisions to optimize efficacy and minimize adverse reactions. Knowledge of one's genetic susceptibility may also help target primary prevention strategies before the onset of certain diseases. The lists of preventable conditions that stand to benefit from such genetic screening often include Type 2 diabetes (T2D), which has significant genetic and environmental components [1] and can be prevented with weight loss or medications such as metformin [2]. There is hope that the knowledge of one's genetic risk for T2D before disease onset will facilitate prevention by motivating patients for earlier and greater improvement in health behaviors, such as diet and physical activity. What follows is a discussion of whether the current scientific evidence supports such hopes.

Genetics of T2D

At least 65 genetic loci contribute to T2D risk [3]. Of these, rs7903146 in the *TCF7L2* gene is associated with the greatest risk: each copy of the T allele carries an odds ratio for T2D of 1.39. The effect sizes of most other T2D loci are generally much smaller (odds ratios typically ranging from 1.05 to 1.15) [3]. This contrasts with the much larger effect sizes of family history: T2D in one or both parents multiplies one's risk up to two- and six-fold, respectively [4,5]. Genotype risk scores that combine multiple T2D-associated loci significantly predict the future risk of T2D, but they may not improve traditional T2D prediction models consisting of routine risk factors such as family history, BMI, and fasting glucose [6,7].

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Review of the evidence on genotype information for motivating health behavior change

Regardless of whether knowledge of genetic susceptibility improves current T2D prediction models, it might still be a clinically useful tool if it motivates patients to make the health behavior changes important for T2D prevention. An emerging research field is investigating this possibility. Two recent trials have examined the utility of genotype testing for T2D prevention [8,9]. The Genetic Counseling and Lifestyle Change for Diabetes Prevention (GC/LC) Study was a randomized trial among 177 primary care patients identified to be at high risk for T2D because of traits of the metabolic syndrome [8]. Participants were randomized to genetic susceptibility testing based on 36 T2D-associated SNPs plus brief genetic counseling, versus no genetic testing. Genotyped participants were given a risk score summarizing their genetic risk as low, average or high. The 108 participants in the low-risk, high-risk and control arms were then enrolled in a 12-week lifestyle-modification program based on the Diabetes Prevention Program [10], where they learned strategies for weight loss to reduce T2D risk. The program was successful: at the study's end, the group overall achieved a mean weight loss of 8.5 lbs (standard deviation: 10.1), with 31% having lost at least 5% of their body weight. However, compared with the control arm, the arms receiving genetic risk information did not differ in their weight loss, attendance at the 12 Diabetes Prevention Program sessions, or motivation or confidence to make health behavior changes [11].

A second trial of T2D genotype testing for behavior change has recently concluded at Duke University (NC, USA), although the final results have not yet been published [9]. In this study, approximately 400 nondiabetic primary care patients undergoing a fasting blood draw were recruited from the phlebotomy waiting room. Participants were randomized to either brief standard T2D risk counseling based on fasting glucose, BMI and family history, or standard counseling plus genotype risk assessment with a DNA test consisting of four T2D-associated SNPs. Preliminary results at 3 months after counseling show no difference in weight loss between the two arms [12]. Outcomes after 12 months will include weight loss, insulin resistance, changes in diet and energy expenditure, and waist circumference [9].

Together, these two studies represent two ends of the spectrum of clinical contexts in which T2D genetic susceptibility testing might be undertaken. In the GC/LC study, all patients were at an elevated phenotypic risk for T2D, based on metabolic traits such as obesity or dyslipidemia [13]. All would therefore benefit from lifestyle modification for T2D prevention, irrespective of genotype [14]. The GC/LC study tested the hypothesis that genotype information might be a useful clinical tool to provide additional motivation for lifestyle modification in high-risk individuals beyond what traditional clinical risk communication alone could achieve. In the Duke University study, on the other hand, participants were not necessarily at high T2D risk. To a degree, this study models the scenario of genotype risk stratification in the general primary care population with average T2D risk. It is also important to note that the two studies differ in the resources provided to the participants to facilitate lifestyle modification after risk stratification. In the Duke University study, a physician extender delivered brief T2D risk assessment and counseling with or without genotype information. Participants were given educational materials but were not otherwise enrolled in a program to support behavior change. In the GC/LC study, all enrollees participated in a resource-intensive 12-week group lifestyle modification program that educated and supported them in their weight loss efforts. Many achieved significant weight loss, but knowledge of genetic risk did not seem to make success more or less likely. If the 12-month results of the Duke University study are consistent with its 3-month results, the summary of trial evidence will suggest that genomic information does not motivate health behavior change for T2D prevention.

At least one large observational study has contributed evidence on health behavior change in response to genotype susceptibility testing in a different and important context: simultaneous testing for multiple conditions. Such multiplex testing is how genomic results will likely be delivered in the future, as the cost of genome-wide analyses decreases. The Scripps Genomic Health Initiative followed 2037 enrollees for 3 months after receipt of SNP-based risk results for 22 different conditions, including T2D, as well as heart disease and various cancers and autoimmune diseases [15]. Overall, participants did not change their dietary fat intake or exercise habits over the study period, although most already had good habits at baseline. Receiving a higher T2D genetic risk estimate was not associated with greater improvement in these behaviors. However, receiving a higher genetic risk estimate for obesity was associated with greater fat intake and lower exercise scores after 3 months, but these results were not significant after accounting for multiple hypothesis-testing among the 22 conditions.

The future of genotype risk information for T2D prevention

At present, the small evidence base does not suggest that T2D genetic risk information can motivate preventive health behavior changes. These results will not surprise clinicians, whose efforts at counseling patients for weight loss and improvement in diet and exercise habits often fail. Behavior change is incredibly difficult. Health behavior theories, such as the Health Belief Model [16], recognize that knowledge of one's increased risk for a certain disease, be it through genetic testing or assessment of routine clinical risk factors such as BMI, is often not sufficient to effect behavior change. For genetic information to find a role in T2D risk reduction, future research should optimize the context in which genetic information is delivered. For example, neither the GC/LC nor the Duke University studies evaluated the strategy of targeting more resource-intensive behavior change interventions only among generally healthy participants with higher genetic T2D risk. As the cost of genotyping decreases, targeted efforts might prove a cost-effective method for T2D prevention among individuals not already at T2D risk based on routine clinical risk factors.

Although the patient-provider relationship is important for the clinical management of T2D risk, the impact of patients' genetic T2D susceptibility on healthcare providers has not received much attention. Genetic risk may have a synergistic effect on health behavior change when both the patient and provider are acting on that information. The GC/LC and Duke University studies have not reported how the participants' providers might have changed their medical decision-making based on the genetic information their patients received. Providers might consciously or subconsciously target greater preventive efforts to those at greatest risk, by addressing patient education more emphatically during an office visit or by referring such patients to weight loss programs more often. Indeed, in a recent survey of physicians, 20% said they would be very likely to spend more time counseling lifestyle change for hypothetical patients with high T2D genetic risk. Among primary care physicians and diabetes specialists, 13 and 24%, respectively, stated that high-risk T2D genetic results would make them more likely to prescribe metformin to prevent T2D for patients with prediabetes [17]. Further research will need to evaluate whether the change in T2D risk perception from genetic testing might act on both the patient and provider to bring about significant T2D prevention. At present, however, genetic testing for T2D risk likely does not improve preventive health behaviors in today's diabetogenic environment.

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Biography

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▪▪ of considerable interest

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