Perceived Impact of Diabetes Genetic Risk Testing Among Patients at High Phenotypic Risk for Type 2 Diabetes

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OBJECTIVE—Rapid advances in diabetes genetic epidemiology may lead to a new era of "personalized medicine" based on individual genetic risk assessment. There is minimal experience to guide how best to clinically implement such testing so that results (e.g., "higher" or "lower" relative genetic risk) improve rather than reduce patient motivation for behavior change.

RESEARCH DESIGN AND METHODS—Between November 2009 and May 2010, we conducted in-depth interviews with 22 overweight participants at high phenotypic risk for type 2 diabetes to explore perceptions of diabetes genetic risk testing compared with currently available prediction using nongenetic risk factors (e.g., family history, abnormal fasting glucose, obesity). We used hypothetical scenarios to specifically investigate the impact of both "higher" and "lower" relative genetic risk results on participants' views about diabetes prevention.

RESULTS—Many participants conferred a unique value on personal genetic risk information relative to nongenetic risk based on the perceived scientific certainty and durability of genetic results. In contrast, other participants considered their genetic risk within the overall context of their other measured risk factors. Reactions to diabetes genetic test results differed by current motivation levels. Whereas most subjects reported that "higher" risk results would motivate behavior change, subjects with lower current motivation often reported that "lower" genetic risk results would further reduce their motivation to engage in diabetes prevention behaviors.

CONCLUSIONS—To be effective, future clinical implementation of type 2 diabetes genetic risk testing should be individualized based on each patient's risk perception and current level of motivation to prevent diabetes.

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Evidence from landmark clinical trials such as the Diabetes Prevention Program has shown that type 2 diabetes can be prevented in high-risk patients by lifestyle changes that result in modest weight loss and increased physical activity (1,2). Patients can be identified as at increased type 2 diabetes risk based on easily available phenotypic markers such as fasting glucose levels, abnormal blood pressure or lipid levels, overweight, and family history (3). Despite available risk stratification tools and effective interventions, however, few patients successfully adopt and sustain the lifestyle changes necessary to prevent diabetes (4,5).

The contribution of heritable (rather than environmental) factors to type 2 diabetes has been estimated to be as high as 40% (6). Current approaches to defining diabetes risk using genome-wide association scans have identified over three dozen genetic loci present at >5% allelic frequency, which are each associated with a small but significant increased risk for type 2 diabetes (7). At present, combining all known, validated risk alleles provides only modest additional risk prediction after accounting for traditional phenotypic risk factors (8–11). Rapid advances in DNA sequencing technology, increased ability to identify rare risk loci, and identification of alternative heritable factors (e.g., copy number variation, epigenetic marks) hold promise that future iterations of diabetes genetic risk testing may provide a more robust assessment of an individual's heritable risk for diabetes (12–14).

Despite limitations of current diabetes genetic testing, the concept of "personalized genetic profiling" has gained increasing popularity and is a stated focus of research within the National Institutes of Health (NIH) (15). There are currently four clinical trials registered with clinicaltrials.gov that are addressing the clinical implementation of diabetes genetic testing (NCT01034319, NCT00849563, NCT01060540, NCT01186354). Before such testing becomes more widely implemented into clinical practice, it is critically important to better understand how patients at risk for diabetes perceive individualized diabetes genetic risk results (16,17).

The rise of direct-to-consumer genetic testing reflects an assumption that personal genetic information can motivate healthy behavior change (18,19). Although this assumption remains unproven, a recent survey of patients without type 2 diabetes provides some evidence that test results could motivate patients: nearly three-quarters (71%) of survey respondents reported that they would be "much more motivated" to make preventive lifestyle changes upon receipt of a higher genetic risk diabetes genetic testing result (20). This very optimistic anticipated reaction to genetic test results suggests that individuals may value genetic risk results differently than nongenetic risk results, although reasons for this anticipated impact are not clearly understood and require further study.

Accurate measurement of an individual's diabetes genetic risk could potentially provide significant clinical utility by identifying patients at particularly high risk for developing type 2 diabetes. Genetic testing may be a double-edged sword, however. Although higher genetic

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risk results may increase perceived risk and motivate individuals to adopt lifestyle changes, lower genetic risk results may decrease perceived risk and thus reduce motivation to adopt healthy lifestyle changes. Alternatively, higher genetic risk test results may induce a sense of genetic fatalism that undermines motivation to change behavior (21).

We conducted in-depth, semistructured interviews with participants at increased phenotypic risk for diabetes to gain insight into how they perceived diabetes genetic risk information. Participants were presented with hypothetical diabetes genetic risk results that placed them at "higher" or "lower" diabetes genetic risk. Responses were analyzed within the context of each participant's current motivation and attitude toward diabetes risk reduction. Our study was designed to *1*) investigate whether (and how) perceptions of genetic risk differed from traditional phenotypic risk factors and *2*) examine the relationship between current diabetes prevention behaviors and response to genetic test results.

RESEARCH DESIGN AND METHODS

Participants and recruitment

We conducted 22 individual interviews between November 2009 and May 2010 with patients recruited from the primary care practices of the Massachusetts General Hospital Practice-based Research Network (Boston, MA). This practice network includes a fully functional electronic health record and has implemented quality improvement programs focused on universal documentation of vital signs. Eligible participants were at increased diabetes risk based on meeting criteria for the metabolic syndrome, defined evidence from the medical record of at least three out of the five following: abnormal glucose results, hypertension, elevated triglyceride levels, low HDL levels, and overweight (22). We used medical chart review and phone screening to exclude patients with significant mental health problems (e.g., schizophrenia) or other barriers to effective communication (e.g., cognitive or language fluency limitations). Patients received a letter cosigned by their primary care physician and the study principal investigator (R.W.G.) inviting them to participate in the study. To avoid biased selection of participants with a specific interest in genetics, the recruitment letter simply stated that subjects were recruited "to participate in a federally-funded research study to understand patients' views about counseling for diabetes risk." All participants received a $20 gift card for interview completion. The study protocol was approved by the Massachusetts General Hospital Institutional Review Board.

Interviews

Structured questions initially elicited participants' views about their risk for developing diabetes and their motivation to adopt lifestyle changes for diabetes prevention. Participants were given a brief description of diabetes genetic risk testing that purposely avoided using numeric or scientific terms ("It recently became possible to estimate whether a person's individual genes make him or her at higher or lower risk for diabetes compared with other people like them"). We then asked participants how learning about their individual genetic risk for diabetes might affect their motivation and whether they perceived genetic risk for diabetes to be different from other kinds of diabetes risk.

To specifically address the contrast between phenotypic versus genetic risk, we asked participants to anticipate how they would react to two clinical testing scenarios, as follows. "Please imagine how you would feel in the following imaginary situations: *1*) Your doctor tells you that your risk of developing diabetes is high compared with other people based on things like weight and other measurements but lowered because of genetics. How would this affect your motivation to reduce your risk for diabetes by improving your diet and exercise over time? And *2*) Your doctor tells you that your risk of developing diabetes is high compared with other people based on things like weight and other measurements and also high because of genetics. How would this affect your motivation to reduce your risk for diabetes by improving your diet and exercise over time?"

After answering these questions, participants completed a brief survey that included a 1–10 scale to rate readiness, importance, and confidence for diabetes prevention. We used these data to categorize participants as having high or low motivation to prevent diabetes. For data analysis, we defined participants who ranked themselves highly for all three components (readiness, importance, and confidence) as the highly motivated group and participants who reported lower levels for one or more of the three components of motivation as the less motivated group.

Data collection and analysis

Interviews were digitally recorded, transcribed, and reviewed for accuracy and completeness. All five study authors participated in the analysis process and initially reviewed the transcripts to identify major concepts. We identified themes within each content area and established that thematic content saturation had been reached. We used open coding to develop categories and then refined definitions and the content of the codes and compared coding lists. Each interview transcript was independently coded by the lead author and at least one other member of the research team. We then conducted analyses to compare participants with low versus high motivation. At each analysis phase, the coders compared their results to resolve discrepancies through discussion and comparison of the raw data.

RESULTS

Study participants

Twenty-two adults (13 men, 9 women) at increased risk for diabetes participated. Mean age was 57.7 years, and the majority (14 of 22) had completed college (Table 1). From coded interviews, we determined that 14 participants were highly motivated in making or maintaining lifestyle changes for diabetes prevention, and eight were less motivated in making or maintaining lifestyle changes for diabetes prevention. Highly motivated participants were similar in age and education level, although more likely to be female and lower income than the less motivated subjects. Most patients (15 of 22) were aware of their increased risk for diabetes, and this awareness did not appear to be related to motivation levels (Fisher *P* value for the association between awareness of increased risk for diabetes and motivational level = 0.67). No significant differences in components of metabolic syndrome traits or treatment regimens were noted between highly motivated and less motivated participants.

Comparison of highly motivated and less motivated participants: diabetes knowledge and current diabetes prevention behaviors

Study participants were very knowledgeable about type 2 diabetes and risk factors for developing the disease, although

Table 1—*Demographics*

Patient characteristics	All participants (n = 22)	Highly motivated (n = 14)	Less highly motivated (n = 8)
Age, years (SD)	57.7 (10.0)	57.8 (9.9)	57.6 (10.9)
Men	13 (59)	6 (43)	7 (88)
Caucasian	17 (77)	11 (79)	6 (75)
≥College education*	17 (77)	17 (77)	6 (75)
Full-time employment	11 (50)	5 (36)	6 (75)
Household income >$50,000*	13 (60)	6 (43)	7 (88)
Aware of diabetes risk	15 (68)	9 (64)	6 (75)
Told of risk by primary care physician	7 (32)	3 (21)	4 (50)

Data are n (%) unless otherwise indicated. *Indicates one missing data point where the participant omitted a response.

several in the less motivated group lacked knowledge about how to engage in diabetes prevention. Both groups shared a basic understanding that environmental factors (e.g., diet and exercise) and heritable factors (specifically, family history) both contributed to diabetes risk. Despite this knowledge, some of the participants in the less motivated group were not aware of their own risk of developing diabetes. When asked about the likelihood of developing diabetes, for example, one participant remarked, "I haven't the faintest idea," and another remarked, "I don't know. I thought diabetes had something to do with sugar, too, and . . . I'm not a sugar person." Several low motivation group participants explained that they did not believe themselves to be at risk because their doctor had never raised the issue with them. As one participant noted, "I'm at the doctor's every month, so if I'm catching on to that, I'd know about it."

A major difference between groups was that the highly motivated participants were thinking proactively about diabetes prevention. Many in the highly motivated group had already spoken to their doctor about diabetes and had made specific changes to their diet or exercise habits. In contrast, participants in the less motivated group were either unaware that they were at increased risk for diabetes or were aware but not actively engaging in diabetes prevention. As one participant explained, "I'm not motivated. . .I'm not afraid. I don't think it's at that point where I've got to, you know, 'rally the troops and let's get after it.'" One participant in the less motivated group expressed fatalism, stating, "If it happens, it's going to happen, and there's nothing I can do about it." Less motivated participants cited various barriers for not actively working to prevent diabetes, including failure with previous weight loss attempts and lack of awareness of their current risk for diabetes.

Beliefs about genetic risk information

When asked to compare genetic risk information with other types of diabetes risk information, most participants in both groups expressed that they perceived genetic information to be more "certain," "factual," or "scientific" than phenotypic risk information. Participants in both groups commented that "there's an absolute certainty in genetics," and genetic information is "more scientific" and the results represents "physical evidence. . .coding that is going to make it easier for me to develop diabetes." In contrast, other participants considered genetic risk information to be of no greater intrinsic value than other risk information. Genetic and phenotypic risk are "two different ways of looking at the same thing; I wouldn't separate them." Several people commented that genetic risk information "is just one more piece of information" and that "it's all part of the same thing."

Impact of genetic testing

Consistent with a prior survey on patient views about genetic diabetes risk testing (20), most participants were enthusiastic about the possibility of getting such a test. Reasons for enthusiasm included the anticipation that genetic test results would more concretely define their risk and would help them maintain their level of motivation. As one participant put it, "It would be nice to know, so. . .I would be able to make changes in my diet if I needed to," and another said, "if I knew that I was really at risk to develop it, I would really want to continue what I was doing and see if there is any way I can be trying a little harder."

Participants in the higher motivation group were consistently enthusiastic about diabetes genetic testing. As one respondent explained, knowing that he was "genetically predisposed, then it would be a dramatic change" in his motivation to prevent diabetes. Interest in genetic testing among the less motivated group ranged from enthusiastic to skeptical. Some participants believed that genetic testing could be very motivating, such as the participants who commented, "I think that if I could have that type of information, I would be *much* stricter, because that would be the biggest motivating factor that I could have," and, "if they say, 'eventually, if you live long enough you'll get diabetes,' I'd do whatever I could to try to push it back further and be prepared for it." Others were more measured in their response, commenting, "I would say a little bit more [motivated]. I would start doing it a little bit more than I do right now," and "I definitely would put some credence into it." Several participants in the less motivated group also acknowledged that genetic testing for diabetes could "open their eyes" to the risk they face and that "it would be one more thing that would say to me, 'Hey, wake up.'" One participant did not believe genetic testing would be motivating to him to prevent diabetes, because getting diabetes is "down the road—there's just too many variables," and he did "not picture [himself] changing" in response to a genetic test.

Of interest, participants anticipated that the benefit of genetic testing would apply whether the test results were "low" or "high". One remarked, "I'll do everything, no matter what the [genetic] risk [result] is, to [reduce my risk for diabetes]." One participant pointed out that the genetic risk information could also be valuable to family members, commenting, "It would be nice to know, so I could tell my kids." A few participants also expressed hesitation related to genetic privacy. As one subject remarked, "The problem being, with something like that is, once you know, what does that do to your healthcare, insurance risks, and all that stuff?" There was also concern about the reliability of the test, such as the participant who commented, "I would have to say, 'how accurate is your genetic testing?'"

Response to high versus low genetic risk scenarios

To better isolate views about genetic risk from general diabetes risk, participants were asked to consider two scenarios in which their doctor informed them that they were at high phenotypic risk and had received either a high or low personal genetic risk result for developing diabetes. Many participants in both groups responded that their motivation to adopt healthy lifestyle changes to prevent diabetes would increase in both situations because of the high phenotypic risk present in both scenarios. As noted by one participant in the highly motivated group, preventing diabetes "is very important; whether you're high or low [genetic risk], it's very important."

In the highly motivated group, many of whom were already actively engaged in diabetes prevention, participants responded that the "high" genetic risk scenario would push them to work harder at diabetes prevention. Examples of this included: "I would re-examine where I might be able tighten things up a little bit," "consult a specialist at that point," "really go into high gear, eating less and try to lose weight," and "start making some changes to further increase the changes that I'm trying to make, already." Some participants in the less motivated group also found the "high" genetic risk scenario very motivating, commenting that it would "make me be totally cognizant of everything I do, and it would really push me to be incredibly strict, incredibly proactive" and "high in everything, it would motivate me!" Other participants in the less motivated group were less enthusiastic, but still believed that this situation "might motivate me a little bit more to do a little better," "would put more urgency toward it; it would give me little more of a kick," and cause me to "deal with it a little more." One participant in this group with a family history of diabetes noted that he would expect to get a result that he was at "high" genetic risk and that it would be "just another piece of the puzzle to confirm what they've been assuming all along." There was one individual in the less motivated group who said he did not "think it would" be motivating, because diabetes has "got to be happening," to motivate him to take action. Another participant in the less motivated group expressed a strong sense of fatalism that would reduce his motivation: "Even if you start to exercise you still can't convince your mind that you can overcome what your past generations have done."

When asked to respond to the "low" genetic (but high phenotypic) risk situation, participants in the less motivated group had more varied responses than those in the highly motivated group. Highly motivated participants said that they would "still continue doing what I was doing," whether because they are "so afraid of that disease that I will continue eating the way I do, and exercising," or "because I want to lose the weight, not because of the diabetes." Some participants remarked that they might "relax" a little more in terms of diabetes prevention but noted that other factors would still motivate maintaining a healthy lifestyle: "if the risk was really low, I suppose it would make me less motivated, but the sort of things that I am trying to do, I want to do anyway, not specifically. . .to prevent diabetes."

Although some participants in the less motivated group responded similarly to those in the highly motivated group, stating "I don't think I would change what I'm doing at the moment at all," it is important to remember that these participants were currently doing less to prevent diabetes than the highly motivated group. In response to this scenario, one participant commented, "I would still be a bit more conscious of what I do, how I eat and my physical activity, and I think that would give me a bit more motivation to change the things that I currently do, or don't do so well." There were, however, participants in the less motivated group who remarked that in the low genetic risk situation, diabetes would become "one less thing I've got to worry about—not that it would mean that I would say, 'well, I don't have to do anything.'" Instead, one participant said that because he "would probably worry less about diabetes" he would "worry more about my blood pressure and heart and all the physical things that I have a higher potential of happening to me, maybe." Of concern, one participant worried that her genetic testing would reveal "a comparatively low risk and then I'll say, 'Oh, fine. I'll be 300 pounds, who cares?' Which is not a good outcome."

Some participants with a family history of diabetes noted that they would expect to have "high" genetic risk, and that confirmation of this suspicion would increase motivation, whereas learning that they were at "low" genetic risk would reassure them and provide substantial psychic relief. One participant commented that getting a "low" genetic risk result would "make me feel safer, but I would probably still do the exercise and the diet." No participants in either group reported that they would substantially reduce current diabetes prevention behavior in response to the either the "high" or "low" genetic risk scenario.

CONCLUSIONS—Diabetes genetic risk testing has been heralded as a potentially useful new clinical tool to motivate behavior change for diabetes prevention (23). Although the current state of diabetes genetic risk testing is likely insufficient for clinical use, research advances may lead to an increased ability to define an individual's heritable risk for type 2 diabetes. Better insight into how patients respond to diabetes genetic risk results can inform how such results should be communicated to avoid the potential unintended consequence of decreasing motivation to adopt lifestyle changes. To better understand how patients might interpret personalized diabetes genetic risk results, we conducted in-depth structured interviews with subjects at high phenotypic risk for developing type 2 diabetes to assess views regarding the impact of such testing on their approach to diabetes prevention and to provide a framework for how diabetes genetic risk testing might be effectively implemented into clinical practice in the future.

Our study had two main findings. First, we identified a dichotomy between study participants who incorporated genetic risk into an overall risk assessment that included usual factors such as overweight and prediabetic fasting glucose levels versus participants who ascribed a unique value to personal genetic test results based on the permanence and perceived unique value of such testing. For these latter patients, there appeared to be an intrinsic value to the genetic test result beyond the simple numeric presentation of risk. This differential weighting of risk based on measurement source must be taken into account in future risk assessment tools and patient communication strategies.

A second main finding of our study was that the impact of the genetic risk results on reported subsequent behavior is strongly mediated by baseline levels of patient motivation (measured as readiness, importance, and confidence in adopting lifestyle changes to prevent diabetes). Whereas highly motivated patients

reported that they would gain further inspiration from a higher genetic risk result and would not let a lower risk result detract from their behavioral modification goals, less motivated patients were more likely to use a lower genetic risk result to reinforce their decision not to actively engage in health prevention. This finding that baseline motivation levels influence response to diabetes genetic test results suggests that providers should assess their patient's current knowledge and practice of diabetes prevention behaviors and motivation to change these behaviors when disclosing their diabetes genetic test results.

Type 2 diabetes represents an example of a complex polygenic disease (others include hypertension, asthma, hyperlipidemia) that differ from traditional Mendelian disorders in that test results convey moderate relative genetic risks that *1*) must be incorporated into an overall risk assessment (including well-defined phenotypic risk factors) and 2) can be modified with behavioral changes. For type 2 diabetes, patients who are identified as high risk must make sustained lifestyle changes (rather than making a single discrete decision, as with most other genetic testing paradigms) to prevent disease onset. Because diabetes prevention is not a single act or decision, but rather a continuous daily effort to eat healthy foods, get adequate physical exercise, and lose weight and/or maintain weight loss, patients must maintain their motivation for a long period of time. Genetic risk is correctly perceived as unmodifiable, and for some patients this persistent risk provides ongoing motivation independent of changes or fluctuations in their modifiable risk factors. Given that all patients with high phenotypic risk for diabetes would benefit from improved diet and increased exercise, we propose that if diabetes genetic risk testing becomes a part of clinical practice, test result disclosure (whether "higher" or "lower" relative genetic risk result) represents a potential "teachable moment" for both assessing and motivating behavior change. Thus result disclosure should be accompanied by counseling that both explains genetic risk (traditional genetic counseling) and also links the test result to subsequent behavior change (traditional diabetes prevention counseling).

Strengths and limitations

This study had several strengths. We contrasted results based on a multidimensional measure of motivation that quantitatively assessed three related motivation domains: readiness, importance, and confidence (24). Dichotomizing our participants by their baseline motivation allowed us to highlight the key role of current behaviors in mediating how diabetes genetic risk information is understood. Moreover, by presenting patients with two scenarios that explicitly contrasted "higher" versus "lower" diabetes genetic risk results in the specific context of increased phenotypic risk, we were able to isolate patient perceptions of the unique value of genetic risk results.

Participants were generally well educated. Further research involving participants with lower literacy and numeracy skills may provide additional key insights into how diabetes genetic risks would be interpreted and how such testing should be clinically implemented in the future.

Practice implications

Preventing diabetes requires motivation and commitment to make sustained lifestyle changes, including increasing physical activity and careful attention to dietary intake. Our study demonstrates that type 2 diabetes genetic risk testing may play a role in motivating patients to initiate or intensify lifestyle changes. For more motivated patients who were already making lifestyle changes, genetic testing results indicating a higher relative risk appeared to increase their sense of urgency to intensify healthy lifestyle behaviors, whereas lower risk results were not likely to reduce current preventive behaviors. For some less motivated patients, genetic testing results that conferred higher genetic risk seemed to represent a greater certainty of risk that lessened denial and increased feelings of vulnerability and urgency to prioritize action. However, lower risk results may have the unintended consequence of undermining motivation to adopt healthy lifestyle changes. To optimize motivation in these patients, the decision to undertake diabetes genetic risk testing should be linked with opportunity to enroll in a lifestyle intervention program to provide the structure, education, skills, and support necessary to facilitate sustainable lifestyle changes for diabetes prevention.

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