



Six-Year Diabetes Incidence After Genetic Risk Testing and Counseling: A Randomized Clinical Trial

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Genetics determine only a small proportion of common disease risk, but the potential to motivate health behavior change remains a proposed benefit of genetic susceptibility testing. Evidence supporting this benefit is scant (1), and studies of long-term clinical outcomes are absent. Type 2 diabetes is heritable yet preventable by behavior change. Although genetic scores predict incident diabetes (2), we demonstrated in the Genetic Counseling/Lifestyle Change (GC/LC) Study that learning one's genetic risk did not impact short-term weight loss or behavior change motivation among participants in a diabetes prevention program (3). Here, we examine 6-year diabetes incidence among participants.

The GC/LC Study was a randomized trial of diabetes genetic risk counseling among primary care patients (3). Eligible participants did not have diabetes but were at high phenotypic risk for diabetes in that they were overweight and met at least one other metabolic syndrome criterion. Participants were randomized to undergo genotyping for a diabetes genetic risk score (tested) versus no genotyping (control). Tested participants in the highest and lowest quartiles of genetic risk (intervention) remained in the

study. A genetic counselor delivered genetic risk results along with a counseling intervention emphasizing the behavioral and genetic risk factors for diabetes. All control and intervention participants were enrolled in a 12-week version of the Diabetes Prevention Program (DPP) (4). Although 33 (31%) participants lost $\geq 5\%$ of their body weight, weight loss and motivation for behavior changes did not differ between study arms (3). In this exploratory follow-up study, we identified incident diabetes among participants using electronic health records and a validated diabetes algorithm (5). Log-rank tests compared time to diabetes among study arms through the date diabetes criteria were met or the last visit in the electronic health records through 2016 (median 6 years). Figure 1 shows diabetes incidence by study group. Time to diabetes did not differ between groups (overall log-rank $P = 0.18$), but the results suggested lower diabetes incidence among control versus intervention participants (27 [95% CI 12–64] vs. 64 [42–97]) per 1,000 person-years, respectively; log-rank $P = 0.08$).

The promise of precision prevention depends in part on its ability to motivate health behavior change. However, a recent systematic review found no evidence

that genetic testing for common diseases motivates risk-reducing behavior (1). Likewise, we previously demonstrated that diabetes genetic risk testing did not impact short-term weight loss or preventive behaviors (3). Still, the hypothesis that genetic risk information acts subtly over a longer period to motivate prevention remains largely untested. Here, we find no evidence that a genetic risk testing and counseling intervention reduced 6-year diabetes incidence among patients at high phenotypic risk for diabetes. Diabetes incidence might actually have been higher among intervention participants, regardless of genetic risk; the relative roles of pathophysiology, health behavior, and ascertainment bias in this observation merit further investigation, ideally in populations with greater diversity. Limited statistical power necessitates that the present findings be considered hypothesis generating.

Context is key for any prevention intervention. Having features of metabolic syndrome, study participants were already known to have high phenotypic diabetes risk. We found no evidence that receiving counseling about genetic diabetes risk as an adjunct to participation in an evidence-based prevention program impacts long-term diabetes incidence.

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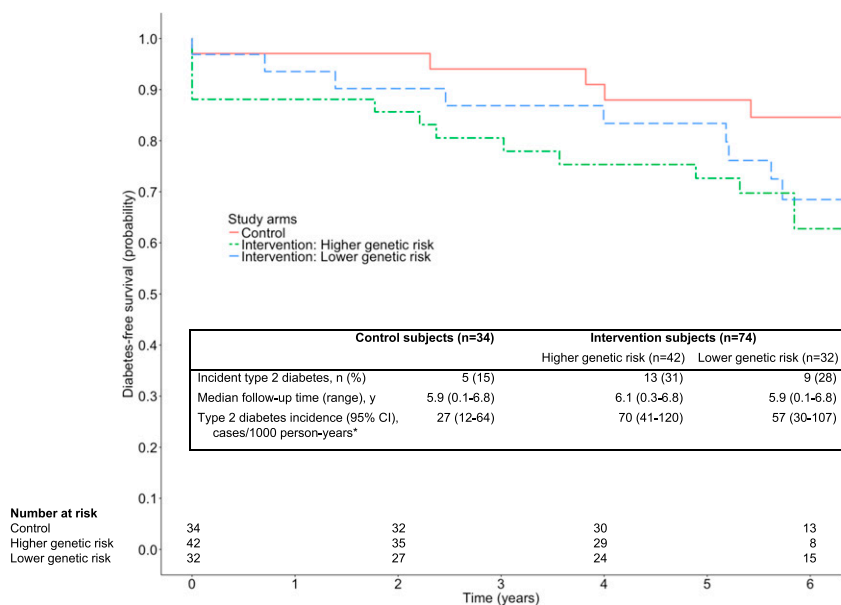


Figure 1—Diabetes-free survival among GC/LC Study participants. y, years. *Log-rank tests comparing time-to-diabetes: intervention vs. control, $P = 0.08$; higher vs. control, $P = 0.07$; lower vs. control, $P = 0.18$; higher vs. lower, $P = 0.63$.

Whether information about genetic risk can lower disease incidence among other clinical and nonclinical populations remains an open question.

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