Associations of Diabetes Genetic Risk Counseling with Incident Diabetes and Weight: 5-Year Follow-up of a Randomized Controlled Trial

Sridharan Raghavan, MD, PhD^{1,2,3} , Kerui Xu, PhD, MPH⁴, Cynthia J. Coffman, PhD^{5,6}, Samantha Pabich, MD⁷, David Edelman, MD^{5,8}, and Corrine I. Voils, PhD^{4,9}

¹Department of Veterans Affairs Eastern Colorado Health Care System, Aurora, CO, USA; ²Division of Hospital Medicine, University of Colorado School of Medicine, Aurora, CO, USA; ³Colorado Cardiovascular Outcomes Research Consortium, Aurora, CO, USA; ⁴Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ⁵Durham Center of Innovation to Accelerate Discovery and Practice Transformation, Durham, NC, USA; ⁶Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA; ⁷Division of Endocrinology, Diabetes and Metabolism, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ⁸Division of General Internal Medicine, Duke University School of Medicine, Durham, NC, USA; ⁹William S. Middleton Memorial Veterans Hospital, Madison, WI, USA.

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INTRODUCTION

Despite advances in understanding the genetics of type 2 diabetes (T2D), the benefits of precision medicine—better disease risk prediction and individually tailored prevention or treatment—remain aspirational. While patients have reported that genetic risk information would motivate preventive health behavior change,^{1, 2} this has not been borne out in short-term studies of genetic risk counseling.^{3, 4} The adoption of risk-modifying behaviors may be delayed as patients accumulate T2D risk factors and learn behavior change skills. We report the 5-year follow-up results of a randomized genetic risk counseling intervention on incident T2D and weight in a population of adults with elevated diabetes risk.

METHODS

The randomized clinical trial has been described.³ Briefly, 601 adults aged 21–65 years with body mass index (BMI) ≥ 27 kg/m², not actively losing weight, and receiving primary care at the Durham Veterans Affairs (VA) Medical Center were randomized to receive conventional T2D risk counseling plus either (a) genetic counseling from a licensed genetic counselor (CR + G; $n = 303$) or (b) control diabetic eye disease counseling (CR + EYE; $n = 298$). Participants randomized to CR + G

were genotyped on three single-nucleotide polymorphisms associated with T2D and categorized as having low, intermediate, or high risk of T2D. Local institutional review board provided human subject approval.

In this analysis, outcomes were incident T2D and electronic health record (EHR) weight over 5 years. Incident T2D was defined as having a diabetes diagnosis code from an inpatient encounter, or any combination of two of the following occurring on separate dates: hemoglobin A1c $\geq 6.5\%$, random plasma glucose ≥ 200 mg/dL, diabetes diagnosis code from an outpatient encounter, or any filled prescription for a hypoglycemic medication. Two successive logistic regression models were used to assess treatment differences in T2D incidence: (1) including only treatment arm indicator; (2) adding randomization stratification variables (BMI < 35 kg/m² versus ≥ 35 kg/m²; and family history of diabetes, unknown/low versus moderate/high), age, and sex. To examine treatment differences in weight trajectories, we fit random coefficient models to all available EHR weight measurements from 3 months prior to study enrollment through 6 years after study enrollment. One hundred seventeen of 19,368 weight values were excluded as outliers.⁵ Random effects for intercept and linear time were included to account for unequally spaced, repeated measurements. Fixed effects were fit to model a common slope for participants prior to enrollment and separate slopes by intervention arm post-enrollment. The linear, rather than quadratic, cubic, or quartic, functional form for time best fits the data based on the Akaike information criteria. We fit the same two models for weight as previously described for T2D.

RESULTS

Of 601 participants randomized at baseline, we excluded 24 individuals who died within 6 years after study enrollment and 4 who had no VA EHR weight measurements after enrollment, leaving 574 participants ($n = 284$ CR + EYE; $n = 290$ CR +

Prior Presentations This work has not been presented previously.

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Table 1 Study Participant Characteristics at Study Enrollment

	All participants, N=574	CR + EYE*, N=284	CR + G†, N=290
Age, years (mean ± SD)	54.1 ± 8.7	54.4 ± 8.3	53.8 ± 9.1
Race, n (%)			
Caucasian	237 (41.3)	108 (38.0)	129 (44.5)
African-American	307 (53.5)	157 (55.3)	150 (51.7)
Other/unknown	30 (5.2)	19 (6.7)	11 (3.8)
Female sex, n (%)	114 (19.9)	223 (78.5)	237 (81.7)
BMI ≥ 35 kg/m ² , n (%)	171 (29.8)	78 (27.5)	93 (32.1)
Family history risk of diabetes, n (%)			
High	133 (23.2)	58 (20.4)	75 (25.9)
Moderate	167 (29.1)	91 (32.0)	76 (26.2)
Low	268 (46.7)	132 (46.5)	136 (46.9)
Unknown	6 (1.1)	3 (1.1)	3 (1.0)
Fasting plasma glucose, mg/dL (mean ± SD)	90.6 ± 10.7	91.0 ± 10.8	90.2 ± 10.5
Genetic risk, n (%)			
High (4–6 high-risk alleles)	n/a	n/a	69 (23.8)
Moderate (3 high-risk alleles)	n/a	n/a	107 (36.9)
Low (1–2 high-risk alleles)	n/a	n/a	112 (38.6)
Unknown	n/a	n/a	2 (0.7)
HbA1c testing in years 4–6, n (%)	418 (72.8)	204 (71.8)	214 (73.8)

*CR + EYE, control eye disease counseling arm

†CR + G, genetic risk counseling arm

G). Participants in the two arms had similar demographics, baseline weight and fasting glucose, family history of diabetes, and HbA1c surveillance in years 4–6 after enrollment (Table 1). T2D incidence was 19.4% (55/284 participants) in the CR + EYE arm and 22.8% (66/290 participants) in the CR + G arm (adjusted odds ratio 1.17 [95% CI 0.78–1.77]). Incident T2D results were unchanged when we limited analysis to participants ($n = 271$ for CR + EYE; $n = 276$ for CR + G) who had an outpatient clinical encounter in years 4–6 of follow-up (data not shown). We also found no difference between arms in weight over 5 years of follow-up (Fig. 1). Among CR + G participants, there were no differences in T2D incidence or weight by genetic risk level (data not shown, all $p > 0.05$).

Figure 1 Association of treatment arm with 5-year weight trajectories in models adjusted for centered body mass index, family history of diabetes, centered age, and sex. CR + EYE indicates control eye counseling, and CR + G indicates genetic risk counseling. Results were similar in an unadjusted model.

DISCUSSION

Individualized T2D genetic risk counseling did not result in short-term³ or long-term weight loss, nor did it reduce 5-year T2D incidence. That the 5-year T2D incidence was 21% in the full study population confirms that participants had elevated risk at trial enrollment, though weight gain was less than expected. Importantly, we did not observe differential diabetes surveillance between treatment arms over 5 years of follow-up. Our results are consistent with those of a smaller, similarly designed randomized trial that found no effect of genetic risk counseling on 6-year T2D incidence in a high-risk, non-Veteran population.⁶ We conclude that provision of genetic risk information alone is insufficient to motivate lifestyle modification to the extent needed to prevent T2D incidence.

Corresponding Author: Sridharan Raghavan, MD, PhD; Department of Veterans Affairs Eastern Colorado Health Care System, Aurora, CO, USA (e-mail: Sridharan.raghavan@ucdenver.edu).

Author Contributions All authors contributed to study design and analysis plan development. Data were collected by CIV, CJC, DE, and KX; KX and CJC performed all analyses; all authors contributed to the interpretation of results, as well as drafting and critical revision of the manuscript.

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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REFERENCES

1. **Vassy JL, Donelan K, Hivert MF, Green RC, Grant RW.** Genetic susceptibility testing for chronic disease and intention for behavior change in healthy young adults. *J Community Genet* 2013; 4: 263–271.
2. **Wang C, Gordon ES, Norkunas T, et al.** A randomized trial examining the impact of communicating genetic and lifestyle risks for obesity. *Obesity*. 2016; 24: 2481–2490.
3. **Voils CI, Coffman CJ, Grubber JM, et al.** Does type 2 diabetes genetic testing and counseling reduce modifiable risk factors? A randomized controlled trial of Veterans. *J Gen Intern Med* 2015; 30: 1591–1598.
4. **Hollands GJ, French DP, Griffin SJ, et al.** The impact of communicating genetic risks of disease on risk-reducing health behavior: systematic review with meta-analysis. *BMJ*. 2016; 352: i1102.
5. **Maciejewski ML, Arterburn DE, Van Scoyoc L, et al.** Bariatric surgery and long-term durability of weight loss. *JAMA Surg* 2016; 15: 1046–1055.
6. **Vassy JL, He W, Florez JC, Meigs JB, and Grant RW.** Six-year diabetes incidence after genetic risk testing and counseling: a randomized clinical trial. *Diabetes Care* 2018; 41: e25–26.

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