Management of Hemoglobin Variants Detected Incidentally in HbA_{1c} Testing: A Common Problem Currently Lacking a Standard Approach

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Although HbA_{1c} is widely used for diagnosis and management of diabetes in clinical practice and research studies, management of the incidental detection of hemoglobin variants (e.g., hemoglobin S [HbS], HbC) by common HbA_{1c} methods, such as ion exchange high-performance liquid chromatography (HPLC), is not well established. Many clinical laboratories do not report the presence of hemoglobin variants, whereas others report them only if they interfere with HbA_{1c} measurement (1). As routine HbA_{1c} testing may incidentally yield information regarding hemoglobin variants that can affect clinical care, planning for appropriate management is warranted.

The Vitamin D and Type 2 Diabetes (D2d) Study is a multicenter, randomized, placebo-controlled trial testing whether vitamin D supplementation reduces diabetes incidence in people at high risk (2). Adults meeting at least two of the three criteria for prediabetes established in 2010 by the American Diabetes Association are eligible for enrollment, and a racially and ethnically diverse study population is sought to ensure generalizability of results. HbA_{1c} testing is performed using an HPLC method (Tosoh G8, Tosoh Bioscience, South San Francisco, CA) at the University of Vermont's Laboratory for Clinical Biochemistry Research. Review of chromatograms can reveal unexpected peaks reflecting the presence of hemoglobin variants. Although HbS and HbC do not interfere with the assay, the presence of other variants, such as HbE, precludes reporting of HbA_{1c} results. When an abnormal peak is seen, hemoglobin electrophoresis is performed to identify the hemoglobin variant. Because reporting of incidentally detected hemoglobin variants is not standardized, D2d investigators sought consultative opinions from colleagues in medical genetics and hematology/oncology, the study's Data and Safety Monitoring Board, and the University of Vermont Medical Center's Ethics Committee (Consultative Subcommittee).

As of 31 May 2016, 4,360 volunteers had undergone HbA_{1c} testing, of whom, 1,136 were black or African American. Overall, 98 participants (2.2%) had a hemoglobin variant detected (Table 1). Among the 95 affected volunteers who were black or African American, 78.9% had the HbS trait, 17.9% had the HbC trait, and 3.2% had other variants. The percentages of D2d participants with HbS and HbC are in keeping with those previously reported (3).

As hemoglobin variant detection is an intrinsic part of HbA_{1c} testing by HPLC (i.e., an "anticipatable" incidental finding, in the parlance of the Presidential Commission for the Study of Bioethical Issues), planning for the handling of this information was indicated. A key consideration favoring notification is that people may use knowledge of their hemoglobin variant carrier status in reproductive decision making to modify risk for offspring of serious conditions such as sickle cell disease (4). Knowledge of carrier status may also potentially provide direct health benefit to carriers. For example, among African Americans, HbS trait is associated with an increased risk of chronic kidney disease. Furthermore, some hemoglobin variants may alter red blood cell half-life, which could affect the accuracy and interpretation of HbA_{1c} levels.

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**A full list of D2d Research Group collaborators is listed in the APPENDIX.*

Table 1—Variant hemoglobins by race/ethnicity

	n	Variant Hb	HbS	HbC	Other*
Race					
Black or African American	1,136	95 (8.4)	75 (6.6)	17 (1.5)	3 (0.3)
Asian	182	0	0	0	0
American Indian/Alaska Native	21	1 (4.8)	1 (4.8)	0	0
Native Hawaiian/Pacific Islander	10	0	0	0	0
White	2,920	1 (0.03)	1 (0.03)	0	0
Other	91	1 (1.1)	1 (1.1)	0	0
Ethnicity					
Hispanic	448	4 (0.9)	3 (0.7)	1 (0.2)	0
Non-Hispanic	3,912	94 (2.4)	75 (1.9)	16 (0.4)	3 (0.08)
Total	4,360	98 (2.2)	78 (1.8)	17 (0.4)	3 (0.07)

Data are *n* or *n* (%). *Other hemoglobin variants included elevated hemoglobin F ($n = 1$) and probable HbE trait ($n = 2$).

Given these considerations, along with the relatively low risk associated with disclosing the finding (e.g., subsequent recognition of misattributed paternity), we determined that notifying participants was appropriate. Consequently, D2d investigators developed a plan for handling the incidental detection of hemoglobin variants. Single-page informational handouts on the two most common variants (HbS and HbC) briefly introduce the topic, suggest that the participant may want to share the finding with his or her primary care provider, and note that meeting with a genetic counselor could be considered if the participant is thinking of having children. A D2d staff member notifies the participant at the next study visit, and the relevant informational handout is shared and discussed. Notification, while occasionally eliciting surprise, has not yielded negative feedback from staff or affected participants.

Many clinical laboratories use HPLC assays for HbA_{1c} and elect not to report hemoglobin variants (1). Likely underlying this practice is the generally asymptomatic nature of carrier status. Additionally, many clinical providers are unaware that hemoglobin variants may be detected incidentally during HbA_{1c} testing (5) and may not be prepared to discuss such findings. Our approach to notification may be generalizable to clinical settings. Although we generated study-specific materials for distribution (available at http://www.d2dstudy.org/hemoglobin-variant), the National Institute of Diabetes and Digestive and Kidney Diseases has developed online resources on this topic for providers and affected individuals. As the detection of hemoglobin variants when measuring HbA_{1c} by HPLC is foreseeable and is common in racially diverse populations, this occurrence should be anticipated and requires a plan for appropriate management in clinical medicine and research.

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Appendix

D2d Research Group Collaborators. Anastassios G. Pittas, MD, MS, Bess Dawson-Hughes, MD, Lisa Ceglia, MD, MS, and Patricia R. Sheehan, RN, MPH, MS, Tufts Medical Center, Boston, MA (coordinating center); Michael R. Lewis, MD, MBA, University of Vermont, Burlington, VT (central laboratory); Lawrence S. Phillips, MD, Emory University School of Medicine, Atlanta, GA, and Atlanta VA Medical Center, Decatur, GA; John Foreyt, PhD, Baylor College of Medicine, Houston, TX; Ranee Chatterjee, MD, Duke University Medical Center, Durham, NC; Richard Pratley, MD, Florida Hospital Translational Research Institute for Metabolism and Diabetes, Orlando, FL; Chhavi Chadha, MD, HealthPartners Research Foundation, Minneapolis, MN; David Robbins, MD, University of Kansas Medical Center, Kansas City, KS; Anne Peters, MD, University of Southern California Keck School of Medicine, Los Angeles, CA; Irwin Brodsky, MD, and Clifford Rosen, MD, Maine Medical Center Research Institute, Scarborough, ME; Vanita Aroda, MD, MedStar Health Research Institute, Hyattsville, MD; Cyrus Desouza, MD, University of Nebraska Medical Center and Omaha VA Medical Center, Omaha, NE; Emilia Liao, MD, Northwell Health, New York, NY; Lisa Neff, MD, Northwestern University, Evanston, IL; Daniel Hsia, MD, Pennington Biomedical Research Center, Baton Rouge, LA; Patrick O'Neil, PhD, Medical University of South Carolina, Charleston, SC; Sun Kim, MD, Stanford University Medical Center, Stanford, CA; Karen Johnson, MD, University of Tennessee Health Science Center, Memphis, TN; Philip Raskin, MD, University of Texas Southwestern Medical Center, Dallas, TX; Erin LeBlanc, MD, Kaiser Permanente Northwest, Portland, OR; Sangeeta Kashyap, MD, Cleveland Clinic, Cleveland, OH; Neda Rasouli, MD, University of Colorado Denver and VA Eastern Colorado Health Care System, Denver, CO; and Myrlene A. Staten, MD, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Saul Malozowski, MD, Bethesda, MD, serves as the National Institute of Diabetes and Digestive and Kidney Diseases program official for the D2d study.

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