The predictive performance of Hemoglobin A1c for incident diabetes in different clinical and non-clinical settings.

b. Abbreviated Title (Length 26 characters):

HbA1c for diabetes prediction

2. Writing Group:

Writing group members:

Aaron Leong, Natalie Daya, Michael McPhaul, James Devlin, Bianca Porneala, Dov Shiffman, Elizabeth Selvin, James Meigs

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AL____ [please confirm with your initials electronically or in writing]

First author:

Aaron Leong
Massachusetts General Hospital
General Medicine Division
50 Staniford Street, 9th floor
Boston, MA 02114
Email: asleong@mgh.harvard.edu
Office Tel: 617-724-3502
Fax: 617-724-3544

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Elizabeth Selvin
Johns Hopkins University
2024 E. Monument Street
Suite 2-600
Baltimore, Maryland 21287
3. **Timeline:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data analysis</td>
<td>November 2016</td>
</tr>
<tr>
<td>Manuscript preparation</td>
<td>December 2016</td>
</tr>
<tr>
<td>Manuscript submission</td>
<td>January 2017</td>
</tr>
</tbody>
</table>

4. **Rationale:**

Hemoglobin A1c (HbA1c) is a widely used test to diagnose type 2 diabetes (T2D) and estimate an individual’s risk of developing T2D. HbA1c has several advantages over glucose measurements for screening and prediction of T2D, including lower intra-individual variability, lower analytic variability, higher repeatability, and use in the non-fasting state. Thus the test can be conveniently performed on individuals who have not fasted, or are unable to fast for prolonged periods.

While HbA1c is often measured as part of a comprehensive health assessment at a physician’s office to estimate a patient’s T2d risk, the test can also be performed in other settings. For instance, HbA1c can be measured on people outside of a clinical setting through point-of-care testing, or measured on non-fasting or fasting blood samples as part of a panel of laboratory tests without a thorough clinical evaluation. *The utility of HbA1c for the purpose of assessing short-term and long-term T2D risk in these various scenarios has not been thoroughly evaluated.*

5. **Main Hypothesis/Study Questions:**

We aim to test the hypothesis that HbA1c is associated with incident T2D over a two decade follow-up period independently of other T2D risk factors obtained in clinical and non-clinical settings. In the first scenario, we will determine the predictive performance of HbA1c measured by point-of-care testing at home, at the pharmacy, or at the shopping mall, during which the individual’s risk for developing T2D based only on their HbA1c value is provided to them. The second scenario describes the added value of measuring HbA1c for T2D prediction over other laboratory measurements, including fasting glucose, but without any other clinical information. The third scenario evaluates the use of HbA1c at a clinic visit for the purpose of estimating T2D risk in patients who have not undergone further laboratory testing. The fourth scenario is a complete clinical assessment in the physician’s office, including a fasting blood collection for fasting glucose and other laboratory measurements, for which HbA1c may still offer additional information for risk stratification. In subsidiary analyses, we estimated the short-term risk
(within 8 years of follow-up) and long-term risk (beyond 8 years) of developing T2D associated with an elevated HbA1c in the context of these scenarios.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Longitudinal cohort analysis with up to 23 years of follow-up data from Framingham Heart Study (FHS) and ARIC.

Inclusion: All participants at ARIC exam 2 and FHS exam 5 with HbA1c measured at baseline (ARIC exam 2, FHS exam 5).

Exclusion: T2D diagnosis at baseline defined by self-report, FG ≥ 7.0 mmol/L, or use of anti-diabetic therapy (ARIC exam 2, FHS exam 5).

Outcome: Incident T2D occurring during the follow-up examinations and annual phone interviews defined by self-report, FG ≥ 7.0 mmol/L, or use of anti-diabetic therapy.

Other variables of interest: body mass index, fasting glucose, high density lipoprotein, triglycerides, age, sex, systolic blood pressure, family history of T2D collected at baseline.

Data analysis: Logistic regression on the following four models, representing the four scenarios described in (5), to test the association of HbA1c and incident T2D and calculation of C-statistics. Effect estimates will be meta-analyzed across both cohorts.

Model 1: T2D ~ age + sex + HbA1c
Model 3: T2D ~ age + sex + HbA1c + FG + HDL + TG
Model 2: T2D ~ age + sex + HbA1c + BMI + SBP + parental history for diabetes
Model 4: T2D ~ age + sex + HbA1c + BMI + SBP + parental history for diabetes + FG + HDL + TG

7.a. Will the data be used for non-CVD analysis in this manuscript?

Yes

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?

Yes

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)
8.a. Will the DNA data be used in this manuscript?

No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
   ____ Yes   ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

Yes

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults.  
Selvin E1, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

No (closed HbA1c ancillary only)

11.b. If yes, is the proposal  
   ____ A. primarily the result of an ancillary study (list number* __________)  
   ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)  

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from