1.a. Full Title: Extended T2D Exome Chip Consortium Meta-Analysis for Type 2 Diabetes (EXTEC)

b. Abbreviated Title (Length 26 characters): EXTEC T2D consortium

2. Writing Group:
   Writing group members:
   Jim Pankow
   Man Li
   Liz Selvin
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   Megan Grove
   Eric Boerwinkle

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

First author: Jim Pankow (submitting on behalf of the leaders of the EXTEC meta-analysis group, Anubha Mahajan and Andrew Morris)

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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).

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3. **Timeline:** ARIC analysis has already been completed. A draft manuscript will be circulated to co-authors by the end of December 31, 2016.

4. **Rationale:**

Recent genome-wide association study (GWAS) meta-analyses and Metabochip meta-analyses have revealed over 100 loci for type 2 diabetes, FG, FI, 2-hour glucose, and hemoglobin A1c. The extent to which rare variants contribute to the variation in such measures, however, remains unknown.

The recent HumanExome BeadChip (“ExomeChip”) designed by Illumina contains nonsynonymous, nonsense, and splice site variants and affords the opportunity to evaluate over 240,000 predominantly rare variants in coding regions of the genome, discovered from over 12,000 individual and whole genome sequences representing diverse populations of European, African, and Native American continental origin. This ExomeChip represents nearly all non-synonymous coding and splice-site variation with a >1:1000 allele frequency in the European population. We propose to join the efforts of the Extended T2D Exome Chip Consortium in their analyses of type 2 diabetes to identify loci harboring rare coding variants associated with this condition.

The Extended T2D Exome Chip Consortium brings together the largest collection of T2D association studies typed with the exome chip from GoT2D/T2D-GENES, DIAGRAM, CHARGE and PROMIS. We estimate that it will have a combined sample size of more than 60,000 T2D cases and 150,000 controls.

The central meta-analysis will enable single-variant and gene-based association testing with T2D susceptibility. The study-level analysis plan has been developed to minimize the burden of analysts by utilizing single variant association summary statistics and covariance matrices. These summary statistics can be combined at the central meta-analysis level to perform a range of single-variant and gene-based association analyses. We propose to perform BMI unadjusted and BMI adjusted analyses to evaluate the impact of obesity on T2D association signals.

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

Analyses of exome chip data will identify novel rare coding variants that are significantly associated with T2D in ARIC and other participating cohorts.

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).**

**Subjects:** Type 2 status and covariates will be drawn from data collected at ARIC visit 1. Only subjects with Exome Chip genotyping will be included.

Two models will be employed:
T2D status, adjusting for age and sex
T2D status, adjusting for age, sex, and BMI

Analysis will be conducted separately in African Americans and whites. Principal components will not be included, as there will be an adjustment for population structure using a kinship matrix in a linear mixed model.

More details are provided in the EXTEC study-level analysis plan (attached).

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes    __x__ No

   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    ____ No
   (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? __x__ Yes    ____ 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”? __x__ 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

   ___x___ Yes     _______ No

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)? There are no related proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes    ____ No

11.b. If yes, is the proposal

   ___x__ A. primarily the result of an ancillary study (list number* _2009.12_____
   ___    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.csc.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 http://publicaccess.nih.gov/ are posted in http://www.csecc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.