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Yanwei Cai	WHI	ycai3@fredhutch.org
Christopher Haiman	MEC	haiman@usc.edu
Kari North	CCHC	kari_north@unc.edu
Piper Below	CCHC	jennifer.e.below@vanderbilt.edu
Laura Wiley	CCPM	laura.wiley@cuanschutz.edu
Chloé Sarnowski	ARIC	Chloe.Sarnowski@uth.tmc.edu
Peter Yang	Calico	peter.k.yang@unc.edu
Laura Jarmila Rasmussen-Torvik	CARDIA	ljrtorvik@northwestern.edu
Others TBD		

Partner studies collaborating with PAGE in this ms. proposal:

Name	Study	Email
Ran Tao	BioVu	r.tao@vanderbilt.edu
Christy Avery	UK Biobank	christy_avery@unc.edu
Bogdan Pasaniuc	UCLA Altas Biobank	pasaniuc@ucla.edu
TBD	BioBank Japan	
Chris Gignoux	Colorado Biobank	CHRIS.GIGNOUX@CUANSCHUTZ.EDU
Sridharan Raghavan	Colorado Biobank	SRIDHARAN.RAGHAVAN@CUANSCHUTZ.EDU
Tim Assimes	Million Veteran Program	tassimes@stanford.edu
Leslie Lange	Regards	LESLIE.LANGE@CUANSCHUTZ.EDU
Alaine Broadway	CEBU	alaine_broadaway@med.unc.edu
Penny Gordon-Larsen	CHNS	pglarsen@unc.edu
Others TBD		

II. SCIENTIFIC RATIONALE (Please be specific and concise)

The rise in diabetes prevalence is a major public health challenge which shows no signs of abating. Without sufficient efforts to combat this pandemic, it has been estimated that 10.2% of the global population will have diabetes [IDF Diabetes Atlas 9th Ed. (2019)] by 2030, at which time its economic burden may equal up to 2.2% of the global gross domestic product [1]. These predictions provide an urgent incentive to improve diabetes risk prediction and stratification. An emerging and promising approach to achieve this goal is the use of polygenic risk scores (PRS), which model the aggregate effect of common variants found across the genome on a disease or trait of interest. Such scores, combined with non-genetic predictors, potentially hold utility for identifying individuals at high risk prior to disease onset, motivate positive health behavior change or repeated screening for those at high risk, or even guide therapeutic interventions [2-4]. Within the Population Architecture using Genomics and Epidemiology (PAGE) Study, we recently showed that a multi-ancestry PRS for type 2 diabetes (T2D) outperformed population-specific scores and explained up to 15.3% of familial relative risk of T2D across diverse populations [5].

With increasing GWAS sample sizes and the development of PRS methods aimed at cross-population polygenic prediction, we are now able to use genetic information to quantify T2D risk. However, given the large number of important modifiable risk factors for T2D, there is a clear need to further characterize these scores. Moreover, it remains unclear whether PRS for T2D risk could hold prognostic value for diabetes-related complications across numerous organ systems in those with clinically overt disease. A recent investigation found that a T2D PRS was associated with T2D-related retinopathy and modest evidence of association with chronic kidney disease, peripheral artery disease, and neuropathy in a sample of European ancestry individuals [6]. The PAGE Study

is uniquely situated to address these questions and identify opportunities for tailoring prediction across multi-ancestry populations.

III. OBJECTIVES AND PLAN (Please be specific and concise)

a. Study Questions/Hypotheses.

Our *primary* study question will investigate whether a multi-ancestry type 2 diabetes (T2D) polygenic risk score (PRS) will be associated with T2D-related phenotypic risk factors and complications across diverse populations. In particular, we hypothesize that the T2D PRS may help identify individuals at greater risk of developing T2D-related complications. Our *secondary* study question will investigate whether the effect of the T2D PRS on T2D risk is mediated by T2D risk factors.

* Note that this manuscript proposal is intended to lead to a single manuscript. Upon determining sample sizes of the proposed traits in the Table based on the phenotype harmonization group's work, we will exclude/combine traits investigated as appropriate to limit the number of traits evaluated.

b. Outcomes, Covariates, OMICs Data Considered.

Outcome	Covariates*	Analysis Strata	Priority
Diabetes			
<i>T2D status</i>	age, age at dx, sex, BMI [1 7]	T2D cases & controls	Highest
<i>Fasting glucose</i>	hours fasting, age, sex, BMI, T2D status [1 4]	T2D controls	Highest
<i>Fasting insulin</i>	hours fasting, age, sex, BMI, T2D status [1 4]	T2D controls	Highest
<i>HOMA-IR</i>	hours fasting, age, sex, BMI, T2D status [1 4]	T2D controls	Highest
<i>HbA1c</i>	hours fasting, age, sex, BMI, T2D status [1 4]	T2D controls	Highest
<i>Gestational diabetes</i>	age, age at dx, BMI [3]	T2D controls	Moderate
<i>Family history of T2D</i>	T2D status, age, sex, BMI [1]	T2D cases & controls	High
Kidney Function			
<i>Nephropathy</i>	age, age dx, sex, BMI, BP, HbA1c, T2D [1 3 5 7]	T2D cases & controls	High
<i>ESRD</i>	age, age dx, sex, BMI, BP, HbA1c, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>CKD</i>	age, age dx, sex, BMI, BP, HbA1c, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>Serum cystatin-c</i>	age, sex, BMI, BP, T2D [1 4]	T2D cases & controls	Moderate
<i>Urine creatinine</i>	age, sex, BMI, BP, T2D [1 4]	T2D cases & controls	Low
<i>Serum creatinine</i>	age, sex, BMI, BP, T2D [1 4]	T2D cases & controls	Low
<i>eGFR</i>	age, sex, BMI [1 4]	T2D cases & controls	Moderate
<i>Urine albumin</i>	age, sex, BMI, BP, T2D [1 4]	T2D cases & controls	Low
Cardiovascular		T2D cases & controls	
<i>Heart attack</i>	age, age dx, sex, BMI, BP, lipid Rx, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>Heart failure</i>	age, age dx, sex, BMI, BP, lipid Rx, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>Stroke</i>	age, age dx, sex, BMI, BP, lipid Rx, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>Systolic bp</i>	age, sex, BMI, lipid Rx, T2D [1 4]	T2D controls	Highest
<i>Diastolic bp</i>	age, sex, BMI, lipid Rx, T2D [1 4]	T2D controls	Highest
<i>PAD/PVD</i>	age, age dx, sex, BMI, smoking, T2D [1 3 5 7]	T2D cases & controls	Moderate
Liver Function			
<i>NAFLD</i>	age, age dx, sex, BMI, alcohol, T2D [1 3 5 7]	T2D cases & controls	Moderate
<i>ALT</i>	age, sex, BMI, alcohol [1 4]	T2D cases & controls	Low
<i>AST</i>	age, sex, BMI, alcohol [1 4]	T2D cases & controls	Low
<i>CRP</i>	age, sex, BMI [1 4]	T2D cases & controls	Moderate
Other T2D Complications			

<i>Neuropathy</i>	age, age dx, sex, BMI, BP, HbA1c, T2D [1 3 5 7]	T2D cases & controls	High
<i>Retinopathy</i>	age, age dx, sex, BMI, BP, HbA1c, T2D [1 3 5 7]	T2D cases & controls	High
Lipids			
<i>HDL</i>	age, sex, BMI, lipid Rx, T2D, fasting status [1 4]	T2D controls	High
<i>LDL</i>	age, sex, BMI, lipid Rx, T2D, fasting status [1 4]	T2D controls	High
<i>Triglyceride</i>	age, sex, BMI, lipid Rx, T2D, fasting status [1 4]	T2D controls	High
<i>Total cholesterol</i>	age, sex, BMI, lipid Rx, T2D, fasting status [1 4]	T2D controls	High
Cancer			
<i>Breast cancer</i>	age, age at dx, stage, BMI, smoking [1 3 5 7]	T2D cases & controls	Moderate
<i>Colorectal cancer</i>	age, age at dx, sex, stage, BMI, smoking [1 3 5 7]	T2D cases & controls	Moderate
<i>Lung cancer</i>	age, age at dx, sex, stage, BMI, smoking [1 3 5 7]	T2D cases & controls	Moderate
<i>Pancreatic cancer</i>	age, age at dx, sex, stage, BMI, smoking [1 3 5 7]	T2D cases & controls	Moderate
<i>Prostate cancer</i>	age, age at dx, stage, Gleason, BMI, smoking [1 3 5 7]	T2D cases & controls	Moderate
Other			
<i>Obstructive sleep apnea</i>	age, age dx, sex, BMI [1 3 5 7]	T2D cases & controls	Moderate
<i>Complete blood counts</i>	age, sex, BMI [1 4]	T2D cases & controls	Low
<i>COVID</i>	age, age dx, sex, BMI, duration of hospitalization [1 3 5 7]	T2D cases & controls	Low

* All analyses will additionally be adjusted for self-reported race/ethnicity, genetic principal components of ancestry, and study site.

1. at T2D dx
2. at most recent visit
3. at dx of complication
4. at blood draw/ascertainment
5. median value between T2D dx and metric/complication dx?
6. controls at first encounter (as adult)
7. controls at last encounter
8. controls median (adult) value

1,2,3,4,5,6,7,8

Outcomes listed in the above table will be prioritized as indicated and based on the available sample size for each outcome. We fully anticipate some data types may only be reasonably derived from biobank data with electronic health records. Depending on sample sizes, some outcomes may be combined to increase our power to evaluate a given outcome. For each dichotomous outcome, *we will focus on incident cases*, where power allows. This will require information regarding age at diagnosis and age at first visit for cases and age at most recent visit for controls. Analyses involving continuous outcomes will require information regarding age at measurement. In the event of incomplete medication/treatment information, we will consider adjusting for DBP/SBP to account for this.

GWAS data imputed to the latest version of TOPMed Freeze 8 will be included.

c. Analytical Approach

Using imputed GWAS data across the PAGE and participating biobanks, we will construct the multi-ancestry T2D PRS used in Polfus, Darst et al., *HGG Advances* 2021 [5], which is based on a large multi-ancestry T2D GWAS meta-analysis (Vujkovic et al., *Nature Genetics* 2020 [6]). We will also consider constructing a PRS based on a more recent T2D GWAS meta-analysis that includes a larger number of non-European ancestry individuals (Mahajan et al., *medRxiv* 2020 [7]). In addition to evaluating a genome-wide significant PRS based on these previous studies, we will evaluate a genome-wide PRS using recent approaches such as LDpred2, PRS-CSx, and others. Prior to

conducting association analyses, we will determine whether the sample sizes of T2D cases with the above listed T2D complications and risk factors are sufficient to perform analyses; for traits that we are underpowered to investigate, we will consider combining traits based on biological similarities, where appropriate.

For our *primary* study question, in analyses stratified by T2D status, we will evaluate the association between the T2D PRS and the outcomes listed in the above Table using linear or logistic regression models adjusted for the covariates specified in the Table. To determine whether the T2D PRS effectively identifies T2D cases with greater risk of developing comorbidities, we will evaluate the improvement of the model performance upon adding the T2D PRS to the model using metrics such as area under the curve (AUC), net reclassification index (NRI), and R^2 , depending on the trait.

For our *secondary* study question, we will evaluate whether the T2D risk factors in the Table mediate the effect of the T2D PRS on T2D status. This will be performed using regression models to assess the relationship between 1) the PRS and T2D risk, 2) the PRS and the T2D risk factor, 3) the T2D risk factor and T2D risk, and 4) the PRS and T2D risk while adjusting for the T2D risk factor. The causal mediation effect (i.e., the indirect effect of PRS on T2D risk mediated by the T2D risk factor) will be calculated as the difference between the effect of the PRS in Models 1 and 4, implemented in the R “mediation” package. To determine whether this difference is significant, standard errors and P-values will be estimated using the quasi-Bayesian Monte Carlo method with 1,000 simulations. Models will include the covariates specified in the Table, with PRS models additionally adjusting for principal components of ancestry.

Analyses will be performed within ancestral populations and meta-analyzed across populations to obtain multi-ancestry effect estimates and to evaluate whether effect heterogeneity exists between populations. If sample sizes are insufficient to perform analyses within populations or if admixture would result in the exclusion of participants from analyses, we will instead perform analyses using mixed models with a genetic relationship matrix to account for distant or recent relatedness and to ensure an inclusive investigation.

An additional sub-analysis of incident complications risks will consider exclusion of incident T2D, to test the degree to which diabetes phenotypic versus genetic risk contribute to complications outcomes. For CVD, for instance, phenotypic risk (having T2D *and* its concomitant CVD risk factors) only explains about 60-70% of the risk for outcomes, meaning that there is something additional that comes with T2D that confers excess risk for CVD. We think that this risk may be revealed by differences in risk conferred by genetic vs phenotypic risk, with a focus on genetic factors conferring risk uncorrelated with diabetes phenotypic CVD risk factors.

d. Anticipated date of draft manuscript to P&P: Summer/Fall of 2022 (depending on availability of phenotypic data)

e. What manuscript proposals listed on www.pagestudy.org/index.php/manuscripts/ are most related to the work proposed here? Approved PAGE ms. numbers: _____

- **If any: Have the lead authors of these proposals been contacted for comments and/or collaboration? Yes__ No__**

IV. SOURCE OF DATA TO BE USED (Check all that apply)

Study Name	Included
ARIC	Y
HCHS/SOL	Y
CCHC	Y

MEC	Y
BioME	Y
WHI	Y
CARDIA	Y
MESA	N

* Note that MESA may be included at a later stage for replication of findings, not in the primary analysis. We will submit a separate study proposal to MESA as appropriate.

I, (initials), affirm that this proposal has been reviewed and approved by all listed investigators.

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Valladares-Salgado, Rob M van Dam, Jan B van Klinken, Rohit Varma, Marijana Vujkovic, Niels Wachter-Rodarte, Ellie Wheeler, Eric A Whitsel, Ananda R Wickremasinghe, Konstantin Willems van Dijk, Daniel R Witte, Chittaranjan S Yajnik, Ken Yamamoto, Toshimasa Yamauchi, Loïc Yengo, Kyunghoon Yoon, Canqing Yu, Jian-Min Yuan, Salim Yusuf, Liang Zhang, Wei Zheng, FinnGen, Leslie J Raffel, Michiya Igase, Eli Ipp, Susan Redline, Yoon Shin Cho, Lars Lind, Michael A Province, Craig L Hanis, Patricia A Peyser, Erik Ingelsson, Alan B Zonderman, Bruce M Psaty, Ya-Xing Wang, Charles N Rotimi, Diane M Becker, Fumihiko Matsuda, Yongmei Liu, Eleftheria Zeggini, Mitsuhiro Yokota, Stephen S Rich, Charles Kooperberg, James S Pankow, James C Engert, Yii-Der Ida Chen, Philippe Froguel, James G Wilson, Wayne HH Sheu, Sharon LR Kardia, Jer-Yuarn Wu, M Geoffrey Hayes, Ronald CW Ma, Tien-Yin Wong, Leif Groop, Dennis O Mook-Kanamori, Giriraj R Chandak, Francis S Collins, Dwaipayan Bharadwaj, Guillaume Paré, Michèle M Sale, Habibul Ahsan, Ayesha A Motala, Xiao-Ou Shu, Kyong-Soo Park, J Wouter Jukema, Miguel Cruz, Roberta McKean-Cowdin, Harald Grallert, Ching-Yu Cheng, Erwin P Bottinger, Abbas Dehghan, E-Shyong Tai, Josee Dupuis, Norihiro Kato, Markku Laakso, Anna Köttgen, Woon-Puay Koh, Colin NA Palmer, Simin Liu, Goncalo Abecasis, Jaspal S Kooner, Ruth JF Loos, Kari E North, Christopher A Haiman, Jose C Florez, Danish Saleheen, Torben Hansen, Oluf Pedersen, Reedik Mägi, Claudia Langenberg, Nicholas J Wareham, Shiro Maeda, Takashi Kadowaki, Juyoung Lee, Iona Y Millwood, Robin G Walters, Kari Stefansson, Simon R Myers, Jorge Ferrer, Kyle J Gaulton, James B Meigs, Karen L Mohlke, Anna L Gloyn, Donald W Bowden, Jennifer E Below, John C Chambers, Xueling Sim, Michael Boehnke, Jerome I Rotter, Mark I McCarthy, Andrew P Morris. medRxiv. 2020.

* We suggest inclusion of PAGE coauthors from all participating studies.