Study Purpose and Rationale

Cardiovascular disease (CVD) is a leading cause of death and disability worldwide, accounting for 17.9 million deaths and the loss of 348 million disability-adjusted life years in 2015 alone[1]. Diabetes and obesity are very strong risk factors for CVD. Individuals with diabetes and obesity have an 82.75% life-time risk for developing CVD[2]. While treatments do exist for both obesity (e.g. bariatric surgery) and diabetes (e.g. pharmaceutical control of blood sugar levels), they only partially attenuate risk of adverse health outcomes and they do not address prevention and upstream causes of cardiovascular diseases, namely sedentary lifestyle and unhealthy diet. Despite the known cardiovascular benefits of regular physical activity and having a balanced diet, it has proven challenging to change health behaviours towards favourable lifestyles[3–5]. Indeed, the prevalence of obesity is increasing in Canada as less than 80% of adults follow the current recommendation of 150 minutes of moderate-to-vigorous physical activity per week and approximately less than 60% of adults consume fruits and vegetables 5 or more times a day[6,7]. The overarching aim of our study is to test the effect of providing personalized genetic information along with diet and exercise plans on adherence to healthy lifestyle habits and cardio-metabolic risk. There is tremendous public interest in genetics and some evidence that providing genetic information can help improve health habits[8]. However, no intervention to date has examined the effect of comprehensive genetic testing using cutting-edge polygenic score (PGS) prediction and an interactive health portal on health behaviours and cardio-metabolic risk.

Hypothesis and Objectives

We hypothesize that providing participants with detailed genetic information about genetic determinants of fitness and nutrition traits will help motivate them to adopt healthy lifestyle habits. Our primary objective is to test the effect of providing genetic information and interactive recommendations for diet and exercise on adoption of healthy behaviours. Our secondary objective is to evaluate the effects of the personalized health recommendations on cardio-metabolic risk markers, such as dysglycemia and dyslipidemia.

Study Design

We propose to conduct a randomized controlled trial investigating whether personalized lifestyle recommendations including genetic information motivates Hamilton Health Sciences employees to adopt healthy lifestyle changes. Study participation will be open to all Hamilton Health Sciences employees. Eligible and consenting individuals will be enrolled starting in March 2017. Enrollment will occur in a staggered fashion. The intervention group will receive (1) a free 3-month GoodLife Fitness gym membership providing access to any Canadian GoodLife Fitness facility, (2) professional trainer-approved workout plans, (3) dietitian-approved meal plans, and (4) genetic information pertaining to their health and fitness. The control group will also receive a GoodLife Fitness membership to ensure that all study participants are granted similar ease-of-access to perform physical activities but will not receive the personalized component of the intervention (workout plans, meal plans or genetic information) until the end of their trial period. Participants will be randomized to treatment or control groups using a minimization scheme for adaptive randomization, which will serve to balance age, gender, and ethnicity across groups as participants are enrolled. Thus, randomization will be performed in a single-blind fashion wherein the study team is unaware of whom is receiving the intervention or control. All study participants will be monitored over the course of 3 months beginning with their baseline assessment and ending with their 3-month follow-up assessment. At these two timepoints, study participants will be assessed for behavioural (physical

activity levels and diet healthiness) and biological markers (lipoproteins, fasting glucose, and inflammation) of cardio-metabolic disease.

Trial Population

The trial will enrol healthy adults (18-65 years) that are employed by any Hamilton Health Sciences site (Chedoke, Hamilton General Hospital, Juravinski Hospital, Juravinski Cancer Centre, McMaster University Medical Centre, McMaster Children's Hospital, West Lincoln Memorial Hospital, St. Peter's Hospital). Individuals will be excluded from the trial if (1) they are unable to or express an unwillingness to comply with core components of our study protocol (i.e. blood draws, fitness assessments, diet plan, workout plan) or if (2) they have a cardiovascular disease or insulin-dependent diabetes. See Table 1 for the full eligibility questionnaire form and schema. There could be a delay between the time when someone completes the eligibility questionnaire form and the time of official enrollment. As such, potential study participants will be told to contact the study team should any of their responses to the eligibility questionnaire change and will also be prompted before performing their baseline assessment (data collection sheet, blood draw, and fitness assessment).

Table 1. Eligibility Questionnaire Form

Number	Question	Exclude if response is:
1	Are you employed by Hamilton Health Sciences?	No
2	Would you be willing to attend a GoodLife Fitness centre in Hamilton or Ancaster?	No
3	Are you planning to take vacation for more than 2 weeks from May 1, 2018 to July 31, 2018?	Yes
4	Are you currently pregnant, breastfeeding or planning to be pregnant from May 1, 2018 to July 31, 2018?	Yes
5	Are you currently taking insulin?	Yes
6	Have you ever had a bone marrow transplant?	Yes
7	Have you ever had a stroke, heart attack, coronary artery bypass graft (CABG) surgery, peripheral artery disease, or coronary angioplasty?	Yes
8	Are you currently taking any of the following medications: blood thinners (e.g. warfarin), ACE inhibitors (e.g. captopril, enalapril, lisinopril, moexipril, quinapril, ramipril), antibiotics (e.g. linezolid), antidepressants (e.g. phenelzine, tranylcypromine)	Yes
9a	One aspect of lifestyle that we are hoping to enhance is physical fitness. If you participate in the trial, you will receive a personalized workout plan. Are you willing to comply to a trainer-approved workout plan from May 1, 2018 to July 31, 2018?	No
9b	Are you willing to perform two physical fitness assessments (baseline and 3 months later)?	No
9c	Do you currently have any conditions that restrict your ability to exercise regularly (e.g. osteoarthritis, knee injury, chronic back pain, arrhythmia)?	Yes
10a	If you participate in the DNA_{ble} trial, you will receive a personalized meal plan. Are you willing to comply to a dietician-approved meal plan from May 1, 2018 to July 31, 2018?	No
10b	Do you currently have any dietary restrictions due to food sensitivities (e.g. gluten, soy, peanuts, eggs, shellfish, etc.), preferences (e.g. vegetarianism, veganism), or medical conditions (e.g. Crohn's disease, bulimia nervosa)?	Yes

11	Blood biomarkers, such as lipid and fasting glucose levels, will be tested to monitor changes in your cardiovascular health. Are you willing to have blood testing performed by a medical professional in a hospital setting on two separate occasions: at baseline and 3 months later?	No

Participant Benefits and Risks

The major incentive for Hamilton Health Sciences employees to participate in this trial is that they will be equipped with new tools designed to improve their fitness and dietary habits. Specifically, study participants will receive personalized exercise plans, meal plans, a 3-month GoodLife Fitness gym membership, and their genetic results. Conversely, major risks of participating in this trial include unintended disclosure of personal information and injury from performing exercises. Protocols have been built-in to reduce mitigate these risks and are detailed in subsequent sections. In accordance with Good Clinical Practice, all study participants may exert their right to withdraw from the trial at any point in time for any reason with no obligation to reveal the reason for discontinuation.

Study Methodology & Workflow

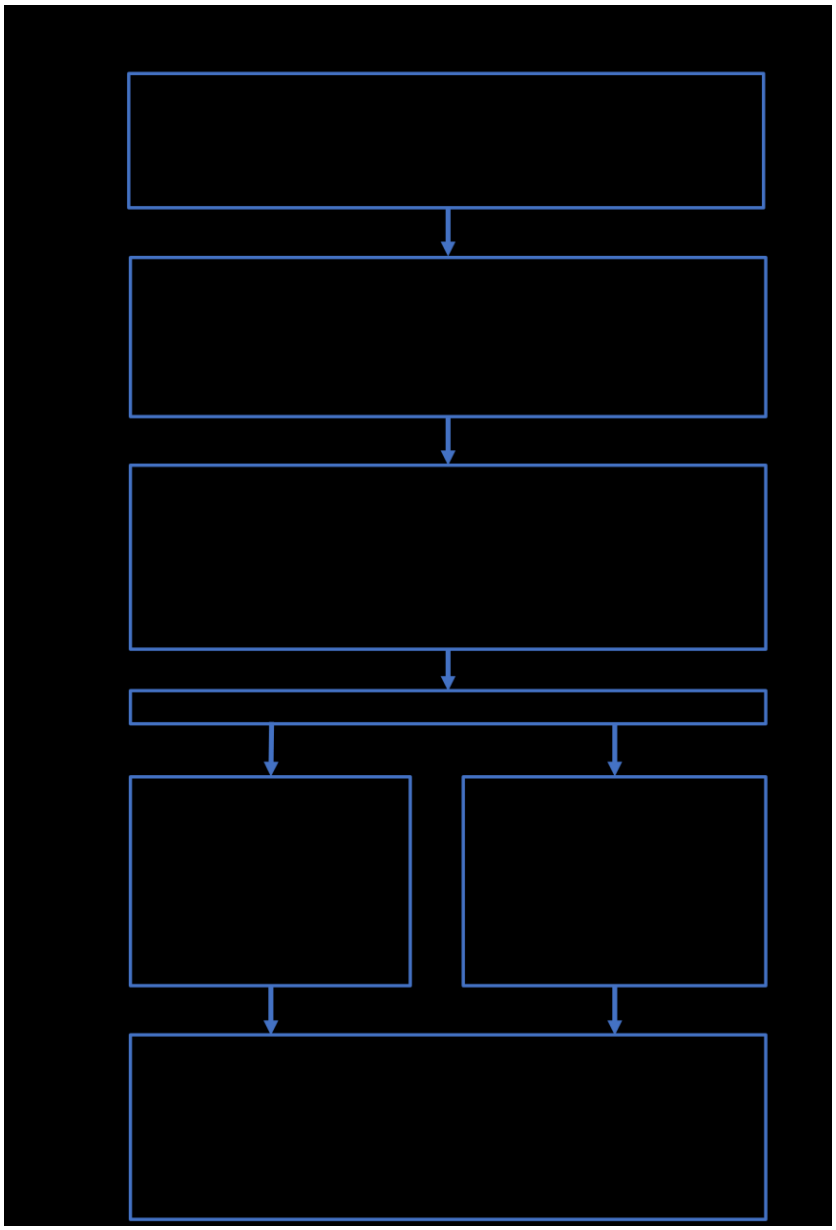

Figure 1. DNAble study workflow.

Advertising, Marketing, Recruitment

The study will be marketed exclusively to Hamilton Health Science employees. All marketing materials will indicate that the study is supported by HHS and Ted Scott, HHS Chief Innovation Officer of Strategy. In an attempt to reach as many HHS staff as we can, we will collaborate with the HHS Public Relations and Communications department. We plan on using channels such as employee email advertisements, employee wellness programs and the employee incentive discount program to maximize exposure. We also plan to advertise through social media platforms, such as the HHS staff (@HHS_staff), and HHS-IBM Innovation Exchange(@HHS_innovationX) twitter accounts. Finally, we will employ flyers and posters to advertise to staff on billboards in HHS hospitals and facilities. As part of our recruitment strategy, each participant will receive a free 3-month membership to any GoodLife Fitness centre in Canada

and a complimentary GeneBlueprint genetic test. Please find in the attached email: Email Recruitment Script, Recruitment Poster Sample and online Registration landing page (https://geneblueprint.com/pages/gbp-hhs-trial-signup2).

Eligibility, Consent, and Enrollment

An electronic questionnaire form will be sent to all individuals that have expressed interest in participating in the trial. This questionnaire will determine their eligibility for trial participation. Individuals that meet all eligibility requirements will be provided with (1) a study information sheet providing further details about the trial (e.g. information on the intervention) and (2) consent form. To allow for timely collection of informed consent data from multiple centres, we propose to administer consent through an electronic form. Electronic informed consent will adhere to guidelines outlined by the FDA (https://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf). As with paper consent, individuals will be asked to initial, date, and sign each section of the consent form. A member of the trial team will be available Monday to Friday during work hours to answer any questions or concerns about the consent form or study via telephone and e-mail. Paper consent forms will also be made available at each study site if individuals are uncomfortable with electronic consent. The first 500 eligible and consenting individuals will be selected for participation in the trial. Subsequently, a follow-up questionnaire gathering demographic information for the purposes of logistical planning and to help to inform the randomization scheme will be issued.

Baseline Assessment

The baseline assessment will be identical for participants assigned to either the intervention or control group and will consist of: (1) completing the study report form, (2) a blood draw which will provide biological material for laboratory testing, (3) and a low-risk fitness assessment which does not involve any physical activity. The study report form will collect information pertaining to demographics, medical history, dietary habits, physical activity levels, mental health and wellbeing, as well as attitudes, feelings, and competency regarding genetic testing. The fitness assessment will involve a simple series of measurements including central adiposity (waste-to-hip ratio), heart rate, blood pressure, and strength (e.g. calf circumference, bicep circumference). To eliminate any possibility of assessment bias during the first assessment, intervention assignment will not occur until after the baseline assessment has been completed.

Randomization

Participants will be randomized to intervention or control groups using a minimization scheme which will adaptively weight probabilities of treatment assignment based on the distribution of age ($\geq$ 40 vs. < 40), gender (male vs. female), and ethnicity (European/African/East Asian/South Asian/Latino/Other). This design has been adopted to minimize unintended covariate biases, which can plague smaller trials. Randomization will be implemented through a centralized database. The intervention will be delivered via automated e-mails, minimizing direct personal contact with the intervention group.

Controls

Upon completion of all three components of the baseline assessment, the control group will receive access to a GoodLife fitness centre of their choosing or if not specified, the location nearest to their home. For safety purposes, an orientation will be provided by GoodLife Fitness staff to all study participants. This will serve to demonstrate best practices within the gym, including how to

properly operate the fitness equipment, what the appropriate footwear and workout attire is, and general operating rules within the gym. To further ensure the safety of study participants when exercising, it will be emphasized that (1) exercises should be performed with some form of supervision when attempting a new exercise or heavy weight (e.g. a GoodLife Fitness staff member to spot), (2) to never perform types of exercises they may be uncomfortable with, and (3) to never attempt to exercise using an excessive amount of weight. Study participants may also consult GoodLife Fitness staff if they have questions about how to perform a specific exercise.

Intervention

In addition to a free gym membership for the duration of the trial (all participants, irrespective of randomization, will receive a free gym membership), the intervention group will receive (1) their genetic results, (2) personalized workout plan and (3) personalized meal plans, all of which will be delivered through a secure web portal accessible via smartphone or computer. See the "data privacy and security" section below for details regarding specific security measures for the web portal.

The genetic results provided to study participants will consist of scores ranging from 0 to 100 based on the population percentile of the combined effects of many (up to several hundreds of thousand) genetic variants, herein referred to as polygenic scores (PGS). The aim of the PGS is to provide participants with entertaining yet scientifically sound and accurate genetic information to encourage the pursuit of healthy living and identify healthy lifestyle habits that best fit each individual. PGS for approximately twenty traits related to health, fitness and nutrition will be provided to study participants. These traits are chosen for their relevance to healthy lifestyle habits (e.g. genetic predisposition to adiposity or muscle strength), entertainment value (e.g. preference for mornings) or both (e.g. bitterness taste perception, which while entertaining can also help guide vegetable choices). None of the PGS are diagnostic and are therefore not medically actionable.

The personalized workout plan includes 5 x 30-minute exercise programs per week, which is in line with the Canadian recommendation of 150 minutes of moderate to vigorous physical activity per week. The programs will propose a set of specific exercises to perform including the number of sets and repetitions. All workout programs have been approved by GoodLife Fitness and developed by a professional trainer to the UK Olympic team and sports scientist, Nicholas Jones. Through the web platform, instructional videos describing and showing how to perform each exercise will be made available. It will be emphasized that if at any point a study participant feels uncomfortable with an exercise, the participant should consult an on-site personal trainer or forego the exercise altogether.

The personalized meal plans are approved by a registered dietician and are consistent with the Canadian recommended dietary allowances (RDA). If new, unexpected food allergies develop throughout the course of the trial, these will be taken into consideration and dietary recommendations for this particular individual will be adjusted immediately. Depending on the severity of the allergy, the study participant may be referred to a doctor for allergy testing.

Final assessment

The 3-month follow-up assessment will be identical for participants assigned to either the intervention or control group and will consist of: (1) completing the exit study report form, (2) a blood draw which will provide biological material for laboratory testing, and (3) a low-risk fitness assessment which does not involve any physical activity (Table 2). The exit study report form will

strongly resemble the original baseline study report form and query information pertaining to demographics, medical history, dietary composition, physical activity levels, mental health and wellbeing, as well as attitudes, feelings, and competency regarding genetic testing. Laboratory testing will not include genetic testing (as this would be completed using the blood samples collected at baseline) but will include testing of lipoproteins, fasting glucose, and inflammatory markers as conducted in the baseline assessment.

To incentivize study participants to complete their final assessment, they will receive: 1) an additional month's worth of exercise and meal plans and 2) a lifetime subscription to the GeneBlueprint web portal which will be updated with new genetic prediction scores and health tools over time. Furthermore, individuals in the control group will be provided access to their genetic results, personalized meal plan, and personalized workout plan upon trial completion.

Endpoints

The primary endpoints will be changes in physical activity levels and healthy diet score from baseline to 3-month follow-up. Physical activity levels will be quantified based on survey responses to the following questions: (1) "In the last 3 months, how many times per week did you perform aerobic exercises?" and (2) "In the last 3 months, how many times per week did you perform strength training?" These two questions align with recommendations from the Canadian Physical Activity Guidelines, which split exercise into the two domains of aerobic exercise (150 minutes of moderate to vigorous activity per week) and strength training (2x per week). Dietary healthiness will be ascertained using the dietary risk score developed by the INTERHEART study which was found to explain 30% of the population attributable risk for acute myocardial infarction[10]. Briefly, the dietary risk score takes into account consumption of meat, salty snacks, fried foods, fruits and vegetables. Secondary endpoints will include cardio-metabolic markers (triglycerides, C-reactive protein, fasting glucose, blood pressure), measures of fitness (waist-to-hip ratio, circumference of thigh, calf, and bicep, body fat percentage) and cardio-metabolic risk as estimated by the validated INTERHEART modified risk score (IHMRS)[11].

Measurements and measurement instruments

a) Fitness and Physiologic Measurements

The same measurements will be taken at baseline and at 3-month follow-up (Table 2).

Table 2. Fitness and physiologic attributes and the corresponding measurement device.

Measurement(s)	Device
Systolic & Diastolic Blood Pressure	Sphygmomanometer
Resting Heart Rate	Stopwatch/Timer
Body Fat Percentage	Scale
Weight	Scale
Waist-to-Hip Ratio	Myotape measure
Circumference of thigh, calf, bicep, neck, and shoulder span	Myotape measure

b) Blood Collection & Laboratory Testing

The Hamilton Regional Laboratory Medicine Program (HRLMP) Core Labs at each HHS site will assist in blood collection. All blood samples will be transported to the Clinical Research Laboratory & Biobank (CRLB) for subsequent testing. At the CRLB, testing will be conducted for (1) lipids (LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides), (2) fasting glucose, (3) C-reactive protein, and (4) DNA extraction. See Table 3 below for a comprehensive list of blood collection items and the subsequent tests for which they will be allotted. The same laboratory tests will be conducted at baseline and 3-month follow-up except for genetic testing which will only be performed once at baseline. In addition to blood, we will also collect buccal (cheek) cells using a non-invasive cheek swab.

After DNA extraction, samples will be sent to the Genetic Molecular Epidemiology Lab (GMEL) for genetic testing. The GMEL is a state-of-the-art genomics centre directed by Dr. Guillaume Paré with a plethora of experience having processed more than 120,000 samples using a variety of genetic testing methods. For each individual, we will test for 920,576 genetic variants using the Axiom PMRA microarray. The primary genetic data will form the basis for calculating for the genetic prediction scores for health and wellness traits, referred to as polygenic scores (PGS).

Table 3. List of blood collection tube types and laboratory tests.

Blood Collection Tube	Laboratory Test
1 x 4 ml EDTA tube (purple top)	Genetic testing
1 x 6 ml plain tube (red top)	Lipids (LDL/HDL/Total cholesterol, triglycerides) Dysglycemia (Fasting glucose)
1 x 4 ml lithium heparin tube (green top)	Inflammatory Markers (C-reactive Protein [CRP])

Data Analysis Plan

Overview

All analyses conducted will follow the "Intention-to-treat" (ITT) principle to avoid biases due to differential adherence or loss-to-follow-up. In other words, no post-hoc exclusions will be made; study participants will be analyzed according to the group to which they were initially assigned even if they did not receive the intended treatment (e.g. due to injury during trial period impeding ability to exercise) or did not comply. Descriptive characteristics of each group will be summarized as the mean, standard deviation and 95% confidence-interval for continuous variables and using frequencies and percentages for categorical variables. Statistical tests will be two-sided, and between-group comparisons will be presented with 95% confidence intervals where possible. The statistical significance level set will vary depending on the number of statistical tests performed. Multiple hypotheses testing will be adjusted for within analyses of primary and secondary endpoints using a Bonferroni-corrected p-value threshold.

Baseline characteristics

Baseline characteristics will be compared using univariate regression to assess the balance of key risk factors between the intervention and control groups. Linear regression will be applied for continuous variables (age, blood pressure, waist-to-hip ratio, body fat percentage, total weekly

physical activity level, and dietary risk score) logistic regression for dichotomous variables (gender, smoking status, diabetes, dyslipidemia), and analysis of covariance (ANCOVA) will be applied for categorical variables exceeding two factor levels (ethnicity, hospital site). Intervention status will be the independent variable in the regression model. Differences in the mean or proportion of categories between groups will be considered statistically significant if the P-value is less than 0.05.

Primary Endpoints

The primary endpoints are changes in physical activity levels as well as dietary risk score (DRS) from baseline to follow-up. Between-group differences in primary endpoints will be evaluated through linear regression. Weekly physical activity level will be represented as a continuous variable (frequency of strength training and aerobic exercise per week) for the primary analysis. Baseline characteristics found to be differentially distributed between intervention and control groups will be included as covariates in subsequent models. Between-group differences for changes in dietary risk score will be assessed through linear regression again adjusting for covariates. The significance threshold for physical activity levels and dietary health will be 0.025 given that two primary endpoints are tested.

Subgroup analysis will be conducted to explore whether changes in dietary health and physical activity levels differ based on key strata (age > 40 vs. age < 40, ethnicity, gender, baseline low/med/high physical activity levels and baseline dietary risk score tertiles). For example, it is conceivable that individuals who begin with the lowest activity levels and least healthy diets have the derive more benefit from personalized health recommendations, whereas others who already adhere to healthy lifestyle behaviours may have an attenuated response to our intervention.

Secondary Endpoints

Between-group differences in changes in levels of dyslipidemia (triglycerides), dysglycemia (fasting glucose), inflammation (C-reactive protein), blood pressure, measures of fitness (waist-to-hip ratio, circumference of thigh, calf, and bicep, body fat percentage) and overall cardio-metabolic risk as estimated by IHMRS will be analyzed using linear regression. Model covariates will include any baseline characteristics found to be differentially distributed between intervention and control groups. These analyses are considered exploratory and the significance threshold will thus be set at 0.05 for suggestive association and 0.005 (i.e. Bonferroni correction for 10 tests) for definitive association.

Technical Considerations

All statistical analyses will be conducted in R version 3.4.0. Outlying values exceeding four standard deviations will be winsorized or removed if due to a data entry error. If a continuous variable is not normally distributed, then log transformation or quantile normalization will be applied. Missing values for continuous variables will be imputed based on the mean value across all samples with non-missing values including both intervention and control groups. For categorical variables, missing values will be imputed using the proportion of non-missing samples belonging to a given factor level to define the probability of assigning a study participant to that factor level.

Power Calculations

At a sample size of 500 participants (250 intervention and 250 control group), we estimate that we will have 90% power to detect a difference of 0.32 standard deviations between intervention

and control groups (alpha=0.025). An alpha of 0.025 is used in lieu of the traditional value of 0.05 in order to account for multiple hypotheses testing of the two primary endpoints (physical activity and diet risk score). For physical activity, this is equivalent to a difference in ~50 MET-min/wk which translates to a difference of 12.5 minutes of moderate exercise or 6.75 minutes of vigorous exercise per week[9]. This power calculation is based on the work by Jurakic *et al.* (2009) who estimated average weekly physical activity levels in adult Croatians to be 3492 MET-min (SD=162.25) using the same validated questionnaire that will be used in the present trial[12]. The translation of the dietary risk score is less straight-forward as the scoring system is comprised of disparate food habits that best predict acute myocardial infarction (e.g. salty meat vs. cooked vegetables). Granted, we will be well-powered to detect a 0.32 standard deviation in INTERHEART dietary risk score between intervention and control groups at alpha=0.025.

Data Security & Privacy

Primary genetic data is defined as an individual's genotypic state generated directly from a laboratory instrument. Primary genetic data is highly sensitive personal information as it represents an individual's genetic code. Consequently, strict security measures will be employed to safeguard these data and mitigate the risk of confidentiality breach:

(1) The primary genetic data for every study participant is stored on a secured server managed by the Information & Communications Technology (ICT) Team at Hamilton Health Sciences (HHS). HHS servers are secured using industry best standards, including nightly backups, high-end firewall systems, regular monitoring to ensure that any vulnerabilities are quickly found and patched.

(2) The primary genetic data comprising nearly a million genetic data points are used as the building blocks for the PGS. PGS are generated using a sophisticated algorithm to consolidate information from many genetic variants into a single numerical value. Having knowledge of the algorithm and the specific set of genetic variants that comprise the PGS is not sufficient to deduce a participant's primary genetic data, as there is a multiplicity of combinations that could lead to the same overall numerical score. In other words, it is impossible to deduce an individual's primary genetic data using the PGS. Only the PGS will be transferred to the web portal server. Importantly, no identifying information (i.e. name, email address, address, etc.) will ever be stored on the same server as the primary genetic data. Primary genetic data for each participant will be issued its own randomized ID number, different from the participants study ID (i.e. double de-identification). The key linking both numbers will be kept in a secure computer different from the genetic server, minimizing the risk of a catastrophic hack.

(3) The GeneBlueprint web portal provides a secure means for participants to access and learn about the genetic basis of their health and wellness. There is minimal risk of participant de-identification. The web portal is password protected and this password is only known to the study participant. Information regarding an individual's genotype at selected (~30) genetic variants will be provided for educational purposes in the form of a "Top Gene Contribution Table"; however, there is minimal risk of de-identification as these genetic variants are commonly prevalent in the general population. Essentially, it is impossible to re-identify a participant if the identifying feature is common, such as hair color to use an analogy. Additionally, the website itself employs many security measures to prevent prohibited access or disclosure through various physical, technical, and administrative means. All connections to the GeneBlueprint website (https://geneblueprint.com) are encrypted using Secure Socket Layer (SSL) technology. Security and privacy of personal information maintained on the GeneBlueprint portal will adhere to both Canadian (Personal Information Protection and

Electronic Documents Act) and US (Health Information Portability and Accountability Act) legislation.

It should also be noted that personal genetic information will not be disseminated to employers or insurers as per Canadian law. The privacy of study participant's genetic information is protected by the "Genetic Non-Discrimination Act" which was passed May 4, 2017. This law prohibits employers and insurers from requiring someone to conducting genetic testing or disclose findings from existing genetic test results as a condition of (1) providing good and services to that individual, (2) entering into or continuing a contract or agreement with that individual, or (3) offering or continuing specific terms or conditions in a contract or agreement with that individual (http://laws-lois.justice.gc.ca/eng/acts/G-2.5/page-1.html#h-1).

Incidental Findings.

Laboratory Results

Blood testing results at baseline and 3-months follow-up could reveal medical diagnoses unbeknownst to the study partiycipant that warrant disclosure. Such findings include but are not limited to diabetes (fasting glucose > 7 mmol/L), hypercholesterolemia (LDLc > 5 mmol/L), and hypertriglyceridemia (triglycerides > 10 mmol/L). Upon identification of an aberrant test result, confirmatory testing will be expedited through the Hamilton Regional Laboratory Medicine Program, which consists of several clinical laboratories approved by the Ontario Ministry of Health. Confirmatory testing will help mitigate the risk of false-positives, a potential source of unnecessary anxiety and stress for study participants. Once confirmatory testing validates the initial positive result, the study participant will be contacted by trial management and referred to the appropriate medical specialist (e.g. endocrinologist or lipid specialist). Continuation in the trial will be based on the physician's discretion as well as the willingness of the study participant.

Genetic Results

There is no risk of incidentally discovering medically actionable genetic conditions or disorders as this is beyond the scope of this project. While the American College of Medical Geneticists (ACMG) has recommended reporting pathogenic mutations within 65 genes that may cause conditions unrelated to the primary indications[13], these recommendations specifically apply to studies involving clinical exome or genome sequencing. Our study does not involve clinical exome or genome sequencing and the proposed method is unable to detect variants of diagnostic value. Therefore, there is no risk of genetic incidental findings.

Fitness Assessment

Extremely elevated resting heart rate and blood pressure are contraindications for exercise. Incidental discovery of previously undiagnosed malignant hypertension (SBP > 180/120 mmhg) or tachycardia (resting heart rate > 100 bpm) during the baseline fitness assessment will preclude an individual from continuing with the fitness portion of the trial. Malignant hypertension is a medical emergency and anyone identified with this condition will be referred to the hospital immediately. Study participants identified with tachycardia will be referred to an appropriate health professional.

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