Protocol of a Pilot Study to Estimate HbA1c from Glucose Monitoring

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Abstract

The goal of this pilot study is to validate an algorithm that predicts glycosylated haemoglobin from instantaneous continuous glucose data from body-worn continuous glucose monitoring devices ("CGM") with glycosylated haemoglobin values obtained from participants. The purpose would be to validate CGMs from participants with Type 2 Diabetes (T2DM) with respect to predictive abilities of machine learning algorithm for CGMs to predict HbA1c

We will set up a predictive machine learning algorithm based on secondary sources on glucose measurements, lifestyle variables (diet, physical exercise) for prediction of glycosylated haemoglobin values obtained three months later from the completion of the CGM data collection. We will recruit 30 participants with T2DM who will wear a CGM for 14 days, and then three months after the completio of their 14 days wearing of the CGM, will provide us their HbA1c data. These data will be used to validate our machine learning algorithm for prediction of HbA1c from instantaneous glucose measurements..

This step is necessary for setting up a human digital twin (HDT) to be built for reversal of T2DM. A human digital twin for reversal of T2DM relies on machine generated predictive model of glycosylated haemoglobin and use of this information for generating messages passed on to patients to modify their behaviours to optimise blood glucose concentration with a view to achieve reversal of Type 2 Diabetes Mellitus

Keywords: Diabetes, Type 2 Diabetes, Machine Learning

Introduction, Goal and Scientific Basis

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterised by high blood glucose levels believed to result from tissue resistance to the actions of insulin produced by the pancreas beta cells [1]. Age-standardised prevalence of T2DM worldwide is in the order of 8.5% of global population and incidence is rising [2]. T2DM disease burden is high in Aotearoa New Zealand with age-standardised prevalence of 6.5% and expected to rise to 7.0% by 2030 according to data from International Diabetes Federation [3]. Prevalence of T2DM is 2.5 times higher among Māori compared with the European NZ population, Pacific Island peoples, and among people of Indian origin [4-5]. T2DM is amenable to outpatient treatment and lifestyle modification, but if unchecked and uncontrolled, the condition is associated with high risk of heart disease, vision impairment due to retinopathy, chronic renal failure,

pathological lesions in microvasculature and neuropathy in the lower limbs, sometimes resulting in gangrenous toes that require amputation [6].

Risk factors of worsening T2DM include sedentary lifestyle brought about and aggravated by consumption of a calorie-dense and nutrient-poor diet, stress, and lack of physical exercise [7]. As these risk factors are also modifiable, T2DM is amenable to lifestyle intervention in community and outpatient-based settings. Failure of outpatients and community based interventions to control T2DM increases the rate of ambulatory hospitalisations; indeed hospitalisations attributed to T2DM is high in New Zealand [8, 9]. It is therefore believed the provision of community-based interventions could significantly reduce the burden of T2DM in the country. Hence, T2DM is amenable to lifestyle modification, as current evidence suggests, further, T2DM is also reversible with exercise and diet adjustment [10].

In clinical settings control of diabetes is measured with three-monthly glycosylated haemoglobin. Glycosylated haemoglobin (HbA1c) refers to the level of non-enzymatic binding of glucose (sugar) molecules on red blood cells expressed in millimoles per mole of haemoglobin (mmol/mol); the higher the levels the worse the control and an optimum level is around 55 mmol/mol. Hence longer term control of diabetes is indicated by a concentration of about 55 mmol/mol of glycosylated hemoglobin in blood [10-11]. T2DM is said to be reversed if a series of three measurements of HbA1c returns each 48 mmol/mol and obtained in the absence of medication following an initial diagnosis of diabetes. Several studies have indicated that it is possible to reverse diabetes with lifestyle modifications including exercise and dietary interventions and stress control. For diabetics and who are not on medications, modification of lifestyle including physical exercise, modification of diet, and stress control contribute to reversal of diabetes [11].

Nudge or nudging is effectively utilised in public health interventions [12]. It is defined as the design of choices offered to people in a way that their non-conscious cognitive processes lead them to select an option that leaves them better off in the long run as judged by themselves [13-14]. In the context of health and behaviour change such that people will adopt a more healthful behaviour, use of nudges where individuals were presented with healthy alternatives that they then accepted has been found to be effective tools for lifestyle interventions. In cases of reversal of diabetes by enabling diabetics to adopt a more healthy lifestyle, one form of nudge might be to provide contextual cues in the form of messages or subtle indicators based on their current state of blood sugar level so as to encourage them to reduce the present level of blood sugar level to a more optimum value. This drive can be delivered via personalised message system. Our research aim is about developing and implementing a human digital twin based behavioural modification programme aimed at controlling T2DM by building a personalised message system.

In order to develop a personalised message system, a structure and a process are needed. The structure refers to the physical and computational units for continuous or regular blood glucose monitoring and transmission. Based on this blood glucose input, subsequent development and delivery of targeted messages via connected devices can be achieved. This structure includes units that can monitor and transmit blood sugar levels continuously, such as wearable devices including continuous glucose monitors, and mobile phones which are integrated into the system via bluetooth connectivity. As mobile phones (smartphones) are widely used, they can serve as suitable tools within this structure, by way of displaying nudge-type messages in real time to people in response to the blood sugar data which is obtained from the glucose monitoring devices in 15-minute intervals or lower frequency of transmission.

The process refers to machine learning algorithms used for prediction of the three-monthly glycosylated haemoglobin values, and then after comparing that value with an optimum value of 55 mmol/mol, the process that generates and transmits tailored nudge-type messages to the mobile devices of the clients. The message would guide the diabetic patient take a behavioural action (such as drinking a glass of water or taking a few steps or an easy form of stress reduction activity) in response to the message and it is expected that these steps, done regularly, will help to reduce the blood glucose level. The resulting reduced glucose level will be transmitted via the devices to the algorithm that will run in background. In this way, the combination of the process and structure will enable achieving the target glycosylated haemoglobin level. This is the objective of developing a digital twin [15], as explained below.

An HDT has three interconnected entities: a human being for whom a digital twin is constructed (this person is a “physical twin” or PT), the corresponding digital twin (DT), and a connector (“bridge”) that connects the PT and the DT in a two-way connection network (15). The connector transfers real-time data from the PT to the DT, and transfers the resulting information from the DT to the PT (Figure 1).

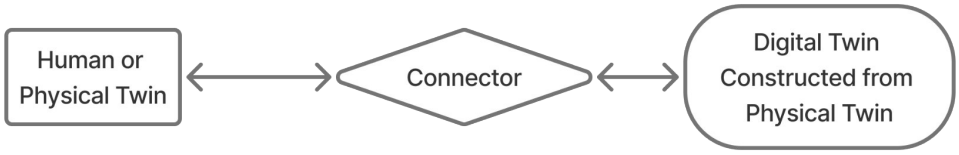

Figure 1. Human Digital Twin, a schematic representation where the human or physical twin connects to the digital twin using a connector or bridge.

Real time data obtained from sensors fitted to the PT are collected. For the pilot study this will be from a continuous glucose monitor that transmits real-time data on blood glucose level. The blood glucose data are transmitted to the DT which runs a machine learning algorithm. This machine learning algorithm uses the input data from the PT and generates an estimate of the glycosylated haemoglobin level and matches it with a target level of 55 mmol/mol. Based on this value, the DT then generates a message for the PT either to take action in an attempt to lower this level if it is found to be higher than the target level, or exits with a positive message (Figure 2).

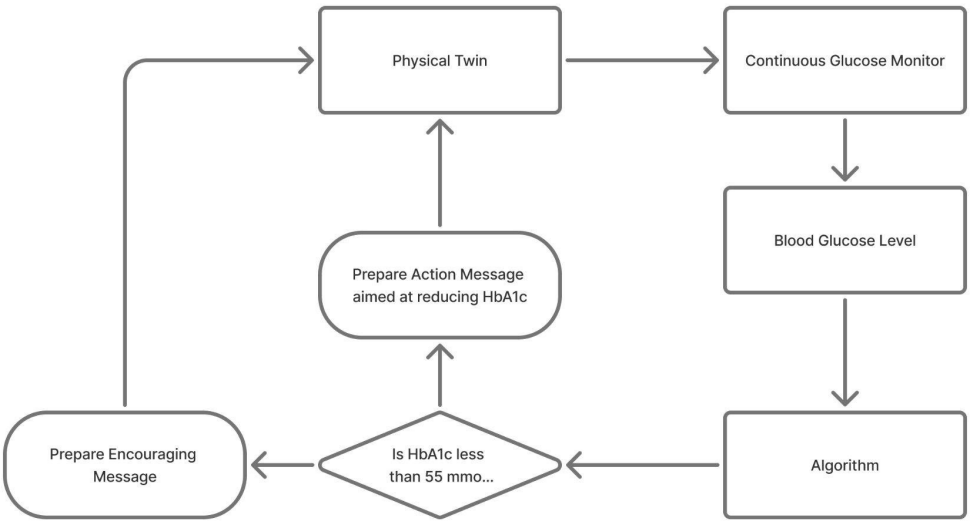

Figure 2. Algorithm of the project: the physical or human twin transmits blood glucose levels to the continuous glucose monitor. The devices then transmit the level to the connector that in turn transmits the data to the digital twin, which incorporates a machine learning algorithm. The machine learning algorithm takes the blood glucose and other parameters and predicts the HbA1c level from the instantaneous glucose level. It then evaluates the HbA1c and accordingly prepares a message which is transmitted back to the physical twin via their smartphone.

Such a continuous back and forth transmission of data and messages between the PT and the DT, the system can achieve an optimum low level of glycosylated haemoglobin level for the diabetic and this will result in a personalised prevention and reversal of T2DM.

In our model, we have incorporated the following variables::

1. Blood glucose data from continuous glucose monitor
2. We will obtain data about diet patterns, exercise and physical activity levels, and stress levels at baseline. This data will also be transmitted via the connector to the digital twin. The data on exercise, diet and stress will be collected at baseline.
3. The digital twin will run a machine learning algorithm (the best algorithm that may have the most sensitive and specific predictive value for HbA1c)
4. On the basis of the predicted value of HbA1c and a pre-specified value of HbA1c 55 mmol/mol, the algorithm will then activate one of the two actions: (a) either it will generate a personalised message about diet, physical activity, and stress control OR (b) it will exit with a positive message
5. The connector in our model is a combination of a smartphone that the participant will use and the server to run the machine learning algorithm we will use at UC. The mobile phone or cellphone is a connector device as it will read the glucose values from the devices and transmit to the machine learning algorithm (DT), and it will also receive the messages from the DT and transmit to the participant. A participant will be included in the study if the person has access to a personal smartphone and can use it.

Here we have considered only modifiable behavioural risk factors of T2DM. These include diet, exercise, and stress control. Although we acknowledge the importance of genetic, socio-cultural & socio-economic determinants of health for T2DM, these are beyond the scope of our research as these are not modifiable at individual levels and thus the focus will primarily be on behavioural interventions.

In order to achieve the desired goal of a potential reversal of T2DM, it is necessary to develop and train a machine learning algorithm and validate the algorithm with real world data from human beings. In the proposed pilot study, we aim to develop and run a machine learning algorithm with secondary data with a view to train the model to reach maximum sensitivity and specificity in the prediction of glycosylated haemoglobin value from an individual's demographic (age, biological sex), physical activity levels, current blood sugar levels, and diet (based on data from a diet questionnaire at baseline). The algorithm will then be validated with real world data obtained from individuals.

Goal of this study

T2DM is defined as reversed when on three consecutive occasions without any medication the glycosylated haemoglobin concentration reaches a value of 48 mmol/mols. The goal of the proposed research project is to use a machine learning algorithm to predict HbA1c from input data on blood sugar levels, exercise patterns, and diet, and then based on the predicted HbA1 level to send messages to the participant to take action.

It is critical that we first develop and test an algorithm that can identify modifiable or mutable parameters and is sensitive enough to predict glycosylated haemoglobin and respond within thresholds of pre-determined parameters. While many algorithms and formulae exist for the prediction of glycosylated haemoglobin, such formulae are based on a single point source estimation of blood glucose level and do not take into account the composite of mutable variables such as physical activity levels, stress, or dietary patterns and therefore cannot be used in meaningful ways to develop nudge based interventions with a view to alter behaviour. Hence there is a need to first develop and test an algorithm that can predict glycosylated haemoglobin.

The goal of the proposed pilot study is to develop and evaluate the performance of a machine learning algorithm using real-world data from diabetic patients. This will be done by obtaining real time data from participants who will use a wearable device such as a continuous glucose monitor that will store glucose data recorded by the device on a 24 hour basis once every 15 minutes.

Participants and Methods

We will conduct a pilot study to validate a machine learning model to estimate the three-monthly value of glycosylated haemoglobin based on continuous glucose monitoring (CGM) data collected for 14 days, point estimates of blood glucose levels from glucometer data, daily exercise levels, baseline diet, and stress levels from people with Type 2 Diabetes. We will first estimate three monthly glycosylated haemoglobin and then assess the sensitivity and specificity of the model predicted glycosylated haemoglobin data with actual three monthly glycosylated haemoglobin data obtained from the same individuals. As we will use a machine learning model, this will enable us to adjust the relative contribution of the predictor variables to identify the best machine learning predictor model that can be applied in the second phase of the study, where nudge-based messages will be delivered to patients in real time and their resultant glycosylated haemoglobin can be monitored. The following description outlines the procedures we aim to use in this study.

Steps of the research process

Step 1. Obtain Ethics Approval from Health Disability Ethics Committee.

Step 2. Recruitment and selection of individuals with the following selection criteria:

The target population for this study are those with Type 2 Diabetes (T2DM) and are managed with lifestyle modifications[16].

Inclusion Criteria:

- Aged 30 years and above, both biological sexes
- Participant must be a resident of Christchurch
- Diagnosed with Type 2 Diabetes (T2DM)
- Has Access to a smartphone
- Agree to get themselves tested for HbA1c

Exclusion criteria:

  - Anyone who do not meet inclusion criteria
  - Type 1 diabetics
  - Gestational diabetes

- Participants of this pilot study will be identified from the following sources:
  - Advertisement in General Practice (GP) clinics in Christchurch requesting them to pass the information about this study to their patients
  - Distribute information sheets and consent forms etc to the GP clinics if any Type 2 Diabetic would express an interest to join the study

Sample Size and Power estimation

This is a pilot study and the goal of this study is to validate a machine learning algorithm for the assessment of glycosylated haemoglobin from several core variables (e.g. age, sex, physical activity level, dietary variables, stress levels, and current continuous glucose levels), with real world data from diabetics. We aim to recruit 30 recently diagnosed diabetic patients who are managed on lifestyle interventions (this includes management of their diabetes with diet, exercise, and stress control).

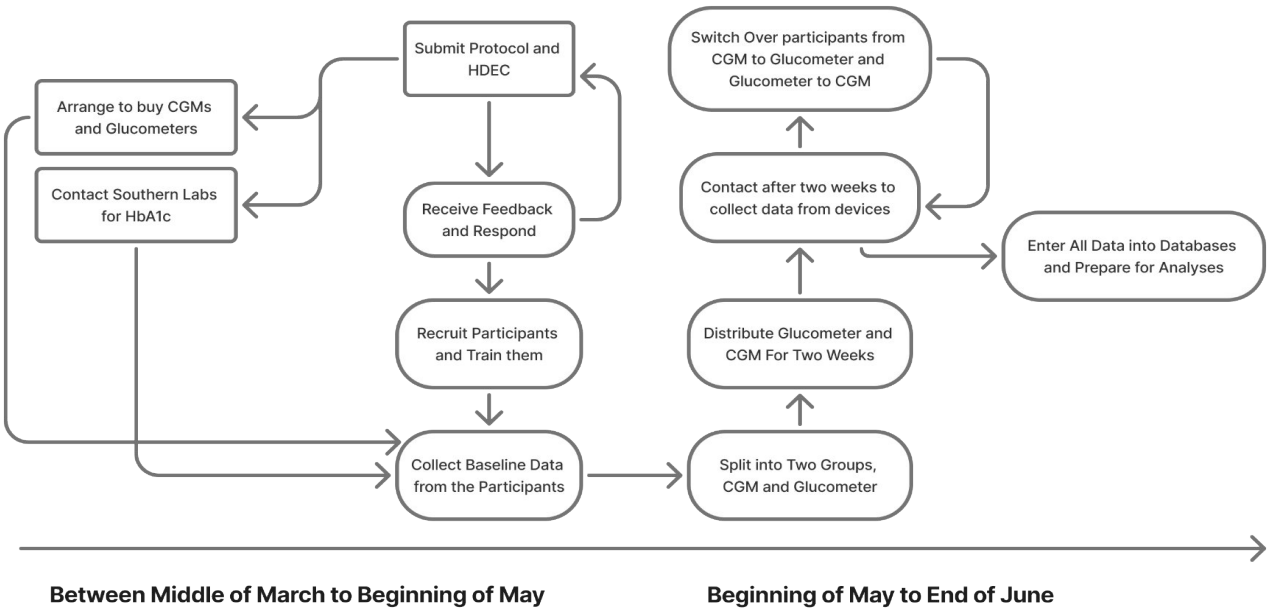

Figure 3. Research flowchart with an approximate timeline

Once recruited and appropriately briefed on the expectations of the study, the participant will be encouraged to do the following:

- The researchers will identify participants by contacting GP clinics in Christchurch City, Rolleston, and Rangiora and informing the GPs about the project and with their help, the researchers will be recruiting adults diagnosed with Type 2 Diabetes (“T2DM”). A list of 122 such clinics have been identified
- The potential participants will receive a participant information sheet describing their eligibility criteria, what they need to do and their time commitment, and they can check their eligibility in the study.
- Once the participants meet the inclusion and exclusion criteria they will contact the RA for the project using a dedicated toll-free 0800 number, the RA will explain to them the procedure further, and answer any questions they may have about the project.
- We will identify 30 eligible individuals who will meet the inclusion criteria. If we get more than 30 participants, we will include only the first 30 participants, and if we are able to identify fewer than 30 participants, we will continue to recruit participants till we get 30 participants and then will stop further recruitment
- The RA will then send each one of the 30 individuals a package that will include an information sheet, a consent form, travel vouchers, and a questionnaire that will include items pertaining to stress, diet, and physical activity levels.
- After the participant will return the questionnaire and the consent form, the RA will then arrange a meeting (“first meeting”) with the participant. In the meeting, the RA will provide the participant a CGM and explain how to use it.
- The participant will be asked to use the continuous glucose monitor and wear for 14 days. This is a non-invasive glucose monitoring device that will be closely similar to other non-invasive tools for glucose monitoring.
- After 14 days of using the continuous glucose monitor device, the participant will be contacted by the research assistant, and the participant will be invited to attend a second meeting. In the meeting, the research assistant will then take the continuous glucose monitor and transfer

data from the monitor to our database at UC. The meeting with the research assistant (“RA”) is necessary because the data from the CGM will be used for modelling at the research site and therefore transfer of data from the CGM devices to the database kept at the UC research site is necessary, and this transfer is to be conducted by the RA for the project. Hence the participant will need to meet with a member of the research team (“RA”) so that the RA can transfer data from the CGM to the computers at the UC where analyses will take place.

- Three Months after completion of wearing of the CGM and data transfer, the participant will schedule an HbA1c estimation in a local laboratory (the participants will need to have their blood drawn at the Canterbury Health Labs and or Awanui Labs) at their cost of travel will be covered by the research.

- After we obtain the data from the participants, we will use such data for validation of our Machine Learning model explained below

The following information will be obtained from each participant:

- Their age, sex, and their lifestyle information (self-reported diet, stress, and physical activity level obtained from SLIQ questionnaire)
- Their blood glucose data

Machine learning model and data collection

These data thus collected will constitute our validation sample. In order to use the validation sample, we will first train our algorithm with training data that will include models built on the following machine learning algorithms:

- Our training sample for the study will be obtained from secondary sources from a range of data sources. The machine learning codes and the associated data are to be found at a **private** github repository (
- https://github.com/arinbasu/hdt_grant/blob/main/diabetes_precition_codes.ipynb

  (as this is a private github repository this link will not be active but the codes we will use are presented later in the document)

An **indicative code** that we may use from other data sets is presented below (this is for illustration, the actual code in Python language may differ)

```
import numpy as np

def vectorize(sequences, dimension = 10_000): results = np.zeros((len(sequences), dimension)) for i, sequence in enumerate(sequences): results[i, sequence] = 1 return results # build models from tensorflow import keras from tensorflow.keras import models from tensorflow.keras import layers

import matplotlib.pyplot as plt

def onehotEncode(labels, dimension=46): results = np.zeros((len(labels), dimension)) for i, l in enumerate(labels): results[i,l] = 1. return results

import pandas as pd

# read the data directly from github data = pd.read_csv("https://raw.githubusercontent.com/arinbasu/hdt_grant/refs/heads/main/diabetes_prediction_dataset.csv?token=GHSAT0AAAAAAC5MRY64QPVDLNUNXXH3SQQ4Z4IE6RQ")

data.head()
```

```
# get the variables we need

data = data.loc[:, ['age', 'hypertension', 'heart_disease', 'bmi', 'HbA1c_level']]

# split the data into test and train sets import sklearn.model_selection as skl X_train, X_test, y_train, y_test = skl.train_test_split(X, y, test_size=0.33)

# Calculate the mean of X train, we will use it for normalisation X_mean = np.mean(X_train, axis = 0)

X_train -= X_mean # deduct from each variable in X_train the X_mean

X_std = np.std(X_train, axis = 0) # calculate the standard deviation for each variable

X_train /= X_std # with the new X_mean, divide by standard deviation to normalise

# set up a k-fold validation for this data k = 4

# four fold validation n_val = len(X_train) // k # floor operation, so that 12 // 5 = 4, not 2.5 n_epoch = 10

# set the number of epochs to 10 so that we only train for 10 runs dm_hists = [] # initialise an empty array # Set up a for loop to create training and validation data from X_train # the validation data takes a quarter # the part data are in between these quarters

for i in range(k): dmval = X_train[i * n_val: (i + 1) * n_val] dmvaltarget = y_train[i * n_val: (i + 1) * n_val] dmpart = np.concatenate( [ X_train[:i * n_val], X_train[(i + 1) * n_val:] ], axis = 0 ) dmparttarget = np.concatenate( [ y_train[:i * n_val], y_train[(i + 1) * n_val:] ], axis = 0 )

# import the necessary modules to conduct deep learning or machine learning from tensorflow import keras from tensorflow.keras import models from tensorflow.keras import layers

# Set up the model as a fully connected. model with # Two layers of 16 nodes each and # One output layer of one node as a linear diabetes = keras.Sequential([ layers.Dense(16, activation = "relu"), layers.Dense(16, activation = "relu"), layers.Dense(1) ])

# now compile the model # the optimizer could be "Adam" as well, mse = mean squared error, # mae = mean absolute error so mean of abs value of y real minus y computed diabetes.compile( optimizer = "rmsprop", loss = "mse", metrics = ["mae"] )

# fit the model and store the values in dmhit # fit the model given partial data, validation data, epochs = 10 # in batch sizes of 16 dmhist = diabetes.fit( dmpart, dmparttarget, validation_data = (dmval, dmvaltarget), epochs = n_epoch, batch_size = 16 )

# plot the model accuracies and losses between partial data and validation data losses = dmhist.history["loss"] val_losses = dmhist.history["val_loss"] epochs = range(1, len(losses) + 1)
```

```
# Plot the data plt.plot(losses, label = "Training Loss")
plt.plot(val_losses, label = "Validation Loss") plt.legend() plt.show()

# How does the model actually work or predict # first preprocess X_test

X_test -= X_mean X_test /= X_std

# then predict using the diabetes model

y_predicted = diabetes.predict(X_test)
```

In order to develop the machine learning algorithm, we will use secondary data sources listed in the **private** github repository created for this purpose (located in https://github.com/arinbasu/hdt_grant) hence only accessible with a password, and this data will be used to train a machine learning model to predict three monthly glycosylated haemoglobin values using two different deep learning models:

1. We will train a recurrent neural network model to predict glycosylated haemoglobin
2. We will also train independently and separately an artificial neural network model for prediction of three monthly haemoglobin from point source data obtained from bluetooth connected glucometers
3. We will obtain the following data from each of the 30 individuals (each individual will be deidentified and anonymised):
    a. Assign a unique identifier code to each individual so we will not know the identity of any individual
    b. Age in completed years
    c. Self-administered instruments to measure their levels of lifestyle variables
    d. Blood glucose readings from CGM

    e. At the end of three months, the participants will report their glycosylated haemoglobin level

After the models are trained with pre-existing data from other sources, the participant data will be used to validate the model. The data for the machine learning models will be split into training and testing data sets, 80% of the data will be used for training and 20% of the data will be used for testing. The sensitivity and specificity of the models will be established based on the training and testing data. The participant data that we will collect using the above procedures will be used for validation. In this process, after the algorithm would be built, we will feed the data from the participants (glucose, diet, and stress levels) and generate the predicted HbA1c. We will then match the predicted HbA1c with the real HbA1c from the laboratory values and compare how well do the algorithms match. If the algorithm does not perform well, we will need to fine tune the algorithm based on the validation data.

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