

INFORMED CONSENT

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Persons who participate in a medical experiment are entitled to certain rights. These rights include but are not limited to the subject's right to be:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should rise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Introduction to Research Studies

A research study is designed to answer specific questions, sometimes about a drug or device's safety and its effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your personal doctor have a great deal of freedom in making decisions about your health care. When you are a research subject, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

The Purpose of the Study

You have been asked to participate in a research project at Stanford University Medical Center under the direction of Dr. Joshua Knowles and associates because you have elevated LDL-C (bad) cholesterol, and/or an elevated inflammatory marker known as high sensitivity C reactive protein, (hs-CRP) and/or a cardiovascular risk score of 5% or higher and may also have elevated triglycerides (fat in blood) and be at risk for type 2 diabetes. There is general agreement that statin-treatment of patients with hypercholesterolemia (high cholesterol) can increase the incidence of type 2 diabetes (T2DM) in a small percentage of some individuals. This research proposal will study what metabolic characteristics and variables (for example high cholesterol or high triglycerides or both) will identify those people at highest risk of statin-induced T2DM. We will evaluate how the medication atorvastatin (trade name Lipitor) works in regards to its effect on insulin action, insulin sensitivity, and insulin secretion to help us further understand the possible cause of the increased occurrences of T2DM in people who are at risk for T2DM.

Everyone will receive the same statin, Lipitor, at the same dose, 40 mg which will be taken once a day. We will screen approximately 150-200 people and to complete approximately 88 people. . This study is expected to be completed in approximately 3 years. If you qualify to participate, your time involved in this study will be approximately 4-5 months.

Under Dr. Snyder, a Co-director of the study, we will collect samples for integrated Personal Omics Profiling (iPOP), a monitoring approach developed by Dr. Snyder and his research colleagues. This is described in detail on page 9 under iPOP samples. The iPOP information is for research purposes only and will not be released to you. To further extend Dr. Snyder's previous research on iPOP, we propose to analyze iPOP of individuals who participate in this study during and after taking the statin. In this study, we will analyze not only the previously-known drug's effectiveness but also untargeted drug's effectiveness, (other unknown benefits this medication may have) and drug effects such as those seen in some participants when given a statin. The hope then is to obtain a better understanding of how to perform a personal omics profile when taking drugs, which would lead to develop better use of drugs.

You must sign this consent to participant in this study. A screening consent will be signed, or verbally agreed to before any screening procedures will be done.

VOLUNTARY PARTICIPATION

Your participation in this study is voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled. Please let us know or call Dr. Knowles or one of his associates at 650-723-7024 if you decide to withdraw from this study, we might ask you to come in for a final visit.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

While participating in this study, you should not take part in any other research projects without approval from all the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interactions of research drugs, or similar hazards.

Are you participating in any other research studies? YES_____ NO_____

Have you donated blood within the last 6 weeks? YES_____ NO_____

Multiple blood samples will be taken throughout the duration of the study for measurement of glucose (sugar) levels, lipid levels, kidney and liver function test and other chemistries. Blood sampling will be done by withdrawing blood from a vein/or placing an IV catheter (intravenous plastic tubing). This may cause some discomfort and carries a slight risk of infection, or bruising.

All study visits will take place in the Clinical and Translational Research Unit (CTRU) at 800 Welch Rd in Palo Alto, CA.

Study Visits

Visit 1 The first visit (screening) will be to determine if you qualify for the study based on your age, height, and weight, vital signs (blood pressure and pulse), medical history, results of your laboratory test, hematocrit (checking for anemia), glucose (sugar) level, cholesterol profile, liver and kidney function. You will not qualify if you have a history of severe anemia, kidney or liver disease, diabetes, a recent heart attack, heart procedure, or history of heart failure, are pregnant or breast feeding or unwilling to use effective birth control methods while you are in the study. Anyone with a history of allergy to lipitor will not qualify. If you have a history of not being able to tolerate statins in the past we will review this with you to see if you would still qualify for the study.

Your responses to questions we ask concerning illicit/illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement on page 13 of the consent, we do not intend to disclose this information.

If you qualify at today's visit, you will be asked to come in for an Oral Glucose Tolerance Test which will be described below.

Visit 2 The second visit will be the oral glucose tolerance test (OGTT) described below. You will be asked to fast for 12 hours prior to the test and the entire visit will take approximately 3 hours. If you qualify, you will be scheduled for the graded glucose infusion test.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

Visit 3 The third test visit will be the glucose infusion test which will evaluate insulin clearance and insulin secretion. This test will be 6 hours in length.

Visit 4 The third visit will be the insulin sensitivity test described below. This test will determine if you are insulin sensitive or insulin resistant. Once you have completed this test you will start the study medication Lipitor 40 mg taking it once a day and then will be seen for follow up visits over the next 4 months as described below.

Visit 4 -10 You will be seen, every 2 weeks from week zero up to 8 weeks and then one and two months later after completing the end of study tests and stopping the study medication (statin). We will check your weight, and blood pressure at each of these visits. We will also check a pregnancy test in women who are of childbearing age at the beginning, week 4 and week 8. You will also see Dr. Knowles research associates (an MD or nurse practitioner) to review how you are doing on the study medication. We will ask you to bring in your study medication at each visit and at the end of the study. At the end of the study we will ask you to stop the statin and not to take any cholesterol lowering medication for two months and will ask you to come in at the end of 1 month and 2 months off the study medication for iPOP samples.

iPOP samples: Samples for Dr. Snyders's iPOP research will be taken on day of OGTT and week 0 (before starting statin), and then at weeks 2, 4, 8, 12 and 16 We will draw 60 ml of blood at each time period (4 Tablespoons) and take other samples of body fluids as described on page 9 under iPOP samples.

Questionnaires:

For the duration of this study you agree to make no changes in your level of physical activity, weight or diet. We will ask you to complete several questionnaires, a physical activity sheet, food log, eating habits and stress level every time you have blood samples drawn for iPOP.

SUBJECT'S RESPONSIBILITIES

If you qualify and agree to participate in this study you will be expected to:

- a) follow the instructions of the Protocol Director and research associates;
- b) answer questions regarding your medical history to the best of your ability;
- c) ask questions as you think of them;
- d) keep your study appointments;
- e) take your study medication as directed and report any side effects;
- f) return your bottle of study medication even if empty at every visit and at the end of the study;
- g) complete all baseline and follow-up tests as well as study questionnaires;
- h) tell us if you think you are pregnant
- i) tell us if you can no longer do the study in case we want to complete end of study testing.

If you decide to participate, all the tests described below will be done at the beginning and the completion of the study.

STUDY TESTING PROCEDURES

Oral Glucose Tolerance Test – This test will be done at the beginning and end of the study. You will be asked to fast for 12 hours the night before but will be allowed and encouraged to drink water during those 12 hours.

You agree to participate in a procedure called an oral glucose tolerance test (OGTT). The OGTT involves a series of blood samples taken before and during the 120 minutes after drinking a sweet cola drink which contains 50 -75 grams (5 tablespoons) of glucose (a form of sugar). This test will be done after you have fasted for 12 hours from the previous evening. An IV will be inserted in one of your arms for the purpose of drawing blood samples to determine your blood glucose (sugar) level during this procedure. Blood samples will be drawn at time 0, 30, 60, 90 and 120 minutes after drinking the cola drink. The total amount of blood taken for this test will be 45 ml (3 tablespoons). The purpose of this procedure is to determine if you have a normal glucose tolerance response, impaired glucose tolerance (a mild abnormality of glucose disposal) or if you have diabetes and to calculate insulin secretion. Although not common, some people may experience nausea when drinking the cola drink.

The results of this test will be discussed with you, and we will give you a copy. The total time for this procedure will take approximately 3 hours.

GRADED GLUCOSE INFUSION TEST This test will be 6 hours in length. This test is designed to assess the ability of your pancreas gland to produce insulin in response to a glucose (sugar) infusion. During this test, you will have two small IV catheters (tubing) placed in your veins. One IV will be for blood drawing and the other for the infusion of glucose. You will be given glucose in specific amounts based on your weight and the glucose rate will be steadily increased over a 4-hour period. The amount of blood taken for this test will be equal to approximately 5 tablespoons (47.5 ml). On rare occasions, the glucose can be irritating to the vein and may cause an achiness or redness in your arm. If this happens let us know and we will either put a warm pack on the IV site or replace the IV to a new site. Although rare a side effect associated with having an IV some discomfort and carries a slight risk of infection, or bruising

INSULIN SENSITIVITY TEST- This test will be done at the beginning and end of the study. You will be asked to fast for 12 hours the night before but will be allowed and encouraged to drink water during those 12 hours.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

The insulin sensitivity test is designed to measure how well your cells remove glucose (a type of sugar) from your blood in response to insulin. This test will involve the infusion of glucose, insulin and octreotide (sandostatin) by vein for three hours. During this test you will have two small catheters (tubing) placed in your veins (I.V. lines). One of these will be used for blood drawing and the other for giving the infusion of glucose, insulin and sandostatin. Blood samples will be taken before, during and at the end of the infusion study. The total amount of blood that will be drawn from you during this study will be 59.5 ml of blood (approximately 4-5 tablespoons).

Insulin is a natural hormone, and sandostatin (a synthetic hormone) is a drug that temporarily blocks the secretion of insulin from your pancreas. There are no serious adverse effects from the brief use of sandostatin in this study. However, there may be a transient (temporary) decrease in your pulse, and occasionally nausea and abdominal cramping can occur in about 5-10% of people. There may also be a 5-10% chance of having abdominal cramping and diarrhea or loose stools, which could occur several hours after the completion of the study.

Insulin will cause your cells to remove glucose from your blood. It is possible that your blood glucose levels could become too low (hypoglycemia) during and immediately after the end of the study. In order to avoid this from occurring, your blood glucose levels will be measured during and after the study, and glucose will be given as needed to prevent hypoglycemia from occurring.

There is the risk of fever and sudden fall in blood pressure if the infusate solutions (substances given in your vein) are contaminated. However, the solutions are made from sterile components or substances tested for sterility before being used in the preparation of the solutions, and the risk of contamination is very slight. This test will be 6 hours in length

After completing these tests, you will be given the study medication Lipitor 40 mg which you will take once a day for 2 months and will stop after completing the end of study tests.

POTENTIAL MEDICATION SIDE EFFECTS and POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Atorvastatin

You will receive atorvastatin (Lipitor) 40 mg to be taken once a day.

Side Effects: Lipitor has been studied over many years and this dose of Lipitor has been well tolerated. The most commonly reported adverse reactions (incidence equal to or greater than 2%) in patients treated with atorvastatin 40 mg in placebo (no medication) - controlled trials regardless of causality were: nasopharyngitis, (inflammation of nasal passage and sore throat) - 7%, arthralgia (pain in joints) -10.6%, diarrhea -14.1 %, pain in extremity - 9.3%, and urinary tract infection 8.0%.

WARNINGS AND PRECAUTIONS

Skeletal Muscle

Lipitor, like other statins, occasionally causes myopathy, meaning muscle aches or muscle weakness. This can also be associated with muscle breakdown measured by a test called CK (creatinine kinase).

Rare cases of rhabdomyolysis (muscle breakdown and kidney failure) have been reported with Lipitor and other statins. A history of kidney impairment may be a risk factor for the development of rhabdomyolysis. People with kidney disease will not qualify for this study. The risk of myopathy, and in rare cases rhabdomyolysis, during treatment with statins is increased when taking certain medications. These include: cyclosporine, certain medications to lower triglycerides (fibric acid derivatives, or niacin), some antibiotics such as erythromycin, clarithromycin, certain medications for treating HIV or hepatitis C, or strong antifungal medications known as azole antifungals phosphokinase. It is important to let us know all medications you are taking whether prescribed or over the counter and any new medications you may be prescribed while you are participating in this study. Although very rare, another side effect is elevated liver enzymes which may cause symptoms of feeling tired or weak, loss of appetite, stomach pain, dark urine (dark brownish orange) or yellowing of the skin or whites of your eyes.

Individuals who are on the medications listed above or have certain diagnoses as noted above will not qualify for this study. Please let your healthcare provider know you are taking Lipitor.

It can also cause muscle tenderness or weakness, and study participants should be advised to report immediately unexplained muscle pain, tenderness, or weakness, particularly if in addition you have fatigue or fever or if muscle signs and symptoms persist after discontinuing Lipitor.

Other Cholesterol Lowering Medications

While on the study medication you will not be able to take any other statins or cholesterol lowering medications such as niacin, fibrates, ezetimibe, bile acid binding resins or over the counter herbs such as red yeast rice which has the similar cholesterol lowering effects. It is advised not to drink grapefruit juice when taking a statin.

Contraindications:

These study medications are not recommended for people with any of the following: a known hypersensitive or allergy to statins, previous intolerance to all statins, severe kidney or liver disease.

Potential Benefits

You will know how insulin resistant you are and your risk for type 2 diabetes and risk factors for heart disease. You will be given a statin that is known to decrease the risk of heart and vascular disease. At the end of the study we will review all of your risk

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

factors for type 2 diabetes and heart disease and make recommendations to help you lower these risks. If appropriate you will have the option to receive dietary counseling for a healthier diet and weight loss for 6-8 weeks after completing the study with a registered dietitian. Personal benefit to you may or may not result from taking part in the iPOP research. However, knowledge may be gained from your participation that might eventually benefit you and others.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY

Participant's Rights

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, please call Dr. Knowles or one of his associates at 650-723-7024.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ALTERNATIVES TO STUDY PARTICIPATION

Lifestyle changes, including dietary changes, regular exercise and weight loss can be effective in increasing insulin sensitivity and lowering risk for diabetes and heart disease. If you choose not to participate and think you are at risk for type 2 diabetes and or heart disease, you can make lifestyle changes including weight loss and increased physical activity. If you have elevated cholesterol and risks for heart disease that qualify you for a statin, you may speak to your health care provider about being prescribed Lipitor or one of the other recommended statins to lower your risk for heart disease.

WOMEN OF CHILDBEARING POTENTIAL

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control, such as a condom, or oral birth control pills to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or breast feeding you may not participate in this drug study. To confirm to the extent medically possible that you are not pregnant, you agree to begin the study after the onset of your next menstrual period. You must avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

TISSUE SAMPLING FOR GENETIC TESTING, OTHER TESTING, OR BANKING FOR FUTURE RESEARCH

Blood Samples: You have been given a consent form because the investigators want to include your blood samples in a research project. Research using blood samples is an important way to try and understand human disease. Blood samples may be stored for future research and testing in the field of insulin resistance and the relationship between early events for the development of atherogenesis (blockages in arteries) or type 2 diabetes. Blood samples are identified by your initials, a number and date of your test; otherwise your identity will not be disclosed.

Because there is no absolute protection against discrimination on the basis of disease or genetic information, the investigator will use the results of this study as research only and it will not be included in your medical records. Because this is a research study the information we learn from this study or any future testing will not be reported directly to you. There is no risk of not knowing this information as you will already be given current information regarding insulin resistance and heart disease risks and advised on methods to modify insulin resistance and your risk factors for coronary artery disease as it pertains to you.

If for some reason you are unable to continue in the study we will keep the blood samples obtained from your baseline studies.

Any tissues you have donated which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of tissues do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

If you do not want to grant permission to save your samples after the completion of analysis for this study let us know now or at the completion of your participation. You understand you have the right to withdraw your consent to save your blood after the completion of analysis now or at any time and this will not affect your ability to participate in the research study.

_____ **Yes: I consent to my samples being saved for future research**

_____ **No: I do not consent to my samples being saved for future research**

iPOP samples

We will perform iPOP analysis on the samples collected, including genomic (including whole genome sequencing, this tells us your DNA sequence and some of your genetic disposition to diseases, as well as the DNA sequence of the microbes in your nasal, tongue and skin surface swab, saliva, urine and stool samples), epigenomic (this shows how genes are regulated at the DNA level), transcriptomic (this informs us how genes are expressed at the RNA level), proteomic (this allows us to know the details of all the

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

proteins in your samples), metabolomic (this measures all the metabolites in your samples) and autoantibodyomic (this gives us information whether your immune system is attacking yourself, and if so, which protein target) profiling, as well as integrative analyses (this will enable us to analyze you and your health with all the molecular information above).

As part of this study, we will collect your name, medical history, sample related records, results of your physical examinations and answers to questionnaires. We will also record your iPOP profiles (including genomic, epigenomic, transcriptomic, proteomic, metabolomics, autoantibodyomic as well as integrative profiles) that we generate in our research lab. All participants for this study will be anonymized (unidentified) and assigned to a coded ID number and only the core personnel of the study will have access to the key. Data may also be looked at by groups who regulate all research, including the Institutional Review Board (IRB), the Food and Drug Administration (FDA), or the federal Office for Human Research Protections

TISSUE SAMPLING FOR GENETIC TESTING iPOP

As part of the analysis on your samples, the investigators will do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease. The iPOP information is for research purposes only and will not be released to you.

Your DNA sample and information will be kept in a secured place in Dr. Michael Snyder's laboratory at the Alway Building of the Stanford University School of Medicine, or another site until it is used up or destroyed. The banked DNA may be used in future studies of genetic factors related to health and disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The National Institutes of Health (NIH) has established a national database of Genotypes and Phenotypes (dbGAP) that was developed to archive and distribute the results of studies that have investigated the interaction of genotypes and phenotypes. These studies include genome-wide association studies, medical sequencing, molecular diagnostic assays, as well as association between genotype and non-clinical traits. dbGaP provides two levels of

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

access - open and controlled - in order to allow broad release of non-sensitive data, while providing oversight and investigator accountability for sensitive data sets involving personal health information. Controlled-access data can only be obtained with authorization by the NIH Data Access Committee (DAC) and includes de-identified genotype and phenotype information. Your tissues contain genes which are made of DNA that is unique to you. Coded information about you may be sent to this national database. Access will be controlled and limited to other researchers.

If you agree we would also like to make your genetic data accessible to the public. In this case, your name and personal information would not be posted, but the results of sequencing and other biological assays will be available. There is the possibility that you could be identified through your genome sequence which means others could have access to your genetic information.

Please note that even in the secure database, there is a risk of breach of confidentiality. When data are stored electronically, there is also a risk of breach of computer security. Since you and your relatives and other members of your ethnic group share some of the same genetic make-up, there is a small chance for breach of their privacy, as well.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. We believe that the benefits of learning more about diseases outweigh these potential risks.

Psychological or social risks associated with loss of privacy:

- Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While neither the public nor controlled-access databases developed for this project will contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic information in our databases with information from you (or a blood relative) in another database and be able to identify you (or a blood relative). It also is possible that there could be violations to the security of the computer systems used to store codes linking your genetic and medical information to you.
- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation can also be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a blood relative).
- There may be other privacy risks that we have not foreseen.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

Every effort will be made to keep research records private. There may be times when federal or state law requires the disclosure of those records, including personal information. This is very unlikely. If disclosure is required, we will take all steps allowed by law to protect the privacy of your personal information.

If you do not want to grant permission to save your samples after the completion of analysis for this study let us know now or at the completion of your participation. You understand you have the right to withdraw your consent to save your blood after the completion of analysis now or at any time and this will not affect your ability to participate in the research study.

Yes: I consent to my samples being saved for future research

No: I do not consent to my samples being saved for future research

Buffy Coat Genetic Blood Test

In an effort to better understand the relationship of insulin resistance, its relationship with metabolic abnormalities and possible genetic links we are asking your permission to collect some blood cells known as a buffy coat (part of the white cells). This sample of cells may help us to find a gene or genes which may be related to insulin resistance. This sample is considered a genetic test and therefore you need to be informed of this test. Since this is purely a research project you will not be notified of the results. Not knowing the results will not be harmful as we will tell you the currently known and recommended therapies to reduce insulin resistance.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

If we elect to save a buffy coat sample this will be done when you are having a study test such as a meal profile or insulin sensitivity test, or glucose infusion study and therefore no extra blood will be obtained. Your sample will be identified by initials, a number, and the date of the test done. This is done to avoid errors in collection of results. Your identity will not be disclosed. Because there is no absolute protection against discrimination on the basis of disease or genetic information the investigator will use the results of this study as research only and it will not be included in your medical records. You have the right to withdraw your consent for this test now or at any time and this will not affect your ability to participate in the research study. This buffy coat sample will be stored in a minus 80 freezer for as long as but not limited to 5 years. We will not use this sample for any other purpose then described above without your specific permission.

STANFORD UNIVERSITY Research Consent Form

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Director: Joshua Knowles, MD

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

I agree that this sample (buffy coat) may be collected for the specific purpose described above.

YES ____ NO ____

Please Initial _____

Withdrawal From Study

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

Please let us know immediately as we may want to do follow-up testing if you agree.

If you withdraw from the study, or the study medication is stopped for any reason,

- There will be no harm to you if you withdraw and stop the study medication.
- You must return all of the unused study medication if you withdraw from the study or are asked to stop the study.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances. Other reasons why you may be taken out of the study may include: failure to follow instructions, the study is cancelled or other administrative reasons. If you have any questions, we expect you to ask us. If you have any additional questions please call Dr. Knowles or his associates at 650-723-7024 and they will be happy to answer them.

In the future if there are other studies you may qualify for may we contact you?

YES NO

Please Initial _____

ClinicalTrials.gov

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified. Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

your identity if this study falls within its jurisdiction. The purpose of this research study is to compare the effects of taking statins versus placebo (contains no medication) on insulin action, insulin secretion, and insulin clearance in overweight/obese, insulin resistant, nondiabetic individuals; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is designed to understand the impact of a statin on insulin action, insulin secretion, and insulin clearance in nondiabetic individuals who may be at risk for type 2 diabetes. It is also to analyze iPOP of those individuals who participate in this study, before, during, and after taking a statin. Any scientific paper written based on the information in this study will not reveal your identity. The sponsors will also receive the scientific paper. As required by law the Food and Drug Administration (FDA) may also receive your information related to this research study.

Do I have to sign this authorization form?

You do not have to sign this authorization form but if you do not, you will not be able to participate in this research study or receive any of the research related treatments. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Joshua Knowles, 300 Pasteur Drive, Falk building, CVRC, Stanford, CA 94305-5406.

What personal information will be used or disclosed?

Your health information related to this study includes but is not limited to, the following: Name, address, phone number, email address, date of birth, medical record number, weight, height, blood pressure and pulse, medical history, current medications and over the counter medications, information from your physical exam and answers from your questionnaires which may be used or disclosed in connection with this research study. Laboratory tests include hematocrit (blood count), glucose, insulin, and lipid levels – fat in the blood-, (cholesterol, triglycerides, (type of fat from what we eat and what the liver produces), high density lipoprotein (HDL-C), good cholesterol and low density lipoprotein (LDL-C), bad cholesterol), inflammatory markers, liver and kidney function tests which may be used or disclosed in connection with this research study. Specimens and information taken for Dr. Snyder's lab will be: answers to questionnaires, iPOP profiles, including genomic, epigenomic, transcriptomic, proteomic, metabolomic, microbial (sampled by nasal, tongue and skin swabs) as well as integrative profiles, that are generated in their research lab.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Knowles
- Research staff
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary.

Who May Receive / Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S, Department of Health and Human Services
- The National Institutes of Health
- The Food and Drug Administration
- Doris Duke Foundation.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

- Outside laboratories that may be utilized to analyze samples.

Your information may be re-disclosed if the recipients described above are not required by law to protect the privacy of the information.

Expiration

Your authorization for the use and/or disclosure of your health information will expire on December 31, 2060 or when the research project ends, whichever is earlier.

Will Access to my medical records be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

Signature of Participant

Date

Printed Name of Adult Participant

FINANCIAL CONSIDERATIONS

- 1) Payment – There is no payment for participating in this study
- 2) Costs - If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.
- 3) The Department of Genetics of Stanford University is providing some financial support and materials for this study.
- 4) The National Institutes of Health (NIH) is providing some financial support for the facility and staff where part or all of the study is taking place.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

5) A scientific grant from the Doris Duke Charitable Foundation is providing some financial support for this study.

6) Dr. Michael Snyder is a paid consultant to, and has stock in Personalis, the company that is doing sequencing for this study.

COMPENSATION

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

Contact Information

- Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this **research study**, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director. You may contact Dr. Knowles or associates at 650-723-7024.
- Injury Notification: If you feel you have been hurt by being a part of this study, or need immediate assistance please contact the page operator at 650 723-6661 and ask them to page Dr. Knowles associates: Dr. Fahim Abbasi, or Cindy Lamendola Nurse Practitioner as an alternate contact.
- Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

STANFORD UNIVERSITY Research Consent Form

Protocol Director: Joshua Knowles, MD

IRB USE ONLY

Approval Date: April 16, 2019

Expiration Date: April 16, 2020

Protocol Title: Relationship Between Insulin Resistance and Statin Induced Type 2 Diabetes, and Integrative Personal Omics Profiling

- Appointment Contact: If you need to change your appointment, please contact Dr. Knowles research associates at 650-723-7024

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form

Signature of Participant

Date

Printed Name of Adult Participant

Person Obtaining Consent

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent