Title: Genomic Outcomes of Metformin
NCT02986659
Date: 9/26/18

Wake Forest®
School of Medicine

Section on Gerontology and Geriatric Medicine

GENOMIC OUTCOMES OF METFORMIN (GO MET)

Informed Consent Form to Participate in Research
Jingzhong Ding, MD, PhD, Principal Investigator

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you are 65-79 years old and have expressed interest in the study. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Medical scientists have found that people with diabetes who take the drug Metformin have less age-related disease than those taking other treatments and researchers believe it may prevent numerous diseases and conditions that effect older people. In addition, metformin extends lifespan in some animal models of human disease. The purpose of this study is to see if taking Metformin causes changes in blood cells consistent with improved health and longevity in people who do not have diabetes. In this study Metformin will be compared to placebo. A placebo is a substance, like a sugar pill, that is not thought to have any effect on your disease or condition. In this study you will either receive the active study medication, Metformin or placebo which is not active. Placebos are used in research studies to see if the drug being studied really does have an effect.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 35 people at Wake Forest Baptist Medical Center will take part in this study. In order to identify the 35 subjects needed, we may need to screen as many as 110 because some people will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

If you agree to participate in this study by signing this consent form, you will be asked to complete a screening visit to see if you qualify for the study. You will then complete a baseline visit before beginning the intervention. The details about all study visits and procedures are provided below. We will make every effort to follow the visit procedures in the order they are outlined below; however, it may be necessary at times to make changes to accommodate different schedules.

Screening Visit (SV)

We will ask that you come to the Sticht Center having fasted for at least 8 hours prior to your appointment time, with nothing to eat or drink except water. You will learn all the details of the study and you will be given time to ask any questions and get satisfactory answers. Then, you will be asked to sign this informed consent form if you qualify for the study. After signing the

consent form, we will:

- Draw blood (approximately 1 tablespoon) from a vein in your arm to collect measurement of lipids (cholesterol), blood counts and chemistries, average blood sugar levels, Vitamin B12, and liver and kidney function for screening purposes
- Provide you with a light snack
- Measure your blood pressure, pulse, height, weight, and waist circumference
- Ask you to do a series of physical performance tests including balance tests, chair rise (stand up from a seated position in a chair 5 times), short walk test (4 meters) and a narrow walk test
- Ask you questions about your memory
- Ask you questions about your background, medical history, difficulty doing different physical tasks , and review of medications and dietary supplements

This visit will take approximately 1 – 1 ½ hours to complete. We will call you within a week to let you know if you qualify to continue for a Baseline Visit. If you do not qualify we will send you a letter with the results of your lab work so that you many share with your doctor, if you would like.

Baseline Visit (BV)

Approximately one week later you will come to the Sticht Center having fasted for at least 8 hours prior with nothing to eat or drink except water. We ask that if you have a fever, infection, or have been taking antibiotics within 24hrs of this scheduled visit that you let us know so we can reschedule your visit. We will:

- Draw blood (approximately 5 tablespoons) to measure your cells response to Metformin and ability to make energy, to measure your blood counts and chemistries, as well as blood for storage.
- Provide you a light snack
- Ask you to do a series of physical performance test that include testing your leg strength on chair-like devices, testing your grip strength with a handheld device, asking you to perform a 6 minute walking test
- Have you watch short video clips of different physical tasks and answer questions related to the video clips.
- Ask you questions about your memory
- Once the visit is complete, you will be randomized and placed in one of the following groups discussed below

This visit will take approximately 2- 2 ½ hours to complete.

You will be randomized into one of the two study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group.

The groups are:

3 months of Metformin then switching to 3 months of placebo
3 months of placebo then switching to 3 months of Metformin

Eligible participants will receive both interventions (3-month metformin treatment and 3-month placebo). Neither you nor the study staff will know which group you will be assigned to. All participants will have the same dose schedule as detailed below.

You will start by swallowing a pill (at a dose of 425 mg or placebo) once a day with dinner for 7 days. After the week, a study staff member will call you to see how it's going and you will be asked to increase dose to one pill with dinner (at a dose of 850 mg or placebo - from a different bottle) for one week. At the end of the second week, you will be called again and if things are going okay, you will be asked to take two (850mg) pills, one in the morning and one at night, (for a total dose of 1700 mg or placebo) for the remainder of the 3 months until you return for your midpoint visit.

Once you are randomized to the study drug you will be provided a Participant Guidelines form that will give you details on how to take your pills and what to do if you have a reaction while taking them. This form will include your study coordinator's contact information and then name of the study physician if you need to call with questions or concerns.

Midpoint Visit (MID)

After being in the study for 12 weeks we will call to schedule you to return to the Sticht Center having fasted for at least 8 hours prior to your appointment time, with nothing to eat or drink except water. We ask that if you have a fever, infection, or have been taking antibiotics within 24hrs of this scheduled visit that you let us know so we can reschedule your visit. At this visit we will:

- Measure your blood pressure, pulse, height, weight, and waist circumference)
- Draw blood (approximately 6 tablespoons) to measure your cells response to Metformin and ability to make energy as well as blood for storage.
  We will also test your liver and kidney function, your blood counts and chemistries, your average blood sugar level, and your lipids (cholesterol).
- Ask you to do a series of physical performance test that include testing your leg strength on chair-like devices, testing your grip strength with a handheld device, asking you to perform a 6 minute walking test
- Ask you to do a series of physical performance tests including balance tests, chair rise (stand up from a seated position in a chair 5 times), short walk test (4 meters) and a narrow walk test
- As you to answer some questions on how much difficulty you have doing different physical tasks and have you watch short video clips of different physical tasks and answer questions related to the video clips.
- Ask you questions about your memory

This visit will take approximately 2- 2 ½ hours to complete. When you return for this visit we will ask that you bring in all your remaining pills and the study staff will then dispense your new pills to take for the remainder of time you are in the study. You will be given the same amount of pills as you did at your baseline visit and instructed to take each amount the same as in the beginning of the study with taking a pill (at a dose of 425 mg or placebo) taken orally once a day with dinner for 7 days. After the week, a study staff member will call you to see how it is going and you will be asked to increase dose to one pill with dinner (at a dose of 850 mg or placebo -

from a different bottle) for one week. At the end of the second week, you will be called again and if things are going well, you will be asked to take two (850mg or placebo) pills, one in the morning and one at night, (for a total dose of 1700 mg or placebo) for the remainder of the 3 months until you come in for your last visit.

Follow up Visit (FV)

After another 12 weeks we will call to schedule you to return to the Sticht Center having fasted for at least 8 hours prior to your appointment time, with nothing to eat or drink except water. We ask that if you have a fever, infection, or have been taking antibiotics within 24hrs of this scheduled visit that you let us know so we can reschedule your visit. At this visit we will:

- Measure your blood pressure, pulse, height, weight, and waist circumference)
- Draw blood (approximately 6 tablespoons) to measure your cells response to Metformin and ability to make energy as well as blood for storage.
- We will also test your liver and kidney function, your blood counts and chemistries, your average blood sugar level, and your lipids (cholesterol).
- Ask you to do a series of physical performance test that include testing your leg strength on chair-like devices, testing your grip strength with a handheld device, asking you to perform a 6 minute walking test
- Ask you to do a series of physical performance tests including balance tests, chair rise (stand up from a seated position in a chair 5 times), short walk test (4 meters) and a narrow walk test
- As you to answer some questions on how much difficulty you have doing different physical tasks and have you watch short video clips of different physical tasks and answer questions related to the video clips.
- Ask you questions about your memory
- Ask you about types of preventative screenings and immunizations you may have received and if you regularly exercise.

This visit will take approximately 2- 2 ½ hours to complete. When you return for this visit we will ask that you bring in all your remaining pills.

You will have blood withdrawn from a vein at a total of 4 study visits. The total amount of blood withdrawn during the study will be approximately (18 tablespoons).

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study. These results include copies of the clinical labs in which the results are received by the study the day after each visit in which blood is drawn.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

As part of this study, blood samples will be obtained and DNA from your blood sample will be purified. DNA, or deoxyribonucleic acid is the substance in your cells that stores and transmits

inherited traits, such as eye color or blood type. Because we do not know how the results of this DNA study relate to your individual health, the results of the research will not be given to you or your doctor. These results will not be placed in your medical records.

Storage of Biological Blood

If you agree to participate in this study, we will draw 4 tablespoons of blood to use for future research. This sample will be kept and may be used in future research to learn more about health and disease. Your sample will be obtained in the Geriatrics Clinical Research Unit at Wake Forest University Baptist Medical Center. The sample will be stored in the Geriatrics Laboratory and it will be given only to researchers approved by Dr. Jingzhong Ding. An Institutional Review Board (IRB) must also approve any future research study using your blood sample. In order to participate in this study, you must be willing to provide this sample for future research.

Your blood sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your blood sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood sample will not affect your care.

Your blood sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

How Long Will I Be in the Study?

You will be in the study for about 24 weeks or 6 months. You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. Before having surgery or any X-ray/scanning procedure using injectable iodinated contrast material, tell your doctor that you are taking Metformin. You will need to temporarily stop this medication before the time of your surgery/procedure. Consult your doctor for further instructions.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the procedures and drug we are studying may include:

1. Study Medications

Metformin is a widely used medication. Common side effects include nausea, gas, vomiting, stomach upset, diarrhea, weakness, or a metallic taste in the mouth may occur. These often go away after a short time. If any of these effects persist or worsen, please tell us immediately. If stomach symptoms return later (after taking the same dose for several days or weeks), tell the study staff immediately. Limit alcohol while using this medication. Participants may see a drop in blood sugar from taking the Metformin. However, Metformin has been used with thousands without diabetes and shown no major concerns. The study staff and study physicians will be monitoring all participants to avoid any issues. Side effects of low blood sugar include rapid heartbeat, fatigue, headache, hunger. If you do experience these effects after taking the medication, we ask you tell us immediately. We will provide randomized participants with exact details once they are in the study on how to handle any situation that may occur in their Participant Guideline form. There are no known side effects of taking a placebo. There is no risk of additional side effects by starting in one group or the other and then switching to the other group. Both groups will start with a low dose and gradually work your way up to a full dose to minimize any side effects.

2. Physical function tests

Your ability to perform certain physical activities will be measured before and after the intervention. There is a slight risk of falls while participating in the balance test. However, you will be positioned beside a step or wall that can be reached immediately if you feel that you are going to lose your balance. Additionally, the person conducting the test will stand next to you at all times. You may have slight hand or leg discomfort during the grip and leg strength tests, but this usually stops once the tests are over. There is a small possibility that you may stumble, fall or aggravate one of your joints/muscles during the walking test or knee strength test.

3. Blood Sampling

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally, some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia). You should not donate blood for at least 8 weeks after completing this study.

4. Body measurements

Several methods will be used to determine the amount of fat, muscle and bone and the location of body fat. A tape measure will be used to measure the size of your waist.

5. Questionnaires

During the clinic visits we will ask you a variety of questions that you may feel are boring or wonder why we need this information. Please know that we only collect information that we feel may be useful to know when studying the effects of Metformin. You may become tired during the questionnaires or memory testing and if this occurs, we can take a break until you are ready to continue.

There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study. There are no standard of care alternate treatments or procedures.

What About My Health Information?

In this research study, any information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** health history, how you respond to study activities or procedures, laboratory and other test results, and information from study visits, phone calls, surveys, and physical examinations.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as

the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.
Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completed and finished.

You can tell Dr. Jingzhong Ding that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Dr. Jingzhong Ding
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study. By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

You will be given a parking voucher so that you do not have to pay for parking when you come for your study visits.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

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.

Participant 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 your identity if this study falls within its jurisdiction.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institutes of Health which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $60 in gift cards if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid with a $20 in gift card for each complete study visit (baseline, mid-point and follow up). You can choose from a Walmart , Target, or Shell Gas card at each of your visits. You will not be paid for the screening visit.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the National Institutes of Health and Wake Forest University Health Sciences. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance

Management, at (336) 716-3467.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Jingzhong Ding at [redacted] or [redacted] after hours and identify yourself as a GO MET study participant.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because:

- it is in your best medical interest,
- your condition worsened,
- new information becomes available,
- you had an unexpected reaction,
- you failed to follow instructions,
- or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Jingzhong Ding at [redacted] or [redacted] after hours and identify yourself as a GO MET study participant.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to

ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent:_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm