RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Energy Metabolism in Thyroidectomized Patients

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SPONSOR: Virginia Commonwealth University

NOTE: In this consent form, "you" always refers to the research participant.

ABOUT THIS CONSENT FORM

You are being invited to participate in a research study because you will undergo total thyroidectomy and you will need thyroid hormone therapy. **It is important that you carefully think about whether being in this study is right for you and your situation.**

This consent form is meant to assist you in thinking about whether or not you want to be in this study. **Please ask the study doctor or the study staff to explain any information in this consent document that is not clear to you.** You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Your participation is voluntary. You may decide not to participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

AN OVERVIEW OF THE STUDY AND KEY INFORMATION

Why is this study being done?

The purpose of this research study is to measure the changes in energy metabolism (how the body burns energy), cardiovascular function (heart function), and lipid metabolism (cholesterol break down and building) before and after thyroidectomy (surgical removal of thyroid gland) in response to two approved therapies for hypothyroidism: levothyroxine (LT4) or Liothyronine/levothyroxine (LT3/LT4) combination therapy.

What will happen if I participate?

In this study, Levothyroxine (LT4) and placebo (a look-alike inactive substance, a "sugar pill") will be compared to Liothyronine/ Levothyroxine (LT3/LT4) combination therapy.

Levothyroxine LT4 and Liothyronine (LT3) are drugs approved by the U. S. Food and Drug Administration (FDA).

VCU Health COVID-19 Procedures

All subjects will be required follow VCU Health COVID-19 standard of Care screening procedures. All subjects will be required to enter the VCU Health Care facility at a location specified by the study team. Please be advised that a mask or face shield will be required before entering and during your visit to all VCU Health Care facilities. If you do not have a mask, one will be provided upon entry. VCU health staff will conduct standard of care COVID-19 screening as you enter the facility. If you suspect that you may be positive, have tested positive or have been around someone who is or suspected to be positive or tested positive, please notify your study team as soon as this information becomes available for guidance. Do not come for your scheduled research appointment. The study team will provide follow-up instructions.

The hospital standard operating procedures require that anyone coming to the hospital for inpatient stay must follow all the VCU Health Care facilities COVID-19 protocols. In addition, they may need to have a COVID-19 test done two days (48 hours) to 3 days (72 hours) prior to any inpatient admission based upon VCU Health policy. This study involves three-(3) inpatient study admission to the hospital: (Baseline, Month 3 and Month 6 study visits). If required, once the study doctor receives the results of the COVID-19 test, he/she will contact you with the results and directions for your inpatient scheduled study visits.

This study requires approximately five study visits. The five-study visits will be a **Screening Visit (outpatient)**, one **Baseline Visit,** (inpatient) one **Six Week Visit,** (outpatient), one **Three Month Visit and one Six Month Visit** (both inpatient). The COVID-19 test maybe required to be done 48 hours (2 days) before each of the three-inpatient visit, **Baseline Visit, Three Month and Six Month Visit** based upon VCU Health policy. If clinically indicated, additional visits can be scheduled.

You will be asked to:

1. Give permission for the researchers to collect information about your medical history from your medical records and you five times during the study visits and for 5 years after the study visits.
2. Have a Physical exam done 5 times
3. Up to 24-hour energy expenditure recording in the Whole room indirect calorimeter studies 3 times (inpatient overnight stays: Baseline, Three months, and Six months visits)
4. Study drug will be dispensed three times
5. Have study drug dose adjustments two times
6. Genomic blood draw for DNA one time
7. Have your blood drawn five times
8. Have an DXA Scan two times
9. Have an Echocardiogram three times

10. Complete questionnaire three times
11. Have Accelerometers sensors laced 3 times (inpatient overnight stays: Baseline, Three months, and Six months visits), based upon availability
12. Be randomized to take either Levothyroxine LT4 + placebo group or LevothyroxineLT3/ Liothyronine LT4 group from baseline through 6 months

Your participation in this study will last up to 6 months after your surgery. Approximately 30 total individuals will participate in this study.

What alternative treatments or procedures are available?
If you decide not to enter the study, you can receive the usual care that you would receive if you were not in the study. This include LT4, LT3, or a mixture (at the judgment of your physician).

What are the risks and benefits of participating?
There are both risks and benefits of participating in research studies. We want you to know about a few key risks right now. We will give you more information in the "WHAT RISKS AND DISCOMFORTS CAN I EXPECT FROM BEING IN THE STUDY?" section.

Risks and Discomforts	Benefits to You and Others
1. Study Drug Risks 1. There is a risk that the study drug may not cause a better outcome as it relates to hypothyroid symptoms, weight gain, lipid profile, or cardiovascular function 2. There is also a risk that you could have side effects from taking study drug. Below are some of the most common side effects: o Irregular heart beat o Chest pain, o Anxiety o Bone loss o Allergic Reaction **2. Key Procedural Risks**	**1. Potential Direct Benefits** The there is evidence that LT4 and LT3 combination therapy is effective in treating Hypothyroidism. This study may help study doctors learn things that may help other people in the future.

• Venous blood draws may cause pain, bleeding, and/or bruising. You may faint and could develop an infection at the site where blood is drawn. • **Radiation exposure** DXA scan produces a low dose of X-ray radiation comparable to 1/10 of the radiation from a chest x-ray. Prolonged exposure to radioactivity or to multiple tests that use radioactivity has been associated with the development of anemia or cancer**.**	

Now that you have a general overview of the study, we want to provide the details about what your participation involves. Please read, or have someone read to you, the rest of this document. If there is anything you do not understand, be sure to ask the study staff.

WHAT WILL HAPPEN IF I PARTICIPATE IN THE STUDY?

Upon entry into any VCU health care facility, all subjects will be required follow VCU Health COVID-19 standard of Care screening procedures.

Screening Visit

At your first study visit (called the screening visit), before any procedures are done, if you have not done so, we will ask you to read and sign the informed consent after having had all your questions and concerns answered to your satisfaction.

During this visit a trained physician, or nurse will obtain and collect the information required for this study. The staff will collect

- Anthropometric information, which include measures of height, weight, temperature, and body composition and blood pressure.
- A physical exam will be performed by the study physician
- The study team will collect the following information about your medical history from your medical records and you:
    - Your age
    - Self-reported race/ethnicity
    - Medical history
    - Surgical history
    - Social history
    - History of medication usage

- Female subjects will be asked to provide a menstrual history,
    - Use of contraception, and
    - Self-reported pregnancy status for the study period.

- In addition, trained staff will collect study blood samples to run the following laboratory tests to determine if you can participate in this study.
    - Thyroid peroxidase antibody (TPO antibodies)
    - Thyroid Stimulating Hormone (TSH)
    - Glycated hemoglobin (HbA1c)

This visit will last approximately 30 to 45 minutes.

The results of this visit help the study doctor decide if you are eligible to participate in the study. If you are not eligible, the study doctor will discuss the reason(s) with you.

If you are eligible to continue, the study coordinator will give (or contact) you with instructions for your next study visit called the "Baseline Visit". To prepare for next study visit the study staff will give you instructions to follow before you come for this visit.

Two days before your next Visit.

- You maybe be required to be tested for COVID-19 based upon VCU Health policy. Directions for getting the test and the results will be provided to you.
- Please do not do any strenuous exercise and stay on a regular a regular diet for two days before you come to be admitted for inpatient Baseline Visit hospital stay.

Baseline Visit

Upon entry into any VCU health care facility, all subjects will be required follow VCU Health CIVID-19 standard of Care screening procedures.

At this study visit, you will be admitted to the hospital and stay in the whole room indirect calorimeter for up to 24 hours before you will undergo total thyroidectomy. During this stay, a 24-hour energy expenditure will be recorded in the whole room indirect calorimeter.

In the morning of the visit, the following procedures will be done before entering the whole room indirect calorimeter for up to 24-hour energy expenditure recording.

- A medical history and physical examination,
- An echocardiogram (test that uses sound waves to create pictures of the heart)
- ThyPRO-39 quality of life questionnaire. If not completed before entering the whole room indirect calorimeter, this test can be completed within the first hour while in the whole room indirect calorimeter.

- You will be fitted with five accelerometers (one on each limb plus chest) to record spontaneous movements (done based upon availability)

You will enter the indirect calorimeter room for up to 24-hour energy expenditure recording at approximately 11:00 am

The following procedures will be performed and data recorded while in the whole room indirect calorimeter:

- You will receive standardized meals at 1:00 pm, (if already entered in the WRIC) and at 6:00 pm. You will be required to fast (From dinner at 06:00 PM until the end of the whole room indirect calorimeter recording at approximately 11:00 AM of the next day), about 8-hours overnight fasting and 4 hours fasting during the study.
- five accelerometers (one on each limb plus chest) will record your spontaneous movements continuously for 24 hours (done based upon availability)
- Approximate total energy needs for weight maintenance will be calculated and the 24-hour energy expenditure will be completed at approximately 11:00 am of the following day,

The following procedures will be done after you leave the whole room indirect calorimeter:

- anthropometric measures: height, weight, temperature, blood pressure
- Body composition by DXA scan.
- Venipuncture to collect study blood samples
    - Free Thyroxine (Free T4)
    - Free Triiodothyronine; Total Triiodothyronine (T3)
    - Serum lipids (cholesterol, triglycerides)
    - Serum for storage
    - Genomic DNA
    - Serum for storage

4 Study drug Randomization

Randomization will be performed at the end of the baseline visit. You will be randomized (like flipping a coin) to the study drugs LT4 plus a placebo (standard of care) or LT3/LT4 combination replacement therapy for a six-month period after the surgery. You have one chance in two of being assigned to LT4 and placebo, and one chance in two of receiving LT3/LT4 combination therapy. Neither you nor the study doctor will know which study drug you are receiving. This information is available to the study doctor if needed in an emergency. This is called blinding, and it is done so that a fair evaluation of results may be made.

The VCU Investigational Drug Pharmacy will provide color-coded capsules so that you will know which tablet to take in the morning “AM” and at night “PM”.

The Thyroid stimulating Hormone (TSH) (a blood test that measures whether you have too much, too little or sufficient thyroid hormone) laboratory result is needed for randomization.

This visit will take approximately up to 30hours.
Your next visit will be approximately six weeks (+7days) following the start of your first dose.

- Reminder to bring in all unused study medication to your 6 week visit

Six Week Visit (+/-7days) window (it can be conducted virtually at the Principal Investigators’ discretion and study participant preference)
Upon entry into any VCU health care facility, all subjects will be required follow VCU Health CIVID-19 standard of Care screening procedures.
This is an outpatient visit. At this visit we the study doctor will:

- Review your medical history
- Perform a physical exam

The study staff will collect

- Anthropometric measures of height, weight, temperature, blood pressure, body composition
- Venipuncture to collect study blood samples
  - Thyroid Stimulating Hormone (TSH)
  - Serum for storage

Venous blood samples will be collected for thyroid stimulating hormone (TSH) and storage for research. The Thyroid stimulating Hormone (TSH) (a blood test that measures whether you have too much, too little or sufficient thyroid hormone) laboratory result is needed for dose adjustment and may not be available before you leave the clinic. If this happens, the study-unblinded doctor will decide the amount of study drug you will need to take once the TSH laboratory results are available; we will contact you and mail the medication to you with instructions on how to take your study drug. Continue taking the current medication until you receive your new medication.

This visit will take approximately 30 minutes.

To prepare for next study visit the study staff will give you instructions to follow before you come for this visit.

Two days before your next Visit.

- You may be required to get a tested for COVID-19 based upon hospital policy. Directions for getting and the test and results the test will be provided to you.
- Please do not do any strenuous exercise and stay on a regular a regular diet for two days before you come to be admitted for inpatient 3-months Visit hospital stay.
- Reminder to bring in all unused study medication from your Baseline and 6 week Visit to your next visit

Three Month Visit (+/-7days)

You may be required to have a COVID-19 test done 2 days (48-hours) to 3 days (72- hours) before the study visit based upon VCU Health policy. Upon entry into any VCU health care facility, all subjects will be required follow VCU Health COVID-19 standard of Care screening procedures.

At this study visit, you will be admitted to the hospital and stay in the whole room indirect calorimeter for up to 24 hours. During this stay, a 24-hour energy expenditure will be recorded in the whole room indirect calorimeter.

In the morning of the visit, the following procedures will be done before entering the whole room indirect calorimeter for 24-hour energy expenditure recording.

- A medical history and physical examination
- An echocardiogram (test that uses sound waves to create pictures of the heart)
- ThyPRO-39 quality of life questionnaire. If not completed before entering the whole room indirect calorimeter, this test can be completed within the first hour while in the whole room indirect calorimeter.
- You will be fitted with five accelerometers (one on each limb plus chest) to record spontaneous movements done based upon availability

You will enter the indirect calorimeter room for up to 24-hour energy expenditure recording at approximately 11:00 am

The following procedures will be performed and data recorded while in the whole room indirect calorimeter:

- You will receive standardized meals at 1:00 pm, (if already entered in the WRIC) and at 6:00 pm. You will be required to fasting (From dinner at 06:00 PM until the end of the whole room indirect calorimeter recording at approximately 11:00 AM of the next day), about 8-hours overnight fasting and 4 hours fasting during the study
- Five accelerometers (one on each limb plus chest) will record your spontaneous movements continuously for 24 hours done based upon availability

- Approximate total energy needs for weight maintenance will be calculated and the 24-hour energy expenditure will be completed at approximately 11:00 am of the following day

The following procedures will be done after you leave the whole room indirect calorimeter:

- Anthropometric measures: height, weight, temperature, blood pressure
- Venipuncture to collect study blood samples
    - Thyroid Stimulating Hormone (TSH)
    - Free Thyroxine (Free T4)
    - Free Triiodothyronine; Total Triiodothyronine (T3)
    - Serum lipids (cholesterol, triglycerides)
    - Serum for storage

This visit will take approximately up to 30 hours.
Dose adjustment of the study drugs, if needed, will be made by the unblinded endocrinologist. The study coordinator will give (or contact) you with instructions for your next study visit called the "6 months Visit". Continue taking the current medication until you receive your new medication.

To prepare for next study visit the study staff will give you instructions to follow before you come for this visit.

Two days before your next Visit. (6 Month Visit)

- You may be required to get a tested for COVID-19 based upon VCU Health policy. Directions for getting the test and the results will be provided to you.
- Please do not do any strenuous exercise and stay on a regular a regular diet for two days before you come to be admitted.
- Reminder to bring in all unused study medication from your 6 week and Month three Visit to your next visit

6 Month Visit (+/-7days) window
Upon entry into any VCU health care facility, all subjects will be required follow VCU Health COVID-19 standard of Care screening procedures.
At this study visit, you will be admitted to the hospital and stay in the whole room indirect calorimeter for up to 24 hours. During this stay, a 24-hour energy expenditure will be recorded in the whole room indirect calorimeter.
In the morning of the visit, the following procedures will be done before entering the whole room indirect calorimeter for up to 24-hour energy expenditure recording.

- A medical history and physical examination
- An echocardiogram (test that uses sound waves to create pictures of the heart)
- ThyPRO-39 quality of life questionnaire if not completed before entering the whole room indirect calorimeter, This test can be completed within the first hour while in the whole room indirect calorimeter.
- You will be fitted with five accelerometers (one on each limb plus chest) to record spontaneous movements done based upon availability

You will enter the indirect calorimeter room for up to 24-hour energy expenditure recording at approximately 11:00 am

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- You will receive standardized meals at 1:00 pm, (if already entered in the WRIC) and at 6:00 pm. You will be required to fasting (From dinner at 06:00 PM until the end of the whole room indirect calorimeter recording at approximately 11:00 AM of the next day), about 8-hours overnight fasting and 4 hours fasting during the study
- Five accelerometers (one on each limb plus chest) will record your spontaneous movements continuously for 24 hours maybe done based upon availability
- Approximate total energy needs for weight maintenance will be calculated and the 24-hour energy expenditure will be completed at approximately 11:00 am of the following day,

The following procedures will be done after you leave the whole room indirect calorimeter:

- anthropometric measures: height, weight, temperature, blood pressure
- Body composition by DXA scan.
- Venipuncture to collect study blood samples
    - Thyroid Stimulating Hormone (TSH)
    - Free Thyroxine (Free T4)
    - Free Triiodothyronine; Total Triiodothyronine (T3)
    - Serum lipids (cholesterol, triglycerides)
    - Serum for storage

This visit will take approximately up to 30 hours.

At each visit, you should bring all of your remaining study drug supply to the research clinic.

The investigators will also collect information from your medical records about other medical conditions (for example but not limited to diabetes, hypertension, high cholesterol level), and other medications you are taking. Medical record information will be collected during your participation in the study and for 5 years after you finish taking the study drug. At the end of the trial, your care will be transferred to your endocrinologist or your primary care provider. We will prescribe three-month supply of the levothyroxine or levothyroxine-liothyronine combination therapy, based on your preference since both drugs are approved for the treatment of hypothyroidism. You or your insurance will be responsible for the cost of this prescription since the study is completed.

Study Procedures

Whole Room Indirect Calorimeters also referred to as (Metabolic Chambers)

Whole room indirect calorimeters are rooms that can measure the calories, or energy you burn; this measurement is called "energy expenditure". Each of the three-inpatient visits will include a 24-hour recording of energy expenditure in the whole room calorimeter. The whole room indirect calorimeter is located in the Clinical Research Service Unit (CRSU) on the eight (8^{th}) floor of the North Hospital, on the MCV campus of Virginia Commonwealth University. The room calorimeter is a 10' x 10' x7'6" room with a window and transparent plexiglass wall. The room is fitted with TV, phone, hospital bed, small desk, a toilet behind a privacy screen and a vanity. Meals are passed through a port. The room is fitted with Wi-Fi and the door has no lock. The enclosed space may cause some minimal discomfort and the ventilation can be noisy, non-dissimilar to a commercial airplane. Study volunteers can step out the room and withdraw from the study at any time, and there is no lock in the calorimeter's door.

Anthropometric Measurements

A series of measurements of the muscle, bone, and adipose tissue used to look at the composition of the body. The core elements of are height, weight, body mass index (BMI), body circumferences (waist, hip, and limbs), and skinfold thickness

Venous Blood Sample Collection.

We will insert a needle in a vein to collect blood samples at specified times. Study subjects will undergo one venipuncture during each of the study visits. Altogether, five blood samples will be collected throughout the study for a total of approximately one and a half cup of blood. All the samples collected will be for the research study, except for the measurement of TSH that will be used to adjust the therapy. We will store and analyze your samples for lipids (fats), (TSH) Thyroid stimulating Hormone TSH (determinations for dose adjustments), Free (T4) Free

Thyroxine and (T3) Triiodothyronine. These blood levels to help evaluate thyroid function and diagnose thyroid diseases, including hyperthyroidism and hypothyroidism, TPO (antibodies sample will be collected to help determine if the cause of thyroid disease is an autoimmune disorder), and other components for hormonal and metabolic factors. Blood samples will be collected at Screening, baseline (pre-surgery), 3-month and 6-month study visits.

Accelerometers

The accelerometers are sensing devices that measure a moving object's acceleration and can detect frequency and intensity of human movement. They are very similar to "Fitbit" or other exercise recording devices.

Genetic Material

This study will use your samples to sequence all or part of your DNA.

> *Deoxyribonucleic acid (DNA) is the "blueprint" or "recipe" that gives the body's cells instructions on how to do their jobs. Scientists can use a test called whole genome sequencing to determine the order of all or part of the molecules that make up your DNA, like reading all the letters in a book. Sequencing is usually done to look for changes in the molecules of DNA that may cause health problems.*

Genetic material will be collected during the study to study whether common gene variations called "Single Nucleotide Polymorphisms" (SNPs) in gene that regulate the thyroid hormone signaling affect the response to the therapy. We do not plan to screen for genetic disease, and the information collected are without clinical interest, thus the information will not be provided to the volunteers. No genome wide association study will be performed, and the genetic material will be disposed of at the end of the study. Study volunteers can opt out the collection of genetic material. A genome-wide association study (GWAS) is a type of research to associate genetic variations with particular diseases. Genetic variations are common in the population. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence or the risk of developing a disease.

Quality of Life assessment

Study participants will be administered ThyPRO-39, a thyroid specific quality of life instrument at the baseline (pre-surgery), 3-month and 6-month visit. This questionnaire helps the researchers to measure the intensity of the symptoms associated with hypothyroidism, and their changes in relation to the therapy. Some individual may experience discomfort by gaining introspection in their condition.

DXA Scan

DXA stands for dual-energy x-ray absorptiometry (also known as a **DEXA scan**). It is a simple, 10-minute test that takes a comprehensive snapshot of your exact breakdown of bone, fat

tissue, and muscle mass. The DXA scan is the most accurate and precise body fat test available. There are not any special preparations needed, except to stop taking any calcium supplements for 24 hours before the test. Study participants are requested to lay still on a table while a sensor (similar to an X-ray machine) moves over the body from the head to the feet. Wear comfortable clothing. You may have to take off any clothes with metal fasteners, zippers, or hooks. Study volunteers will undergo (DXA scan) at the baseline and six-month visits. The only potential risk associated with DXA scan is the exposure to radioactivity.

Echocardiogram (echo)

An echocardiogram uses sound waves to produce images of your heart. This common test allows your doctor to see your heart beating and pumping blood. Your doctor can use the images from an echocardiogram to identify heart disease. For most types of echo, you will remove your clothing from the waist up. Women will be given a gown to wear during the test. You will lay on your back or left side on an exam table or stretcher. Soft, sticky patches called electrodes will be attached to your chest to allow an EKG (electrocardiogram) to be done. The study personnel will spread gel on a device (transducer) then presses the transducer firmly against your skin, aiming an ultrasound beam through your chest to your heart. The transducer records the sound wave echoes from your heart. Study volunteers will undergo Echo at the baseline three and six-month visits. The procedure will take about 20-30 minutes to complete.

WHAT RISKS AND DISCOMFORTS COULD I EXPERIENCE FROM BEING IN THE STUDY?

Your condition may not get better or may become worse while you are in this study.

Potential Risks

Research-related risks in this study include those associated with study procedures, namely blood drawing, study medications, radiation exposure, and dissemination of Protected Health Information (PHI), including genetic data.

No significant risk can be expected from the whole room indirect calorimeter or echocardiogram, ™ apparatus. Some individuals may experience anxiety during the stay in the indirect calorimeter. Potential additional risks are associated with the collection of genetic material and the possible infringement of the study participants' privacy with dissemination of protected health information (PHI).

Possible Risks associated with Study Drug

Risks associated with excess of LT3 (and to a lesser degree with LT4) include development of hyperthyroid symptoms, among them:

- Irregular heart beat
- Chest pain

- anxiety
- bone loss

Levothyroxine allergic reaction may include (less common)

- skin rash
- hives
- flushing

Possible Risks Associated with Liothyronine allergic reaction may include (less common)

- Skin rash
- Hives
- Itching
- Fever
- Swelling
- Shortness of breath
- Wheezing
- Runny nose

An allergic reaction to drugs is possible, but rare. Severe allergic reactions can be life threatening.

Only the study participant can take the study drug. It must be kept out of the reach of children and persons who may not be able to read or understand the label.

Thyroid hormone medications are considered “narrow index” drugs, and their dose needs to be accurate. Many medications can interfere with the thyroid hormone drugs. Please inform the study team if during the study your providers make any change in your medication regimen. We will provide a card with the information of the study you can show to your other providers. We will be happy to talk with your providers if they have any questions related to the study and study medications.

Possible Risk Associated with having Energy expenditure recording:

The only risk is anxiety or discomfort due to extended period of time fasting (From dinner at 06:00 PM until the end of the whole room indirect calorimeter recording up to 11:00 AM of the next day), about 8-hours overnight fasting and up to 4 hours fasting during the study) limited space available in the whole room indirect calorimeter. Study staff, experienced nurses, and hospital physicians will be available to help if you become anxious. If at any time you feel too

anxious or uncomfortable, you can simply walk out of the room, as there are no locks on the doors.

Possible risks associated with Echo: There is minimal risk associated with this procedure. Some individuals are allergic or sensitive to adhesive or latex and may experience skin rash (dermatitis) from the electrodes.

Possible risks associated with DXA Scan
There is minimal risk associated with this procedure. DXA scan produces a low dose of X-ray radiation comparable to 1/10 of the radiation from a chest x-ray.

Possible risks with having Blood collection:
There may be pain at the site where the needle is inserted. Bruising and very rarely infection may occur. Some people may experience nausea or faint when the needle is inserted or when they see blood. Please inform the study personnel if you have experienced any of these reactions before. Bandages used to cover the catheter site may cause a skin rash (dermatitis) in some people who are allergic or sensitive to adhesive or latex.

Possible risk with completing ThyPRO-39 quality of life Questionnaire
There is minimal risk associated with this procedure. You may experience some emotional discomfort as you assess your perceived quality of life.

Non-Physical Risks
Participation in research might involve some loss of privacy. There is a small risk that someone outside the research study could see and misuse information about you.

Questionnaires may contain questions that you may find as sensitive/personal/upsetting in nature. You may refuse to answer any question that makes you feel uncomfortable.

This study will ask you questions about personal topics that might be embarrassing to talk about and that could affect your family relationships if this information were to become known outside of the study. You will also be asked about illegal activities, which could have legal and financial consequences if this information were to become known outside of the study.

Genetic Risks:
If known to employers or insurance companies, the results of genetic tests might affect a person's ability to obtain a job or health or life insurance. If this information were released, it

could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty obtaining insurance coverage and/or a job.

A federal law called the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, this legal protection still may not keep someone from trying to discriminate against you in this way. It is possible that a genetic test might identify a change in the genetic code. This change in the genetic code is called a "polymorphism". Polymorphisms are common: some are associated with disease, and some are not. Some polymorphisms are being studied for differences in response to thyroid hormone therapy, but at this time the data are not clear. We do not expect to find polymorphisms that have a known link to diseases. Furthermore, we are not performing whole-genome analysis. Therefore, we do not expect that any of the genetic studies' results will cause any potential risk if this information were released.

Unknown or Unforeseeable Risks
The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in the study.

Levothyroxine (LT4) and/or Liothyronine/levothyroxine (LT3/LT4) combination therapy may involve risks that are currently unknown or unforeseeable. The use of Liothyronine (LT3) is not recommended in pregnancy, and if you are or may become pregnant, your participation in the study will be terminated and you will be prescribed Levothyroxine (LT4) and referred to an endocrinologist for continuity of care.

Reproductive Risks
As the study procedures might injure an unborn child, pregnant women may not participate. Women who might become pregnant should use a medically accepted form of birth control such as total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should a woman become pregnant there is a potential risk of injury to an unborn child from exposure to radioactivity via the DXA scan. The use of Liothyronine (LT3) is not recommended in pregnancy. For similar reasons, women who are nursing an infant may not participate.

WHAT ARE THE COSTS?

Study drugs will be provided by the sponsor at no cost to you. You will not be charged for any study visits, tests, or procedures related to the study. Charges related to the surgery will not be covered by the study.

WILL I BE PAID TO PARTICIPATE IN THE STUDY?

You will not be paid for participating in this study. We will provide meals during the inpatient visits, meals vouchers for the outpatient visits, and parking vouchers.

Please be aware that the investigative team and the University may receive money for the conduct of this study.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THE STUDY?

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness, it is very important to follow all study directions.

CAN I STOP BEING IN THE STUDY?

You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health. Tell the study staff if you are thinking about stopping or decide to stop.

If you leave the study before the final regularly scheduled visit, please notify the study doctor or the study team. We will help you arrange for your continued care with your physician and transition off study medication to standard of care treatment. We would like you to complete the Month 6 Study Visit. Return all unused study medication.
Your participation in this study may be stopped at any time by the study doctor without your consent. The reasons might include:

- You become pregnant
- The study doctor thinks it necessary for your health or safety
- You are found to not be eligible for the study
- The sponsor has stopped the study
- You have not followed study instructions
- Administrative reasons require your withdrawal
- If you are unable to follow the study instructions

If you withdraw from the study, data that has already been collected about you will remain part of the study database and may not be removed.

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed.

In the future, identifiers might be removed from the information and samples you provide in this study, and after that removal, the information/samples could be used for other research studies by this study team or another researcher without asking you for additional consent.

Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study:

- The study Sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System
- Officials of the Department of Health and Human Services or the Federal Food and Drug Administration

It will be noted in your protected electronic health record at VCU Health that you are in this study. Information about the study levothyroxine (LT4) and placebo (a look-alike inactive substance, a “sugar pill”) will be compared to Liothyronine/levothyroxine (LT3/LT4)

combination therapy will be included in the record. This information is protected just as any of your other health records are protected.

In general, we will not give you any individual results from the study. If we find something of medical importance to you, we will inform you, although we expect that this will be a very rare occurrence. You will be informed of the results of the screening tests, phenotype studies, including body composition, energy expenditure, and echocardiogram.

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 Website will include a summary of the results. You can search this Web site at any time.

If you tell us that you may hurt yourself or someone else, the law says that we must let people in authority know.

There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value.

Certificate of Confidentiality

To help us protect your privacy, we will apply for a Certificate of Confidentiality from the National Institutes of Health. If this certificate is obtained, it will offer the protections described here. A Certificate of Confidentiality helps the researchers keep your information private. For example, researchers can refuse to give out your information in a court case. Researchers may have to give your information if the study is audited, or if the information is required by the Food and Drug Administration (FDA).

The researchers may share information about you or your participation in the research project without your consent if you intend to make voluntary disclosure about things such as child abuse, elder abuse or intent to hurt self or others, or other voluntary disclosures

The researchers cannot prevent you or others, for example a member of your family, from sharing information about you or your involvement in this research. If you give an insurer, employer, or other person permission to receive research information, then the researchers may not use the Certificate to withhold that information.

HOW WILL MY HEALTH INFORMATION BE USED AND SHARED DURING THIS STUDY?

As part of this research study, we will ask you to share identifiable health information with us and/or permit us to access existing information from your healthcare records. New health information may also be created from study-related tests, procedures, visits, and/or questionnaires. This type of information is considered "Protected Health Information" that is protected by federal law.

What type of health information will be used or shared with others during this research?
The following types of information may be used for the conduct of this research:

☒ Complete health record	☒ Diagnosis & treatment codes	☒ Discharge summary
☒ History and physical exam	☐ Consultation reports	☒ Progress notes
☒ Laboratory test results	☐ X-ray reports	☐ X-ray films / images
☐ Photographs, videotapes	☐ Complete billing record	☐ Itemized bill
☐ Information about drug or alcohol abuse		☐ Information about Hepatitis B or C tests
☐ Information about mental health		☐ Information about sexually transmitted diseases
☐ Other physical or mental health information (specify):		

Who will use or share protected health information about me?
VCU and VCU Health are required by law to protect your identifiable health information. By consenting to this study, you authorize VCU/VCU Health to use and/or share your health information for this research. The health information listed above may be used by and/or shared with the following people and groups to conduct, monitor, and oversee the research:

- Principal Investigator and Research Staff
- Health Care Providers at VCU Health
- Institutional Review Boards
- Government/Health Agencies
- Others as Required by Law
- Study Sponsor
- Data Coordinators
- Research Collaborators
- Data Safety Monitoring Boards

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

When will this authorization (permission) to use my protected health information expire?
This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

Statement of Privacy Rights

You may change your mind and revoke (take back) the right to use your protected health information at any time. However, even if you revoke this authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization, you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator at

Angeliki Stamatouli, M.D.
Virginia Commonwealth University
Sanger Hall 7th Floor, Room 7-0108
1101 East Marshall Street
Richmond, VA 23298

OPTIONAL STORAGE FOR FUTURE RESEARCH STUDIES

To advance science, it is helpful for researchers to share information. They do this by putting data or samples into one or more scientific databases (called registries or repositories), where it is stored along with information from other studies. Researchers can then study the information in other ways and combine information from many studies to learn even more about health and disease.

As part of this study, we would like to keep the information and/or samples that you provide, along with your name, phone, address and email a registry to be available for other research studies in the future. Your information and samples would be stored at VCU by Angeliki Stamatouli, M.D. for three years after the analysis of the study is complete and could be used for other research studies about hypothyroidism. Your data/samples will be protected, but there is always a possibility that information could be accessed by individuals without authorization.

In the future, if you decide that you do not want to be part of this registry, you can request that your information/samples be removed and destroyed by contacting Angeliki Stamatouli, M.D.. However, information that has already been shared with other researchers will continue to be used.

Angeliki Stamatouli, M.D.
Virginia Commonwealth University
Sanger Hall 7th Floor, Room 7-0108
1101 East Marshall Street

Richmond, VA 23298
Phone: (804) 828-3495
Fax: (804) 828-8389

Permission to Store Data and Samples for Future Research Studies
Please circle your answer: I agree that my data and samples may be stored and used for future research as described above.

YES NO

WHOM SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

The investigator and study staff named below are the best person(s) to contact if you have any questions, complaints, or concerns about your participation in this research: Contact the principle Investigator or the research Coordinator:

Principal Investigator
Angeliki Stamatouli, M.D.
Virginia Commonwealth University
Sanger Hall 7th Floor, Room 7-0108
1101 East Marshall Street
Richmond, VA 23298
Phone: (804) 828-3495
Fax: (804) 828-8389

Research Coordinator:
Joyce R Ruddley BSN, RN, CCRP
Virginia Commonwealth University
Sanger Hall 8th Floor, Room 8-062
1101 East Marshall Street
Richmond, VA 23298
Phone: (804) 828-9684;
Fax: (804) 828-5717

What if you have l questions about your rights as a research participant?
If you have general questions about your rights as a participant in this or any other research, or if you wish to discuss problems, concerns or questions, to obtain information, or to offer input about research, you may contact:

Virginia Commonwealth University Office of Research
800 East Leigh Street, Suite 3000, Box 980568, Richmond, VA 23298
(804) 827-2157; https://research.vcu.edu/human_research/volunteers.htm

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

STATEMENT OF CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form for my records.

Signature Block for Enrolling Adult Participants	
_____ Adult Participant Name (Printed)	
_____ Adult Participant's Signature	_____ Date
_____ Witness Name (Printed) if available	
_____ Signature of Witness	_____ Date
_____ Name of Person Conducting Consent Discussion (Printed)	
_____ Signature of Person Conducting Consent Discussion	_____ Date
_____ Principal Investigator Signature (if different from above)	_____ Date