Keto Brain: Investigating the Use of Ketogenic Diets in Brain Metastases

The Ohio State University

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The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: Keto-Brain: Investigating the Use of Ketogenic Diets in Brain Metastases

Principal Investigator: **Jeff Volek, PhD**

Sponsor: Kroger

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

The brain can be a home for many cancer cells and remains a challenging site to treat. Surgery and radiation therapies are the most common treatments used for patients with limited numbers of brain tumors. Overall survival has also improved significantly for patients with cancer in the brain, so the complications of radiation is becoming more important. Preclinical studies have demonstrated the ability of certain diets and caloric restriction to improve radiotherapy outcomes. One of the main side-effects of radiation therapy is the inflammation response in the area around the cancer. Some basic research indicates that a ketogenic diet may help dampen inflammation and be helpful in treating cancers. No current research exists in a clinical population investigating the effects of a ketogenic diet in the context of radiation therapy

outcomes in individuals with cancers in the brain. The primary objective of this study is to compare a ketogenic diet to the current standard American Institute of Cancer Research diet in patients with cancers in the brain.

In brief, this study will randomly assign you to one of two intervention arms: a low carbohydrate, high fat 'ketogenic' diet or a low fat, low sugar, nutrient dense American Institute of Cancer Research diet. After enrollment you will be asked to complete a series of research tests including standard of care imaging to determine baseline cancer volumes and brain structures, body composition, blood work, cognitive tests, and surveys. Following baseline testing you will start your assigned dietary intervention and undergo your standard of care routine radiation therapy for a period of 16-weeks. Various tests will be performed according to the schedule described later in the document.

1. Why is this study being done?

This study is being conducted to investigate whether a ketogenic diet (a low-carbohydrate, moderate-protein, high-fat diet) or an American Institute of Cancer Research Diet focused on low-fat, nutrient dense foods is better for individuals undergoing radiation therapy with brain metastases. The main outcomes will be feasibility and tolerability of the diets, disease progression (tumor and other related health markers) and quality of life measures.

Specific diets have been used for decades to manage a variety of clinical conditions and have been documented to be safe. A ketogenic diet increases the production of ketones and the use of fat for fuel, which we think will be associated with several positive health effects in individuals with brain mets. Previous research has demonstrated that a ketogenic diet is safe to consume in a patient population with advanced metastatic disease. Furthermore, ketogenic diets are currently being investigated in numerous other disease states including pre-diabetes, type-2 diabetes, various neurological diseases, and cancer models including most notably, brain cancer. The American Institute of Cancer Research (AICR) dietary approach is a highly researched cancer prevention dietary approach. World leading cancer experts have generated what can be considered as a wholesome, complete nutritional program that focuses on nutrient dense foods to improve health. While both diets have the potential for improving outcomes, neither has ever been tested in this specific patient population.

Your doctor has ordered a radiation therapy regimen to treat your cancer. You are invited to take part in this study to help find out the effects of diet as a possible therapeutic treatment for changes in quality of life, cognitive function, inflammation and tumor-related changes, in combination with your standard therapies.

2. How many people will take part in this study?

We plan to enroll a total of 24 patients with advanced stage cancer of various subtypes. The ketogenic diet arm will have 12 patients randomly assigned, and the AICR diet will have 12 patients randomly assigned.

3. What will happen if I take part in this study?

You will need to have the following exams, tests or procedures if you decide to be in the study. They are being done in order to better understand how well you are tolerating chemotherapy as well as the study intervention.

- Medical history
- Physical exam
- Questionnaires asking about your mood
- Questionnaires asking about your memory and thinking
- Food Frequency Questionnaires and Diet Records
- Blood tests for metabolic markers
- Cognitive tests
- Magnetic Resonance Imaging (MRI) for advanced brain and cancer structures
- Body composition assessment to determine body fat percentage and quantity of lean mass via dual energy x-ray absorptiometry (DEXA).

Dietary Changes:

You will be provided individualized counseling by trained dietitians who will educate and support you in following either the AICR or Ketogenic diet. The dietitians will provide educational materials, meal plans, food lists, and ongoing support throughout the 16-week intervention. You will have the opportunity to ask questions via phone or text as often as you need. You will be given up to 7 days worth of meals to help you transition into your diet before testing days. These meals will supply 100% of your calories, so you will not need to eat anything other than the food provide.

AICR Diet

The cohort receiving the AICR dietary guidelines will be asked to shift their dietary intake to a more plant-based approach. Participants will be asked to approximate 2/3 of their plate to plant based vegetables, whole grains, beans or fruits and 1/3 of their plate to protein sources. An example menu will be provided.

Ketogenic Diet

Ketogenic diets are low in carbohydrate, high in fat, and moderate in protein. This is likely a very different approach to eating than you have previously followed. We will ask you to limit foods with a high sugar or starch content such as cereal, pasta, sweets, some vegetables (peas, corn), fruit juices, and regular soda. Foods permitted include non-starchy vegetables, eggs, cheese, cream, butter, sour cream, nuts/seeds, oils (olive, canola, coconut), certain fruits (tomatoes, berries, olives, avocado), meats (beef, chicken, fish, pork) and other naturally low-carbohydrate foods.

Screening

The purpose of the screening meeting is to determine if you meet our initial qualifying criteria, outlined below. During this meeting you will meet with either a research or a clinical

coordinator to discuss any questions that may arise. If you qualify and enroll in the study you will be randomized into either the AICR or ketogenic diet group.

Treatment Plan

All participants will receive standard of care radiation therapy. They will have counseling by the attending physician for additional applicable medications for any therapy related side effects or toxicities.

Cognitive Tests

Cognitive assessment will be done using computer-based tests of attention, concentration, reaction time, memory, processing speed, decision-making, and executive function.

Finger Stick Testing

Throughout the duration of the dietary intervention, you will be asked to finger-stick testing for each day. This will provide us with the information we need to adjust your diet so that you maintain a specific level of ketones in your blood. You will be provided with the meter and we will teach you how to use it.

Activity Monitor*:*

A physical activity tracker will be worn around the wrist daily for heart rate and step counting.

Continuous Glucose/Ketone Monitor.

An adhesive patch with a tiny needle will be placed on the back of your arm. This will provide 4 weeks worth of glucose/ketone readings to make sure you are responding well to your diet.

Participant Testing

As part of the study, you will undergo a history and physical examination including review of your medications and supplements. You will also have a blood test to check markers of metabolic function. You will be asked to keep a record of any side effects or changes in your body or health that occur during the study period. You will be asked to complete questionnaires about how you are feeling at the beginning of the study, monthly during the study, and at the end of the study. These are very general questions about any emotional symptoms you have but you do not have to answer any questions that you do not feel comfortable about. These forms will all take approximately 30 minutes and will be done as part of your clinic visit (such as the time when you are waiting for your doctor to see you.) These forms will let us know how you are feeling in terms of anxiety and depression symptoms at the beginning of the study and throughout the study period. The blood tests and questionnaires are being performed solely for research purposes. The history and physical examination will be part of your regular follow-up care whenever possible but may be performed solely for the purpose of this study. Imaging of your brain will be completed at the beginning of the study and after 8 and 16-weeks according

to standards of care. You will also undergo DEXA scans to determine the density of your bones as well as to assess your body fat percentage at baseline and study end. A battery of cognitive tests will be performed at baseline, 8 and 16-weeks. In the event of progressive disease, the final testing battery will be completed prior to study removal.

Below you will find a general overview of testing to be completed during the study.

	Week				
Tests & observations	**0**	**4**	**8**	**12**	**16**
Signed informed consent	x				
History and Physical Exam	x				x
Height/weight	x	x	x	x	x
Imaging (standard of care)	x		x		x
Continuous Glucose/Ketone Monitoring	x		x		x
Ketone Finger Sticks	x	x	x	x	x
Activity Tracker	x	x	x	x	x
DXA Bone & Body Fat Quantification	x				x
Cognitive Testing	x		x		x
Review of medications	x	x		x	
Performance status	x		x		x
Questionnaires	x		x		x

4. How long will I be in the study?

You will be enrolled in the study for a 16-week duration following the initiation of radiation therapy.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Because we will be obtaining information about a participant's medical history, lifestyle behaviors, and measuring biomarkers that will become part of the electronic health record, there is a chance that we will uncover or discover sensitive information regarding a person's health status. Although unlikely, this information could cause emotional distress, increase personal expense for treatment, or, if obtained by insurance companies or employers, could be used as justification to raise insurance rates or affect employability. To ensure

privacy/confidentiality, information that is received from patients will be kept confidential to the extent allowed by law. Patient data will be entered into the electronic health record and hard copies will be kept in a secure filing cabinet on site for the duration of the study. We will assign all patients a code number to be used on forms, sample collection containers and other research materials. Subject codes will be employed for database management and when statistical analyses are performed. There will be a single key to the coded data kept on a password protected computer. Computer files containing names, addresses or other identifiers will be limited to authorized personnel at the site who have access to the computer data base using a password protected program. All investigators, professional medical staff, and technicians are aware of the confidentiality involved with the proper conduct of such a study. Consistent with the conduct of human research studies, the data will not be available or divulged to anyone outside of the experimental research team. The results from the study may be published, but will have no identifiers.

Ketogenic Diet. There are no significant risks associated with consuming a well-formulated ketogenic diet. For patients using medication to control blood sugar and blood pressure, there is a need to reduce these medications rather quickly at the onset of the diet to prevent low blood sugar and low blood pressure. In this study, we will exclude those patients who have type-2 diabetes using insulin. In our prior research we have assessed thousands of metabolic panels in patients assigned to ketogenic diets. Abnormal responses are rare, but it is expected that there will be modest changes in some blood markers. These markers are expected to remain within normal limits and not pose a serious concern. Nutritional ketosis is associated with natriuresis (increased loss of sodium in the urine) and fluid loss. If the extra sodium excreted is not compensated for in the diet, the subsequent contracted plasma volume can manifest in side effects and adrenal stress including a hormonal response that disrupts body mineral status. Our diets contain adequate sodium and potassium to ensure mineral nutriture. The diet intervention may be challenging for participants since it will require them to limit foods they are accustomed to eating. Participants will be made aware of the general dietary requirements including lists of foods they will need to restrict (as well as foods that will be permitted) during the informational session, so they can make an educated decision to participate.

Body Composition. The DXA scan has a very low risk as the skin entrance dose of radiation due to the application of the exam is very small. In a whole body scan, which is the mode used in this project, the skin entrance dose of radiation per scan is ~0.04 millirem. On average in the US a person receives ~0.85 millirem per day of background radiation. For another comparison, a chest X-ray delivers ~10-20 millirems per scan. Thus the level of radiation exposure is extremely low. Since we don't know what effect the radiation could have on an unborn baby, we will perform a urine pregnancy test before the scan for all women of child bearing age in the study.

Blood Draws. Blood draws by needle may cause discomfort at the puncture site and the development of a slight bruise. Participants may also experience lightheadedness or fainting during the blood draw and there is a slight risk of infection. All blood draws will be taken by

trained phlebotomists. The total blood volume at each testing session will be less than 50 mL, which translates into less than 200 mL over 6 months.

Ketone Testing. Ketone testing will be done by finger stick using a small 26G lancet. There is slight discomfort associated with this procedure.

Continuous Glucose/Ketone Monitor. An adhesive patch with a small needle will be worn. There is slight discomfort associated with this procedure.

Cognitive Testing. Testing administered in this study are designed to evaluate your behavior, thinking, memory and development. Although there is no physical risk, the testing has potential to cause you to feel discomfort, stress, embarrassment, etc. You can skip any question(s) that make you uncomfortable. Research key personnel will help to provide contact information for resources such as the student health center, medical center, or emergency department if necessary, to aid with intense psychological distress induced by cognitive testing.

Activity Tracker. You will be provided with a fit bit to track daily steps and your heart rate. We will work to make sure that no one sees your step count or heart rate without approval. But, because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you.

7. What benefits can I expect from being in the study?

You may not benefit directly from participating in the study. Either of these dietary regiments may help reduce symptoms due to radiotherapy. We hope that the information learned from this study will benefit other patients with advanced stage cancer in the future. There is always the risk of uncommon or previously unknown side effects occurring.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. What are the costs of taking part in this study?

The blood draw, DEXA body composition, and specialized testing is for research purposes only, therefore you and/or your insurance company will not be charged for the research testing. This study will pay for all the additional research tests not covered by your health plan.

The following tests and procedures will be done for research purposes only and will not be charged to you or your health plan:

- Diet consulting
- Blood analysis for Inflammatory biomarkers

- Study questionnaires
- Cognitive tests

All of the other medical tests, evaluations, and procedures are considered standard cancer care and will be billed to you and your insurance plan. You and/or your health plan may also have to pay for other drugs or treatments which are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects. You will be responsible for meeting co-pay and deductible requirements by your insurance plan while on study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

10. Will I be paid for taking part in this study?

Both AICR and Ketogenic Diet groups will receive compensation for their time. $250.00 will be provided in the form of direct deposit or check upon completion of the first half of the study. An additional $250.00 will be provided in the form of direct deposit or check upon completion of the trial. By law, payments to participants are considered taxable income.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information be used or shared for future research?

Yes, it may be used or shared with other researchers without your additional informed consent.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If we find information that significantly impacts your health, we **will** share it with you and your oncologist. This includes any novel information garnered from the MRI and metabolic tests.

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record;
- Others: *[include specific names of the sponsor, collaborators, study monitor (CRO, SMO), healthcare providers, persons or organizations that analyze health information for the study, data safety monitoring boards, etc..]*.

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact ***Madison Kackley, 740-817-1622.***

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact HIPAA Privacy Officer, Suite E2140, 600 Ackerman Road, Columbus, OH 43201

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For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact ***Jeff Volek, PhD, at 614-688-1701.***

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
Relationship to the participant	**AM/PM** **Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time