

The Cleveland Clinic Foundation Consent to Participate in a Research Study

Study Title: “Vitamin D supplementation as a neoadjuvant for photodynamic therapy of actinic keratoses”
Sponsor: Investigator-initiated (Dr. Maytin)
ClinicalTrials.gov NCT# NCT04140292
Principal Investigator: Dr. Edward Maytin, PH#216-445-6676
Study Coordinators: Beverly Doyle 216-636-1196
After hours phone contact: Dermatology Surgical Fellow on call, PH#216-444-2200

KEY INFORMATION

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

What should I know about a research study?

- Someone will explain this research study to you.
- You can choose whether or not to take part.
- You can agree to take part and then later change your mind.
- Your decision whether or not to participate will not be held against you.
- You can ask all the questions you want before you decide.

What is the purpose, procedures and duration of this study?

We invite you to take part in a research study because you have been diagnosed with actinic keratoses (skin lesions that have the potential to turn into skin cancer), and you are receiving photodynamic therapy (PDT) as part of your clinical care. The purpose of this study is to test and demonstrate that vitamin D pretreatment can enhance PDT efficacy in the treatment of actinic keratoses.

You will be asked to take vitamin D supplements prior to your standard of care photodynamic therapy treatment.

Your participation in the research will last about 3-4 months.

More detailed information can be found under the section labeled: “Information on the Research.”

Why might you choose not to participate in this research study?

You may not want to participate in this study if you:

- Do not want to take Vitamin D
- Are unable to have your blood drawn.

More detailed information about the risks of this study can be found in the section labeled

“Risks.”

Why might you choose to volunteer for this study?

Taking part in this study may help patients with actinic keratoses receive better care in the future. In addition, by participating in this study, you will learn the result of your Vitamin D blood test (whether your Vitamin D level is normal, low, or deficient) and receive advice from the study physicians about how to achieve or maintain a normal Vitamin D status

More detailed information about the benefits of this study can be found in the section labeled “Benefits.”

What are my other choices if I do not take part in this study?

Your participation in this study is voluntary. You do not have to be in this study to get treatment for your skin cancer. If you choose not to participate, your actinic keratosis will still be treated using PDT or other standard treatment modalities, such as cryosurgery or 5FU cream.

More detailed information about the alternatives to this study can be found in the section labeled “Alternatives.”

DETAILED INFORMATION

The following is more detailed information about this study in addition to the information listed above.

1. INFORMATION ON THE RESEARCH

Why is the research study being done?

This study is designed to establish what the optimal conditions are for treating actinic keratoses - with PDT. Previous research suggests that taking Vitamin D, also called Vitamin D3, prior to the start of PDT could help improve the effectiveness of the treatment in eliminating the actinic keratoses. Overall, your participation in this study will help us learn whether oral Vitamin D3/PDT is effective as combination therapy for actinic keratoses.

Photodynamic Therapy (PDT) is a technique that works by combining a photosensitizing topical agent and an intense light source to kill tumor cells. PDT is currently approved for the treatment of actinic keratoses by the Food and Drug Administration (FDA).

Overall, your participation in this study will help us to improve our blue light therapy regimens for patients in the future.

How Many People Will Take Part in this Study?

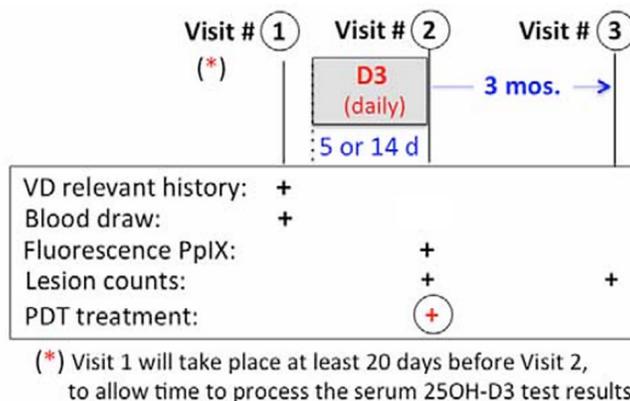
Approximately 30 people will take part in this study at Cleveland Clinic.

What is involved if you decide to take part in this research study?

Before your PDT treatment, you will donate a blood sample (up to 5 tablespoons of blood, placed in two separate tubes). One tube will be used to measure your Vitamin D (25-hydroxy-D3) level. The other will be used to obtain DNA from white blood cells, to test for several biomarkers that allow the investigators to study several proteins that are important for the body to use and break down Vitamin D. You will receive a course of daily supplementation with 10,000 IU of vitamin D3 for up to 14 days, depending on your baseline vitamin D level, leading up to your PDT treatment. If you have a normal vitamin D level, you will be instructed to take your vitamin D3 supplementation once per day for 5 days. If you are deficient in vitamin D, you will be instructed to take your vitamin D3 supplementation for 14 days.

You will also be expected to return for a routine follow-up visit in 3-6 months after PDT treatment, which is important to assess whether any precancerous lesions remain. You will need to return for this follow-up visit regardless of your decision to participate in this study, because a 3-6 month follow-up is considered routine standard of care.

The results of your Vitamin D test will be reported to you, and available in your medical record. If your vitamin D levels are found to be low or deficient, your study physician will offer you advice on how to correct this through over the counter Vitamin D supplementation.



Photodynamic Therapy (PDT)

PDT is a noninvasive cancer treatment in which a topical agent (referred to as Levulan or ALA) is applied to the AKs and then exposed to a particular type of light. The topical agent, Levulan, is a liquid preparation with a fixed concentration of 20% aminolevulinic acid (ALA) that is delivered topically as a uniform film that dries upon application to the skin. The application of Levulan is not associated with any risks or side effects. The light source used, known as Blue Light (Blue-U, 400 nm), will target and kill the precancerous cells.

Pharmacokinetic (PK) studies

PK studies measure the amount of Vitamin D you have in your blood. About 10 ml (2 teaspoons) of blood will be drawn for research purposes, including several biomarkers (genes and proteins related to your cancer).

Vitamin D

Cholecalciferol (Vitamin D3) is not a drug. However, there is some evidence of a link between patients who take Cholecalciferol and developing hypercalcemia. Hypercalcemia is a condition in which you have too high a concentration of calcium in your blood. Symptoms of hypercalcemia range from mild to severe. They may include increased thirst and urination, belly pain, nausea, bone pain, muscle weakness, confusion, fatigue, and in rare cases even death. Therefore, if you are at risk for hypercalcemia (renal disease, sarcoidosis, etc.), you will not be permitted to participate in the study.

Photographs

Photographs of all treated areas will be taken during the study. These will be used to determine the clearance of actinic keratoses with treatment. The photographs will be maintained in a secure area with limited access. Safeguards are in place to protect from any inappropriate access to data including: use of codes, encrypted and/or password protected computers and phones, and limiting access to data to only the research team.

Noninvasive Fluorescence (NIF)

NIF refers to the measurement of an organic compound known as protoporphyrin IX (PpIX). Sites of actinic keratoses will be measured during the PDT treatment. NIF is helpful in evaluating the success of the PDT treatment.

Genetic Testing

This research includes genetic testing that studies the characteristics and genes that are found in the body's cells. Genes are made of DNA. DNA (deoxyribonucleic acid) contains the instructions for your body's development and function. This information determines traits that are passed on from parent to child, such as eye and hair color and the risk/chance you will get certain diseases. Genes also tells your cells to make substances (including proteins) that appear in your blood. RNA (ribonucleic acid) is made from DNA. RNA is a genetic material that has a major role in making proteins. Researchers are examining DNA, proteins (biomarkers) and RNA to look for genetic changes that cause cells to not work properly and cause disease. Some of the genetic changes that can cause disease are known. Researchers are working on finding other genetic changes causing disease.

Note that we will be collecting your DNA to specifically test for normal variants in genes related to Vitamin D and thymidine metabolism, neither of which are associated with any known inheritable diseases. However, it is still important for you to know that additional safeguards against improper use of your genetic information are in place, as described below under "Risks of Genetic Research."

How will my data be used?

Your data may be sent outside of the Cleveland Clinic for further analysis. Any personal information that could identify you will be removed before data is shared.

Will I be notified of the results of the tests/studies on my samples?

When samples are collected and analyzed, there is the chance of finding something that may be important for your care. You will be informed of any results that are relevant to your clinical care.

We will take photos and/or videos of you during the entire length of each study visit. We will use the photos and/or videos to collect data about your actinic keratoses. We will store the photos and video on Cleveland Clinic hospital network drives that are password protected and behind the institutional firewalls. If you do not agree to have photos and/or videos taken then you cannot participate in the research study.

2. ALTERNATIVES

What are the alternatives to participation in the research study?

Your participation in this study is voluntary. You do not have to be in this study to get treatment for your Actinic Keratosis. If you choose not to participate, your actinic keratosis will still be treated using PDT or other standard treatment modalities, such as cryosurgery or 5FU cream.

3. RISKS

What are the risks of participating in the research study?

- The risks of phlebotomy (having your blood drawn) are minimal, and include temporary bleeding, and bruising at the needle site.
- Having your blood drawn should not affect the outcome of the PDT treatment in any way.
- Vitamin D supplementation can rarely cause hypercalcemia, or elevated levels of calcium in the blood

Risks of Genetic Research

Note that we will be collecting your DNA to specifically test for normal variants in genes related to Vitamin D and thymidine metabolism, neither of which are associated with any known inheritable diseases. However, it is still important for you to know that additional safeguards against improper use of your genetic information are in place, as follows:

The Genetic Information Nondiscrimination Act (GINA) is a federal law designated to protect you from health insurance and employment discrimination based on genetic information. It is illegal for health insurance providers and most employers to ask for genetic information to make decisions about a person's eligibility or coverage or to make employment decisions.

The law will not stop health insurance companies from using genetic information to decide whether to pay claims and also does not apply to life insurance, disability insurance or long-term care insurance.

Reproductive Risks

If you are pregnant or nursing at the time of study participation, you cannot be in this study. You should not get pregnant, breastfeed, or father a baby while in this study. If you are unwilling to do this, we ask that you not participate in this study. If you or your spouse become pregnant

while taking part in this study you must notify the study doctor immediately. Any potential reproductive risks are associated with the standard of care PDT treatment and should be discussed with your physician.

Confidentiality Risks

There is a potential risk of loss of confidentiality of your data. Every effort will be made to keep your information (data) confidential through the use of the following safeguards: You will be assigned a study code and all clinical data required by the protocol will be identified using that code. All data is stored using a unique subject assigned number and no personal identifying data will be entered. Members of the Cleveland Clinic and Case Comprehensive Cancer Center will have access to your data.

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. While the chance that someone could access and misuse your information is believed to currently be very small, it is possible that the risk may increase in the future as people find new ways to access information.

Blood Draw

The insertion of the needle to draw blood can be painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Questionnaire/Survey Research

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.

4. BENEFITS

What are possible benefits of participating in the research?

By participating in this study, you will learn the result of your Vitamin D blood test (whether your Vitamin D level is normal, low, or deficient) and receive advice from the study physicians about how to achieve or maintain a normal Vitamin D status. Further, your participation in the study may help to develop more knowledge to improve PDT treatment so as to prevent pre-cancers and SCC cancers in future patients.

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your actinic keratoses, which may give you relief from some symptoms, improve your quality of life or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study will help us to obtain information about treating subjects with a new combination therapy of oral Vitamin D3/PDT as a treatment for actinic keratoses.

5. COSTS

Are there any costs to you if you participate in this study?

Your participation in this study does not alter the cost to you. You and/or your insurance company will be responsible for the PDT treatment, which you would receive regardless of whether or not you participated in this study, and are considered standard-of-care:

The following research activities are being done only because you are participating in this research study and therefore **will be paid for by the study sponsor and not billed to you or your health insurance plan**. These “research only” activities include:

- Vitamin D3 supplementation
- Vitamin D blood tests (25-hydroxy-vitamin D3 serum level).

The following research activities will **not be paid by the study sponsor and will be the responsibility of you or your health insurance plan**:

- PDT treatment

The Cleveland Clinic Foundation will not pay for the costs of additional visits or hospitalizations in connection with this research. Any such costs will be the responsibility of you, your insurance company, or a third party.

The Cleveland Clinic is available to assist you in determining whether or not your insurance will cover the procedures associated with this study, whether or not the procedures are being performed solely for research purposes. You and your insurance company will be billed the usual and customary charges for all items and services except those required specifically and solely for this study. The Cleveland Clinic will assist you (our Financial Counselor at 216/445-8662) as reasonably as possible in seeking reimbursement for the cost of these items and services. You will be held personally responsible for any charges, deductibles, or co-payments not covered by your insurance company.

6. PAYMENT

Are there any payments to you if you participate in this study?

Your involvement in this research study is voluntary and you will not be paid for your participation. However, you will receive a free parking voucher on the day of each of your study visits. In addition, you will receive a \$25 stipend at the completion of your final follow-up visit that takes place 3-6 months after PDT.

The IRS requires CCF to report payments to an individual of \$600 or greater (in a calendar year) on a Form 1099-MISC. Your name, address and social security number will be collected to track the payments made to you and, if you receive \$600 or greater, will be used to process a Form 1099-MISC.

7. RESEARCH RELATED INJURY

What will happen if you are injured as a result of taking part in the research?

In the event you suffer a research related injury as a result of being in this study, Cleveland Clinic will provide appropriate medical treatment for such injury in a timely manner. Provision of such medical treatment does not imply any negligence or other wrongdoing on the part of Cleveland Clinic or any of the physicians or other personnel involved in the study. If you believe that you have been injured as a result of participating in the study, please immediately contact your Cleveland Clinic study doctor even if you may have already been seen or treated by another doctor. If you are seen or treated by a doctor other than the study doctor, you should inform such doctor that you are in this study and, if possible, take this document with you as it may help such doctor treat you.

In the event you suffer a research related injury as a result of being in this study, the costs for medical treatment may be billed to you or your medical insurance plan, if applicable. Medical insurance plans may or may not cover costs for medical treatment of research-related injuries. If you have insurance, you should check with your medical insurance plan before deciding to participate in this research study. In the event your medical insurance plan covers some or all of the treatment costs, you may still be responsible for co-pays or deductibles as required by your medical insurance plan.

Cleveland Clinic has not set aside any money to pay you or to pay for your treatment if you suffer a research related injury as a result of being in the study. There are no plans for Cleveland Clinic to provide other forms of compensation (such as lost wages, pain and suffering, or other direct or indirect losses) to you for research related injuries. You are not waiving any legal rights by signing this form, including the right to seek compensation for an injury. Further information about research related injury is available by contacting the Institutional Review Board at (216) 444-2924.

If you have any questions, concerns or complaints about the research, or develop a research-related problem, contact Dr. Edward Maytin, Department of Dermatology at 216-444-5139.

Cleveland Clinic Foundation Clinical Research Unit (CRU) study participants may also contact the CRU Research Subject Advocate (RSA), at 216-445-7846 with regard to questions about study participation and research subject protections.

8. PRIVACY AND CONFIDENTIALITY

What will happen to your information that is collected for this research?

Cleveland Clinic may share your study information, without anyone knowing that it is related to you specifically, with others or use it to research projects not listed in this form. Your data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your data, we will no longer be able to identify and destroy them.

Study results may be shared in medical journals, at scientific meetings, and in other mediums without your identifying information. Your records will be confidential and your identity will not be shared in medical journals, at scientific meetings, and in other mediums without your express consent.

Authorization to Use/Disclose Protected Health Information

Cleveland Clinic has rules and procedures to protect information about you. Federal and State laws also protect your privacy.

The research team working on the study will collect information about you. This includes your health information, data collected for this research study and personal identifying information including your name, address, date of birth and other identifying information.

Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at Cleveland Clinic may see or give out your information. These include people who review research studies including the Institutional Review Board and Research Compliance, their staff, lawyers, or other Cleveland Clinic staff.

People outside Cleveland Clinic may see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and the sponsor of the research and their agents. Cleveland Clinic will do our best to ensure your information is kept confidential and that only the health information which is minimally required to conduct the study is used or disclosed to people outside Cleveland Clinic; however, people outside Cleveland Clinic who receive your information may not be covered by this promise.

You do not have to give this permission to use and give out your information; however, you will not be able to participate in this research study without providing this permission by signing this consent form. The use and disclosure of your information has no expiration date.

You may cancel your permission to use and disclose your information at any time by notifying the Principal Investigator in writing, Edward Maytin, M.D., Ph.D. at The Cleveland Clinic, 9500 Euclid Avenue, Desk A61, Cleveland, Ohio 44195. If you do cancel your permission to use and disclose your information, your participation in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

9. QUESTIONS

Who do you call if you have any questions or problems?

If you have any questions or concerns about the research, or develop a research-related problem, you should contact Edward Maytin, M.D., Ph.D. at (216) 444-5139. During non-business hours, weekends and holidays, please contact Dermatology Surgical Fellow on-call at (216) 444-2200. If you have questions about your rights as a research subject, you should contact the Institutional Review Board at (216) 444-2924.

10. VOLUNTARY PARTICIPATION

What are your rights as a research participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to withdraw from the study you should discuss with your study doctor your decision to ensure a safe withdrawal.

If you leave the study early, Cleveland Clinic may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities. Scientific or medical information from this study, including photographs of lesions, may be presented at meetings or published so that the information can be useful to others. However, your identity would not be revealed. If you do not wish this to happen, you should not agree to take part in this study. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at Cleveland Clinic Foundation or elsewhere; however, the Cleveland Clinic Foundation will not provide free care or compensation for lost wages.

The investigator may stop your participation in the study at any time for any of the following reasons:

- If it is determined that your continued participation would be harmful for your health as shown by a change in your laboratory values or medical condition, or
- If you do not follow the schedule of visits and treatments for any reason, or
- If the study objectives are changed or the study is cancelled.

Can I withdraw my samples?

If you agree to allow your data to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact the Principal Investigator in writing and let to withdraw your permission for your identifiable data to be used for future research. The mailing address is 9500 Euclid Avenue, Desk A61, Cleveland, Ohio 44195. At that time, we will ask you to indicate in writing if you want the unused identifiable data destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

11. SIGNATURES

Statement of Participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my

legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

Printed name of Participant

Participant Signature

Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

Printed name of person obtaining consent

Signature of person obtaining consent

Date

CALENDAR. Timeline of procedures for patients enrolled in the study.

Yellow: Clinic visits. **Gray:** events taking place at home. **Green:** steps that are critical to decision-making.

	VISIT 1 No PDT	Start VD	VISIT 2 PDT 1	Phone Call	VISIT 3 No PDT
Scheduled visit: → Procedure: ↓		5 d or 14 d before PDT	Day 0		Month 3 *
Review previous clinical records	X				
Blood draw	X				
Dispense Vitamin D3	X				
Call, and tell the patient to start taking pills		X			
Pill Count (verify patient took pills)			X		X
Skin exam and lesion counts	X		X		X
Photograph lesions			X		
Topical ALA application			X		
Measure PpIX fluorescence on selected lesions at 30 minutes			X		
Blue light exposure (20 J/cm ²)			X		
Phone call to patient, to record side effects at 24-48 hr post PDT				X	

*Time window for scheduling Visit 3 will be 3-6 months after Visit 2, to match the protocol of the control group (IRB 16-1615).