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^{68}Ga-DOTATATE PET for Localization of Phosphaturic Mesenchymal Tumors in Patients with Tumor Induced Osteomalacia

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IRB Greater Than Minimal Risk Protocol

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Study Title: ^{68}Ga-DOTATATE PET for Localization of Phosphaturic Mesenchymal Tumors in Patients with Tumor Induced Osteomalacia

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Research Question and Aims

Hypothesis: ^{68}Ga-DOTATATE PET/CT will help localize phosphaturic mesenchymal tumors and thus aid in the diagnosis and treatment of tumor-induced osteomalacia (TIO).

Aims, purpose, or objectives: This study aims to identify cases of FGF23-mediated oncogenic osteoomalacia in which the underlying phosphaturic mesenchymal has not been found and perform ^{68}Ga-DOTATATE PET in these patients to localize the tumor.

Background:
Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome which presents as a clinical spectrum that can include hypophosphatemia, fractures, bone and muscular weakness. The osteomalacia is mediated by excess production of a hormone called FGF23 that causes renal phosphate wasting. In this syndrome FGF23 is usually secreted by phosphaturic mesenchymal tumors (PMTs). These tumors can occur anywhere from the head to toe, can arise in bone and soft tissue, and are usually small and slow growing. As such, they are often difficult to localize. However, localization is critical, as surgical resection is curative in these patients. Various imaging modalities including FDG-PET/CT, CT, and MRI; selective venous sampling of FGF23 has also been used with variable success to localize these tumors. PMTs have been shown to variably express 5 somatostatin receptors (SSTR 1-5), and this has also allowed utilization of SSTR based functional imaging by octreotide scintigraphy (*Gonciulea and Jan De Beur, Endocrinol Metab Clin North Am 2017*) and more recently, ^{68}Ga-DOTATATE PET/CT. ^{68}Ga-DOTATATE PET/CT is a novel imaging modality which is currently not very widely available, but early reports indicate that this may be superior to all other available imaging modalities at PMT localization. A recent multicenter case series reported 6 patients in which this imaging modality was used for PMT localization (*Clifton-Bligh et al., J Clin Endocrinol Metab 2013*).

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Study Design and Methods

Methods:
This will be a prospective cohort study.

We have searched the Mayo Clinic – Rochester medical records between January 1st, 2000 and January 30th, 2018 for subjects that have "FGF 23 osteomalacia", "oncogenic osteomalacia", "tumor induced osteomalacia", or "hypophosphatemic osteomalacia" (under RPR-6054-18). From this list, we have excluded patients who were diagnosed to have hypophosphatemic rickets or those in whom the underlying tumor has already been identified. After January 30th, 2018, patients evaluated for TIO at Mayo Clinic without a localized tumor will be reviewed quarterly through the same search strategy and inclusion/exclusion criteria noted in this document.

Subjects in whom a tumor was not localized will be recruited prospectively to undergo imaging by ^{68}Ga-DOTATATE PET/CT. These subjects will be contacted (phone script attached) to inform them of the study and the imaging modality. The first 22 patients that agree to participate in the study will be asked to present to the Clinic where they can provide a written consent and perform the imaging study.

Enrolled subjects will be evaluated in the clinical practice prior to having ^{68}Ga-DOTATATE PET/CT imaging performed. The treating endocrinologist will be informed of the imaging results and will review the results with the subject using a follow-up visit or phone call; when a tumor is localized, he/she will discuss appropriate management options. These visits/conversations will be standard of care and not part of the research protocol.

Medical records will be accessed for up to one year following the date of the PET/CT scan to obtain subject-specific clinical, laboratory and radiographic data. If the subject is to undergo an intervention related to the localized tumor, the pathology report will also be accessed during this time-frame to collect pathology data.

Information retrieved from patient's medical records will be kept confidential. Unless required by law, only the investigators as well as the institutional review board (IRB) will have direct access to subject information. Collected personal information, research data, and related records will be coded, and this code will be used on all documents to prevent subject identification. Each patient will be assigned a unique code. One document only will relate patient identifiers to the unique codes. The PI will ensure that this document is password-protected, and that both the document and the password are kept in a secure, private hard-drive. This document will be destroyed at the end of the research study. Subjects will not be identified in any publications or presentations that result from this study. Data will be entered into a separate database which will not contain any patient identifiers.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

This study will be performed by the above listed investigators. All aspects of the study including data collection, analysis and preparing the abstract and manuscript will be done at Mayo Clinic Rochester. The PI will supervise all aspects of the study and will have final say in terms of manuscript preparation and submission. We plan to conduct this study over a period of 2 years starting from the time of IRB approval.

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Subject Information

Target accrual is 22 subjects. To achieve this number of subjects, we will have to access medical records for 400 patients.

Subject population: Adults (more than 18 years of age) seen at Mayo Clinic, Rochester for tumor-induced osteomalacia (FGF23 mediated osteomalacia caused by tumor).

Inclusion Criteria: Adults (18 years of age or older) seen at Mayo Clinic, Rochester for FGF23 mediated osteomalacia who provide informed consent to participate in the study.

Exclusion Criteria:

1. Pregnant
2. Prisoners
3. Subjects diagnosed with heritable hypophosphatemic rickets/osteomalacia
4. Subjects who do not consent for the study or withdraw consent during the duration of the study.
5. Subjects in whom tumor localization and successful resection has already occurred.

At the discretion of the investigator, it may be appropriate for a subject to undergo an additional DOTATATE PET/CT examination if the phosphaturic mesenchymal tumor is not localized or if there are recurrent biochemical abnormalities. The maximum number of PET/CTs a patient can undergo as part of this study is two. The patient must still meet the criteria for enrollment in the study. The subject will receive a new subject ID and the subject will be reconsented.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
No blood samples will be obtained.

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
No blood samples will be obtained.

(3) Prospective collection of biological specimens other than blood: NONE

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Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: All records through 10/12/2022

Check all that apply (data includes medical records, images, specimens).

☐ (5a) No data will be collected beyond the IRB submission date.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be collected after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

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HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data		
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Data Analysis Plan:
Sample size has not been calculated as analysis will only include descriptive statistics. Results for continuous variables will be expressed as median and interquartile range, and for categorical variables as proportions.