CLINICAL RESEARCH PROTOCOL
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

DATE: December 17, 2020 **PROTOCOL NUMBER: 91-DK-0085**
[IND] [IDE] NO: Appx. C substudy: 119098 and 35513

TITLE: STUDIES OF HYPERPARATHYROIDISM AND RELATED CONDITIONS

SHORT TITLE: HYPERPARATHYROIDISM

IDENTIFYING WORDS: PTH, MEN1, CASR, FHH, CDC73, HRPT2, IMAGING, CANCER, CALCIUM, BONE, NEPHROLITHIASIS, OSTEOPOROSIS

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ESTIMATED DURATION OF STUDY: 40 Years

START DATE: 1991 END DATE: 2031

NUMBER AND TYPE OF PATIENTS:

	Number	Sex	Age Range
Patients	**Indef**	**M & F**	**all**
Volunteers	**none**		

PROJECT USES IONIZING RADIATION:
__x__Medically indicated
__x__Research radiation under imaging substudy (Appendix C) with separate consent form:
The Radiation Safety Committee has reviewed and approved radiation use in this study
(RAD Authorization # RA2682)

PROJECT USES "DURABLE POWER OF ATTORNEY": __NO
OFF-SITE PROJECT: ___NO
MULTI-INSTITUTIONAL PROJECT:___NO
PROJECT (Appendix C substudy only) DOES INVOLVE AN IND/IDE:

IND/IDE Number: ^{68}Ga-DOTATATE will be administered under IND # 119098.
For Ga68 DOTATE the IND sponsor is: NIH Clinical Center; the Sponsor's Authorized Representative is: Gini Guptill, PhD.

IND/IDE Number: [^{18}F]-DOPA is administered under # 35513.
For [^{18}F]-DOPA the IND sponsor is: NIH Clinical Center; the Sponsor's Authorized Representative is: Gini Guptill, PhD.

Précis: Patients with confirmed or suspected primary hyperparathyroidism or complications therefrom (such as postoperative hypoparathyroidism) will be admitted for diagnosis and treatment. The principal diagnostic components are calcium in serum and urine, parathyroid hormone in serum, and mutation tests on germline or tumor DNA. Patients with moderate to severe primary hyperparathyroidism will be treated. Treatment will be mainly by parathyroidectomy. Preoperative testing to localize parathyroid neoplasm(s) will be used usually and with more extended methods in cases with prior neck surgery. Other options are medications or no intervention. Patients with a hyperparathyroid syndrome may be managed for their extraparathyroid features (medical management or surgical treatment). Preoperative tumor localization tests will be selected according to clinical indications from the following: ultrasound, technetium-thallium scan, computerized tomography, magnetic resonance imaging, somatostatin receptor imaging, fine needle aspiration for parathyroid hormone assay, selective arteriogram, and selective venous catheterization for parathyroid hormone assay. Options for management of postoperative hypocalcemia include calcium, vitamin D analogs, parathyroid autografts and synthetic parathyroid hormone. Research specimens may consist of blood or tumors. In addition, a substudy for patients with multiple endocrine neoplasia type 1 (MEN1) will assess the utility of two PET/CT scans with radiotracers (^{68}Gallium-DOTATATE and ^{18}F-DOPA) as indicated in Appendix C.

Introduction: Primary hyperparathyroidism is a common disorder (1, 2, 3). Its complications include generalized weakness and fatigue, kidney stones, bone thinning and bone fracture. As a sporadic disease, it is commonest in postmenopausal women. It can also occur on a hereditary basis (4), the five commonest of these being familial isolated hyperparathyroidism (FIHP), multiple endocrine neoplasia type 1 (MENl) (5), familial hypocalciuric hypercalcemia (FHH), hyperparathyroidism-jaw tumor syndrome (HPT-JT) and multiple endocrine neoplasia type 2A (MEN2A). Primary hyperparathyroidism can often be cured by removal of one or more parathyroid tumors (these are almost always benign) (1). But many patients with mild disease might be followed for long periods of time without any intervention (2, 3).

Objectives: The purpose of this study is to understand the causes of primary hyperparathyroidism, to evaluate and improve methods for diagnosis and treatment, and to provide insight into the mechanisms of normal parathyroid function. Hereditary causes of primary hyperparathyroidism will be characterized. Methods of pre-operative parathyroid gland localization will be evaluated (6, 7, 8). Genes that contribute to development of parathyroid tumors will be analyzed (4, 9, 10).

Subjects: Patients (male or female any age) with known or suspected primary hyperparathyroidism or a related disorder (such as MENl) will be evaluated. There are no absolute exclusions. The vast majority of patients will be greater than age 18. In the rare occasion where special resources might be appropriate (uremic patient, young child), the availability of special resources would be confirmed prior to admission.

Study Design:
Initial outpatient workup not necessarily at NIH will include tests deemed necessary to diagnose primary hyperparathyroidism and to make preliminary assessment of its severity. The essential elements of this workup include measurement of calcium, phosphorus, and creatinine in serum and also measurement of parathyroid hormone by immunoassay in serum. Other features may include evaluation of family history, urinary calcium, bone density and evaluations relating to kidney stones. This workup will often have been partly done by the referring physician prior to admission to NIH.

Currently enrolled patients or patients in long-term follow up will receive a “Patient History Intake Form” via a secure electronic web application such as a REDCap, to be completed prior to inpatient admission or visit. This form will mainly be used to capture new medications that may interfere with testing, changes in family history, or new symptoms. This will allow the principal investigator and study team to better structure the visits and schedule the proper tests.

Evaluation at NIH has six goals; (a) evaluate the diagnosis and severity of presumed primary hyperparathyroidism, (b) evaluate the indications for parathyroid surgery, (c) conduct the appropriate preoperative parathyroid gland localization tests, (d) treat primary hyperparathyroidism, (e) treat extra-parathyroid associated conditions, and (f) collect data and specimens for research.

Informed Consent:
The following sections describing informed consent processes apply to any consent form on this study, including the standard study consent and the consent for the research imaging substudy described in Appendix C. The subset of patients who participate in the research imaging substudy will be consented to both the standard and research imaging substudy consent forms.

One of the investigators on this protocol marked on page 1 with an asterisk will obtain informed consent from patients participating in this study. The consent discussion will review the scope of the study as well as the risks, benefits, and limitations of participating, and the patient will have the opportunity to ask questions about the protocol and/or consent. The investigator will also review with the participant the option to indicate on the standard consent form those family members with whom the research team may share genetic test results in the event that the subject becomes deceased or incapacitated, and the investigator will facilitate decision-making with regard to receiving or opting out of incidental findings in order to be sure that the participant fully understands the decision, the potential consequences, and the ability to alter this decision in the future by re-consenting. Informed consent will be obtained before any study-related procedures are performed, and this typically occurs upon admission of the patient to the clinical center.

The consent form will be completed and signed by the patient and the investigator obtaining the informed consent. A copy of the completed consent will be given to the patient to keep for his or her records. The original signed consent will be transmitted to the Medical Records Department for placement in the subject's permanent Clinical Center medical record. The informed consent process, including its time and date, will be documented in a progress note, and a copy of the note and the signed informed consent will be filed in the subject's electronic medical record.

Consent by Telephone:
A participant's initial informed consent will rarely, if ever, be obtained by telephone because participants in this study typically come to the NIH as patients and the consent process occurs in-person in the clinical center. The telephone consent process would be used primarily for re-consenting participants to the study.

The subject will receive a copy of the protocol consent in the mail prior to being consented. After he or she has had an opportunity to review the consent, the investigator will contact the subject by telephone. The investigator will review the investigational nature of the protocol with the subject and answer questions for the subject. If the subject chooses to participate, the subject will sign and date the consent form. The informed consent documents will be mailed to the principal or associate investigator who led the discussion, who will sign and date and mail back a copy for the subject's records. The original signed consent will be transmitted to the Medical Records Department for placement in the subject's permanent Clinical Center medical record. The informed consent process, including its time and date, will be documented in a progress note, and a copy of the note and the signed informed consent will be filed in the subject's electronic medical record.

Consent for Spanish Speakers:
A Spanish version of the standard consent, assent, and research imaging substudy consent forms have been acquired from the NIH Library translation service. These will be used for obtaining informed consent from Spanish-speaking subjects, whether in-person or by phone, if they prefer using Spanish instead of English for that process. An interpreter or interpretation telephone service will be used to facilitate the consent discussion when needed. If there are significant changes to the consent form of this study in the future, then this might require an updated translation of these Spanish forms, which could result in a delay between the approval of that amendment to the standard English consent and the

approval of the updated Spanish version of the consent and/or assent; in that situation, the short form consent process described below would be used in the interim.

Consent for Non-English Speakers:
We do not plan or anticipate the enrollment of non-English speaking subjects. However, they are not excluded from participation either. If there is unexpected enrollment of a research participant for which there is no translated extant IRB-approved consent document, the Principal Investigator and/or those authorized to obtain informed consent will use the short form consent process as described in MAS Policy M77-2, NIH SOP 12, and 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (a). The summary that will be used is the English version of the extant IRB-approved consent document. We request prospective IRB approval of the use of the short form consent process for up to a maximum of 5 requests (either for individual participants or families of participants) in a given language, and will notify the IRB at the time of continuing review of the frequency of the use of the short form. Should we reach the threshold of 5 subjects and/or families speaking a single language, we will request an additional use of the short form from the IRB and will notify the Board that we plan to have any consent documents frequently used with that population translated into the language(s) they speak.

Participation of NIH employees:
NIH employees may participate in this study, although they will not be specifically targeted or solicited for participation. Neither participation nor refusal to participate as a subject in the research will have any effect, either beneficial or adverse, on the participant's employment or position at NIH. Given the nature of this study, there is no foreseeable risk that research outcomes will be influenced by the inclusion of employees; however, in order to protect employee subjects' privacy and confidentiality of medical information, additional precautions will be taken for these subjects.

Employees who are considering enrolling in the study will be provided with the NIH Information Sheet on Employee Research Participation (NIH HRPP SOP 14F Appendix B) to help them understand the possible consequences. The consent session with an NIH employee will begin with a discussion of any potential issues that either party could see arising, the subject's concerns or feelings related to any such issues, the subject's right to refuse participation or raise a concern at any time without impact on employment, the safeguards in place to protect the patient's privacy and confidentiality, and the limitations of those protections. Study staff will be trained that communication of any personal or medical information about a subject (especially an NIH employee), including the fact that they are participating in this study, should be restricted to those investigators who need to know this information, and such information will not be discussed with anyone outside of the study without permission from the subject. If the employee is within the same branch, section, or unit such that the individual obtaining consent is a supervisor or co-worker, then independent monitoring of the consent process will be included, as outlined in SOP 14F.

Obtaining Consent for Minors:
The signature of a single parent or guardian will be required when obtaining consent for minors, consistent with category of research approvable under 45 CFR 46.405 since this research presents the prospect of direct benefit to the participant, such as the early detection of a neoplasm in the subject or identification of a predisposition to develop such neoplasms. The investigator and the parent/guardian will decide if the minor is capable of providing assent. If the minor is determined to be capable of doing so, then his or her refusal to participate will be respected. An Ethics Consult will be arranged to determine the appropriate course of action if it occurs that such a minor refuses to participate but the parent/guardian and the investigator agree that participation in the study is in the minor's best interest because the research presents a prospect of direct benefit that is important to the health or well-being of

the child and is available only in the context of the research. If the minor is determined to be capable of understanding the standard consent form, then the standard consent will be used for the informed consent process; however, the minor will still read and sign the assent form and the standard consent form will be signed by the parent/guardian.

As with any participant in this study, research samples and data obtained from minors will continue to be stored and used for research as described in the protocol, even if the minor's direct involvement with the study has ended, unless a parent/guardian or the participant himself/herself, having since reached the age of majority, specifically requests in writing that these samples and/or data be destroyed. If a participant who was consented as a minor reaches the age of majority, then he or she will be re-consented if there is an ongoing or new interaction between the participant and the research team, which would make re-consent a practical exercise. Minors who reach the age of majority will not be specifically contacted for re-consent as adults unless there is another reason to attempt re-contact, such as the investigators' interest in using the participant's sample in a manner that is beyond the scope of the protocol version to which the participant consented, and in such a case, if the participant cannot be re-contacted, then this may fall under the waiver of consent described in this protocol.

Waiver of Consent for NGS Analysis on Archived Specimens from Subjects We Cannot Re-Contact for Re-Consent:

A waiver of informed consent will be utilized for performing next-generation sequencing analysis, such as genome-wide testing as described in the "Testing DNA and RNA" section, on archived samples from subjects previously consented to the study who are not able to be contacted for re-consent if 1) such analysis of the sample is believed by the investigators to be critical to the research being done, 2) the extensive, documented efforts by the research team to re-contact the participant reveal that the participant is a) deceased or b) not able to be contacted using the information available to the research team, and 3) the request to use the waiver of consent for that individual, submitted to the IRB for expedited review, is approved. Such a circumstance meets the requirements for a waiver of informed consent because the research involves no more than minimal risk to the subjects as the gene testing is for research and will not affect patient care, it will not adversely affect the rights and welfare of the subjects since the results and data will be kept confidential, the research could not practicably be carried out without the waiver since the purpose of the waiver is to allow important research testing on samples deemed critical to the research, and, if it happened that a subject contacted the research team after the waiver was used, then, whenever appropriate, the subject would be provided with the pertinent information and given the option to re-consent.

It should be noted that, in almost any conceivable circumstance, it would be advantageous for our study to successfully re-contact subjects in order to re-consent them before proceeding with NGS analysis of archived specimens. This would be advantageous not only for informing the participant and following his or her wishes, but also for confirming, clarifying, or updating the phenotype and family history information before committing the significant time and resources involved with NGS analysis of a specimen. Therefore, the waiver of consent is only intended to be used in the case that the subject cannot be contacted despite the extensive efforts outlined below and the investigators are confident that analysis of the archived specimen is critical to the research question being studied.

In order to re-contact a subject, we will give our best effort and use all of the contact information available to us in the NIH medical record and in our office files.

Re-Contact Procedure:

- An investigator on the protocol will begin by calling the telephone number(s) listed for the subject in the electronic medical record and, if there is no answer, leaving a voicemail if possible to elicit a call back. In order to protect the subject's privacy, the voicemail will not include the name or topic of the study. Although the investigator may try calling the same number a second or third time at a different time of day, or day of the week, a voicemail will not be left every time.
- If there is an e-mail address listed for the subject, then an e-mail will be sent as well.
- An internet search may be performed to look for a public listing or obituary fitting the subject. The information from such a search, such as a telephone number, address, or obituary indicating the patient is deceased, will only be used if it is specific enough to our subject such that the investigator is confident that it belongs to the subject.
- At this point, additional contact information that is documented in our office records from previous interactions with the subject, such as a telephone number or email address different from those listed in CRIS, will also be used.
- If necessary, a letter will also be sent by surface mail to the subject's street address listed in the medical record or in our office records. The letter will not contain the name or topic of the study.
- If these attempts to re-contact the subject are not successful, then the investigator will use the telephone numbers listed in the medical record for the subject's
    - next of kin,
    - emergency contact, and
    - physician(s) to receive reports,

  so as to ask for updated contact information for the subject. Once again, a voicemail will be left, when possible, if there is no answer. Voicemails and correspondence with these individuals will involve the minimal amount of information adequate to convey the appropriateness and importance of the inquiry while still protecting the subject's privacy by not disclosing the name or topic of the study (i.e., the caller is a researcher from the NIH trying to get in contact with the subject who has participated in our study in the past, and, while it is not an emergency, it is important that the study team get in contact with the subject as soon as possible). If one of these sources provides updated contact information for the subject, then that information will be used next.

The investigators will document each step in the effort to re-contact a subject, and this information will be retained in a corresponding office file. After all of the above resources are exhausted, the investigators will wait an additional month after the last voicemail, e-mail, or letter was sent, in order to allow further time for return of contact, before considering the subject as unable to be re-contacted and the waiver of consent to be appropriate. If at any point during this process the investigator gathers reliable information that the subject is deceased, then this will be documented and the effort to re-contact will stop. We retain the right to perform NGS testing on samples previously collected from subjects who are now deceased, although we may work with the family, especially if it was through interaction with the family that we discovered the subject to be deceased, to respect their wishes regarding testing the subject's sample, returning any primary findings to them, or even returning incidental findings that might happen to be discovered through this analysis.

For each use of the waiver of consent, the study team will submit for expedited review a request memo to the IRB explaining the circumstance and appropriateness of the waiver for that individual case, and the waiver of consent will be in effect for that participant only after that request is approved.

Although a subject may meet these criteria for a waiver of consent, NGS analysis might never be initiated or may not be initiated right away, so if the subject happens to contact the research team before testing is initiated, then the waiver of consent would no longer be appropriate; similarly, if a relative, friend, or physician contacts the team before testing is initiated, providing updated contact information for the subject, then the waiver of consent would no longer be appropriate and the re-contacting process would reopen with the new information. If this contact occurs after the testing has been initiated, then testing may still proceed, but the subject will be contacted if possible to explain that the test was or is being performed. The subject will be given three options at this point: 1) request that the data from this test is destroyed and not used for research, 2) allow us to keep and use the data from the test that was performed on their sample under the waiver of consent but decline to participate further by re-consenting to the research protocol, or 3) re-consent to the protocol.

In the event of an unexpected occurrence that is not covered by the outlined plan, the research team will consult with the IRB and/or the NIH Department of Bioethics to determine the appropriate course of action.

This plan is consistent with the requirements for a waiver of consent because:

i. The research involves no more than minimal risk to the subjects.

This research does not physically affect the individual: reading the genes does not change the genes. Therefore, the possibilities for harm or discomfort come from either 1) the data resulting from the NGS analysis being used in some way to discriminate against the subject or to breach his or her privacy or 2) the potential for psychosocial distress resulting from disclosure of genetic information found by this NGS analysis; however, the first possibility has already been mitigated in this protocol through the use of a code to protect the subject's identity, and the fact that these subjects cannot be contacted prevents the disclosure of any results, which eliminates the second potential risk.

The protocol already has safeguards in place to protect the subjects' genetic information and confidentiality; specifically, a code is used to protect the subject's identity when sending a specimen for testing and when storing the data resulting from testing. Results of the research will not affect clinical care of subjects since they are no longer in contact with the NIH, and the results of this research testing will not be entered into the patient's medical record. Furthermore, these specimens will not be analyzed for incidental findings since there is no one to whom such a finding could be returned and therefore no purpose for analysis unrelated to the primary research question. Also, genome-scale data produced on a subject via waiver of consent will not be uploaded to a genomic data sharing (GDS) database because the specimens would have been collected before the effective date of the GDS policy and that use of the subject's genetic information would be inconsistent with the previous informed consent, which stated that the subject's DNA would only be used by our study to further our understanding of hereditary disorders of mineral metabolism.

ii. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

Results of the NGS analysis will not affect clinical care of the subject since he or she is no longer in contact with the NIH, and the results will not be entered into the medical record. In order to protect the subject's confidentiality, a code will be used for sending a specimen for testing and for storing the data resulting from testing.

Furthermore, the use of this new gene testing technology is believed by the research team to be congruous with the spirit of the original consent. By previously consenting to participate in the study, subjects have given their permission for gene testing to be performed on their DNA in order to look for a genetic cause or predisposition for the development of hyperparathyroidism. This is the same and sole purpose for which NGS analysis will be used. The difference is the gene testing technology, which did not exist or was not in use previously and so could not be included in the previous consent. This new technology offers an improved likelihood of finding an answer to the research question, which is a research question that the subject has indicated his or her willingness to participate in trying to solve by allowing gene testing on his or her blood or tissue samples. Therefore, this use of the subject's specimen is fitting with what was previously consented to, and it is expected that the subject would give consent for the use of this new gene testing technology for this purpose if he or she could be contacted.

iii. <u>The research could not practicably be carried out without the waiver or alteration.</u>

The waiver of consent will only be used if it is necessary for the research. That is, the research would require that 1) NGS technology be used and 2) that it be used to study archived specimens from a subject who cannot be contacted for re-consent.

One reason that the research would require the use of NGS technology is that the landscape of genetic testing has changed such that this technology is quickly becoming the primary option, or even the only commercially available option, for gene testing, especially for genes that are rarely tested or studied, which are important genes to analyze in order to research and discover the as-yet-unexplained etiology of some of these conditions.

The reason this type of testing would need to be performed on archived specimens from a subject who cannot be re-contacted for re-consent is that, given the nature of this research, some of the specimens collected under this protocol represent potentially invaluable sources of information for studying hyperparathyroidism. While hyperparathyroidism as a whole is not necessarily a rare disease, we know that there are numerous different etiologies of hyperparathyroidism (even within its different subtypes), some of which remain to be explained, and elucidating those etiologies requires separating the disease into its subtypes and studying them individually. This separation drastically reduces the available sample size, which is a critical factor in drawing significant conclusions from such research; therefore, even a single archived specimen, and the genetic information gleaned from performing this type of testing on it, could be the key to making a meaningful discovery. The waiver is needed because the research of certain study questions cannot practicably be carried out without performing NGS analysis on archived samples, especially on particularly valuable samples of certain disease subtypes or variants that have taken years to collect due to their rarity, and without the waiver, if a subject cannot be contacted for re-consent, then the inability to perform this testing on a critical research sample could undermine the feasibility of the research. Furthermore, over the years we have collected samples from multiple members of some unique families manifesting rare or interesting variants of the conditions that we

study. Such families are valuable and present a promising route for discovery as the inheritance of a familial predisposition suggests the presence of a shared genetic factor that could be found with this expanded gene testing, and this waiver of consent could be crucial for studying such families in the event that one or more members cannot be re-contacted for re-consent because it is imperative to have as many family members genotyped as possible when performing familial genetic studies.

iv. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

If it occurs that a subject cannot be re-contacted during our extensive efforts but then contacts the research team later, after the team has used the waiver of consent to perform NGS analysis on the subject's archived sample, then it would be explained to the subject that a newer type of genetic test, which has become available since he or she last participated in the study, was performed on the subject's sample for the same reason as the gene testing to which he or she previously consented: to learn more about hyperparathyroidism and hopefully uncover answers about the condition for patients like him or her. The type of testing performed would be explained, as well as the potential risks, benefits, and limitations of that testing. The subject would have the option to be re-consented at that point, or at any point in the future, if he or she chooses; like any re-consent to this protocol, this would involve a discussion of the potential risks of participating, including the risk for psychosocial distress when receiving results of genetic testing, as well as the possibility of incidental findings and the option of whether or not to receive them. If the subject chooses to be re-consented, then any primary findings from the NGS analysis could be returned to the subject and entered into the medical record, and, if the subject chooses to receive incidental findings, then his or her stored NGS data could be re-analyzed to look for those.

Waiver of Consent for Sharing with a Non-NIH Collaborator De-Identified Clinical and Research Data on Thirty Patients Who Have Had Parathyroid Cancer Treated Under this Protocol:

A waiver of informed consent will be utilized for sharing with our non-NIH collaborator Nancy Perrier, M.D., of MD Anderson Cancer Center, de-identified data collected on the thirty patients who have had parathyroid cancer treated at the NIH over the life of this protocol. The purpose of sharing this data is to help Dr. Perrier validate a new staging system for parathyroid cancer. In the opinion of our research team, this would be an important advancement in the medical care for this rare and deadly hyperparathyroidism condition and, therefore, it is a goal consistent with the purpose of this study and the spirit of the consent form. Previous versions of the consent form that were signed by these thirty patients did not mention whether de-identified data may be shared with other researchers, so we are asking the IRB to waive the informed consent requirement in this specific instance because we believe it meets the requirements for a waiver and is in the best interest of the research and the research participants. The consent form has been amended concurrently to add language specifying that de-identified samples or data may be shared with outside investigators, so, in the future, any patient consented or re-consented to this study using the latest version of the consent form will be aware and have given permission for this type of data sharing.

Before any data is shared, a technology transfer agreement specific to this project will be arranged by the NIDDK Technology Advancement Office and signed by Dr. Perrier. In this agreement, she will

agree to use the de-identified data only for this research project and to not attempt to identify the individuals who may be the sources of the data. Only the data required for this validation will be pulled from the medical or research records, de-identified, and then shared. The data requested for this task at this time include clinical demographics, history and physical examination, preoperative and postoperative laboratory values and radiographic studies, genetic testing results, peri-operative information and details of surgery, pathology, outcome, treatments, and follow up.

This circumstance meets the requirements for a waiver of informed consent because:

1) The research involves no more than minimal risk to the subjects because the data has already been collected by our study and will be de-identified before it is shared with the collaborator.

2) It will not adversely affect the rights and welfare of the subjects since the shared data will not be linkable back to the subjects and the research to be done with the data is consistent with the research for which the subjects gave their consent.

3) The research could not practicably be carried out without the waiver because, although some of these subjects may be contactable for re-consent, these subjects and data were accrued over multiple decades and it is likely that many of these patients who had parathyroid cancer are now deceased or are otherwise no longer contactable using the information that we have. Given the rarity of parathyroid cancer, the data from each of these patients is potentially quite valuable to the research, especially because the sample size will likely be a crucial factor in validating a new parathyroid cancer staging system. The waiver of consent is necessary to ensure that we can share data from enough of these important, rare cases to give our collaborator a sufficient sample size and the best chance of success with her research.

4) If one of these thirty patients who had parathyroid cancer treated under this protocol, and whose de-identified data is being shared with this non-NIH collaborator, returns to the NIH to receive care under our protocol, then he or she will be re-consented using the latest version of the consent form and, through that re-consent process, explicitly informed that this type of de-identified data sharing is a part of this study. If medically actionable information is discovered through the analysis of this patient data, then attempts will be made to re-contact the affected subjects and inform them of the finding(s); we would follow the re-contact procedure outlined in the “Waiver of Consent for NGS Analysis on Archived Specimens from Subjects We Cannot Re-Contact for Re-Consent” section of the protocol.

Tests and Procedures:
Tests and procedures (explanations included below) will be done according to standard clinical indications. All the data collected during clinically-indicated NIH evaluations will be used in analyses of methods of diagnosis, parathyroid gland localization, and treatment. Tests and procedures will be chosen principally from the following 17 categories:

GENERAL EVALUATION OF DIAGNOSIS AND SEVERITY AND INDICATIONS FOR PARATHYROIDECTOMY

l) Analyses from serum or plasma: calcium, ionized calcium, albumin, magnesium, phosphorus, creatinine, sugar, sodium, potassium, chloride, alkaline phosphatase, uric acid, cholesterol, SGOT, SGPT, 5'-nucleotidase, protein electrophoresis, thyroxine, tri-iodothyronine, thyroid stimulating hormone, parathyroid hormone, parathyroid hormone related protein, gastrin, prolactin, chromogranin A, 25hydroxyvitamin D, 1,25-dihydroxyvitamin D. These are necessary for diagnosis and for monitoring response to treatment.

2) Analyses from urine (usually 24 hour collections): calcium, magnesium, phosphorus, creatinine, oxalate, uric acid. Routine urine analysis and urine culture. These are necessary for evaluation of possible renal complications. Women of childbearing age will have urine sent for pregnancy test. Pregnancy is not an absolute contraindication to inclusion. If a subject is pregnant or becomes pregnant, only her informed consent will be required for enrollment, or continuation, in the study. A pregnant woman could be included in aspects of the research study that present no greater than minimal risk to patient or fetus, such as DNA testing of maternal blood. Research testing of maternal blood DNA might hold out the prospect of direct benefit to both the mother and the fetus. A pregnant woman might also be considered for more complex interventions that are not part of the research study, such as endocrine surgery, if careful clinical evaluation suggests the potential benefit outweighs the risks. Such decisions would be made in close consultation with the OB/GYN physicians of the reproductive endocrinology service.

3) Complete blood count, prothrombin time, partial thromboplastin time, platelet count.

4) Electrocardiogram.

5) Noninvasive imaging studies to evaluate conditions associated with hyperparathyroidism:
- Skeletal x-rays (evaluate bone thinning, fracture, focal lesions)
- Pyelographic x-rays (if history of urolithiasis)
- Bone mass (evaluate complications of hyperparathyroidism)
- Renal Ultrasound

6) Isotope tests to evaluate extra-parathyroid manifestations or conditions associated with hyperparathyroidism (see also sestamibi parathyroid scan in #9) –
- Bone scan (for evaluation of type, distribution, and activity of metabolic bone disease).
- 68Gallium-DOTATATE PET/CT when clinically indicated and available, will be used instead of Octreoscan, for those patients not participating in the research imaging substudy (68Gallium-DOTATATE vs. 18F-DOPA PET/CT) described in Appendix C

- (see Appendix C for description of substudy in which a subset of patients, who will also be consented to a separate consent form specific to this substudy, will receive 18F-DOPA PET/CT and 68Gallium-DOTATATE PET/CT as research imaging tests)

7) Ophthalmologic evaluation including slit lamp exam and perimetry (to evaluate effects of altered mineral metabolism on eye; perimetry is used to evaluate pituitary compression of optic nerves in FMENl).

8) Dental examination (to evaluate effects of altered mineral metabolism).

PREOPERATIVE LOCALIZATION OF PARATHYROID TUMOR

9) Noninvasive imaging tests (7, 8, 11): Computerized tomography, Sestamibi isotopic, parathyroid scan with isotopes, ultrasound, and magnetic resonance imaging of neck and mediastinum for parathyroid tumor(s). These noninvasive tests are optional in patients without prior neck surgery. All will be done in patients with prior neck surgery. Each of these tests shows some value in localizing parathyroid tumors. Their results are only partly redundant.

10) Fine needle aspiration of suspected parathyroid tumor with guidance by ultrasound or CT for assay of parathyroid hormone - gives hormone specific identification of possible mass previously identified with noninvasive test (12). Performed in some patients with prior neck surgery after noninvasive testing is judged suggestive but inconclusive.

11) Angiograms (11) -

Selective parathyroid arteriogram, done in some patients with prior neck surgery and inadequate parathyroid tumor localization from parathyroid aspiration and/or noninvasive tests (ultrasound, computerized tomography, MRI, parathyroid scan) can show a tumor as a "shadow", can define venous anatomy to aid performance and interpretation of venous sampling (below), and may be combined with hypocalcemic challenge.

In hypocalcemic challenges, the arteriographic agent will lower ionized calcium in the perfused vessels. This can cause PTH release from a perfused tumor. Several peripheral venous blood samples are taken to measure for step up of acutely released PTH.

Selective venous sampling for immunoassay of parathyroid hormone (PTH) - done in some patients who already met criteria for selective arteriogram (see above) but had inadequate tumor localization by that test. PTH gradient (more than 2-fold) defines vein(s) that drain a parathyroid tumor.

TREATMENT

12) Treatment of primary hyperparathyroidism -

When indicated, cure of primary hyperparathyroidism (benign or cancerous) will be attempted by surgical (6, 7, 14) or arteriographic ablation (15). Two alternate treatments are available: follow-up without intervention, or medical therapy with calcimimetics, denosumab, bisphosphonates, phosphates, estrogen, or other drugs.

Medical therapy with a calcimimetic. Calcimimetic drugs can directly bind to and inhibit the parathyroid cell (16). One has been approved by the FDA for use in refractory cases of primary hyperparathyroidism. It has also been approved in primary hyperparathyroidism caused by parathyroid cancer (16). Trials for up to one year in typical primary hyperparathyroidism have shown rapid normalization of serum calcium but only partial suppression of PTH.

Some patients with mild or severe disease and patients with contraindications to ablative treatments will be selected for these alternate treatments. If so, these treatments will be supervised by their local physicians with no requirement for follow-up visits to NIH. Alternately, patients residing near NIH may be followed for this purpose in our clinic.

13) Management of postoperative hypocalcemia -

Patients will receive standard treatments for postoperative hypocalcemia (6). The main elements are combinations of calcium (orally or intravenously) and vitamin D analogs In adults only, who have postoperative hypocalcemia, we may choose to use commercially available synthetic (1-84) human PTH as treatment of hypoparathyroidism, particularly in cases with difficulty in regulation of treatment with calcium and a vitamin D analog. According to standard clinical indications certain patients (specifically, those with MEN l and no prior neck surgery) will undergo total parathyroidectomy with simultaneous autograft of fresh parathyroid tissue. Patients that develop long-term permanent hypoparathyroidism, diagnosed more than 3 months post-operation may be offered autografts of their own cryopreserved parathyroid tumor (6).

EVALUATION AND TREATMENT FOR ASSOCIATED TUMORS

14) Patients with familial forms of hyperparathyroidism sometimes have syndrome-specific associated tumors outside of the parathyroids as follows:

-MEN1 associated with:
gastrinoma (30%), insulinoma (15%), other enteropancreatic neuroendocrine tumors including nonfunctioning (20%), foregut carcinoid (5%), prolactinoma (10%), other anterior pituitary (20%), nonfunctioning adrenocortical (20%), and other rare tumors (pheochromocytoma, ependymoma, muscle tumors; each less than 1%). MEN1 cases should have lifelong surveillance for emergence of new tumors (5, 18). Some will be offered periodic evaluations in the outpatient or inpatient service.

-Hyperparathyroidism-Jaw tumor syndrome associated with:
parathyroid cancer (15%), cemento-ossifying fibromas of the jaw (15%), multiple renal cysts (15%), Wilms tumor (2%), renal hamartomas (5%)%), uterine tumors (unknown percentage of affected women).

Patients likely to have either syndrome will receive medically appropriate evaluations for the specific conditions likely to be associated with the syndrome in their family.

Standard treatment will be offered for associated conditions as recognized.

MEN2A associated with medullary thyroid cancer or pheochromocytoma.

15) Cancer in the parathyroid or in a tumor related to a hyperparathyroid syndrome. Cancer of the parathyroid is very rare except for being found in 15% of cases with HPT-JT. Cancer is frequent (approximately 50% of cases beyond age 40) outside of the parathyroids in MEN1 (in duodenal submucosa, pancreatic islets, bronchial carcinoid, or thymic carcinoid). Approximately one third of MEN1 carriers will eventually die from an MEN1-related cancer. Standard evaluation and treatment

may be offered fully or in cooperation with outside resources for any of these cancers. These evaluations include imaging plus pathology examination of tissue specimens. The NIH investigators will decide, after discussion with the patient, what additional management that the NIH will offer. The principal evaluation for tumor emergence in MEN1 is imaging with several methods, which will be offered typically at 3-5 year intervals. If a patient elects not to come to Bethesda for these periodic evaluations, then any evaluations would be through their local resources.

RESEARCH TESTS

16) Certain specimens, offering no immediate benefit to the patient, will be obtained for research.

- Tumor tissue from PT and other tissues not required for pathology analysis or for cryopreservation will be used in research. Uses include analyses of oncogenes activated in the tumors and analyses of metabolic defects expressed in the tumors (for example loss of normal suppression of parathyroid hormone secretion and of gland growth by extracellular calcium).

17) Testing DNA and RNA. DNA and RNA testing will be done with tumor, with blood, saliva, or oral rinse, and/or with tissue from the inner cheek obtained by buccal swab. This includes patient tumor, blood, tissue, or DNA samples previously collected and stored under this protocol. Previous versions of this consent included the possibility of DNA testing, including the statement that any information gained by the analysis of DNA is solely to further our understanding of hereditary disorders of mineral metabolism. Some versions did not specify the type of DNA testing technology that could be used, while others explained that only targeted testing would be performed on individual genes known to be associated with hyperparathyroidism. With this consent, we are expanding the options for testing on those previously collected samples to include next-generation sequencing technology such as genome-scale testing and gene panels. While the technology has advanced, the purpose and primary focus of the DNA testing remains the same: to further our understanding of hereditary disorders of mineral metabolism.

RNA testing may be performed to help the investigators understand the expression of genes related to hyperparathyroidism in the patient's normal or abnormal tissue. It is hoped that this will help us understand which genes, DNA mutations or variants, and cellular processes are involved in hyperparathyroidism and related disorders. Because RNA production can vary with time and between tissues and is not directly transmitted between generations the way that DNA is, RNA testing does not carry the same implications or potential risks for the research subject as DNA testing; however, the subject may benefit from RNA testing performed on his or her sample if it improves our understanding of the disorder being studied and our ability to interpret the results of DNA testing.

The total amount of blood drawn will vary among subjects, depending on the number of clinical studies performed. The total amount of blood drawn from a person over 18 years of age will never exceed. 10.5 mL/kg or 550 ml, whichever is smaller, over an eight week period. For patients below age 18, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg over any eight week period.

The NIH investigators will provide a patient identification code for the stored DNA. The research subject's identity will be known only by the NIH investigators. Analyses of specimens (Blood, DNA, cells, serum, plasma) may be done at NIH or in collaborating laboratories.

The investigators will decide which genes, if any, to test for each patient. One or more among several different methods and selections of genes for testing may be performed.

a) Targeted gene testing may be performed by selecting among the genes known to be associated with disorders of calcium metabolism, which include MEN1, CASR, GNA11, AP2S1, CDC73/HRPT2, GNAS, AIP, and four CDKIs (p15, p18, p21, p27). Genes may be tested individually, or a single multi-gene test called a gene panel may be used to test several target genes at the same time. Next generation sequencing may be used. Targeted testing may look for mutations using gene sequencing and/or deletion/duplication analysis. The results of targeted gene testing on targeted genes or on actionable genes will be verified in a CLIA certified laboratory and entered into the patient's NIH medical record.

b) A genome-scale testing method such as exome sequencing, whole genome sequencing, or genome-wide copy number analysis (e.g., SNP array) may be used to analyze the genes known to be associated with hyperparathyroidism and/or to search for new gene changes that may be contributing to the disorder of calcium metabolism (19-21). The data generated from genome-scale testing may be stored for future analysis relating to this protocol, in which case the data will be stored on encrypted hard drives which will be stored securely in or near the MDB lab under the supervision of the PI or an associate investigator. Mutations found using genome-scale testing which are judged by the investigators to be informative to the medical condition being studied or to the patient's immediate health (such as the incidental finding of known-pathogenic mutations in highly-penetrant medically-actionable genes) will be verified in a CLIA certified laboratory and entered into the patient's NIH medical record.

There is the possibility of an incidental finding with genome-scale testing. Returned incidental findings will be limited to mutations that are found, which are known to be disease-causing, in medically actionable genes. The list of medically actionable genes will be based on the published recommendations by a professional genetics group, such as the American College of Medical Genetics, for return of incidental findings at the time that the data is analyzed. This list currently includes 56 genes but is expected to evolve over time (22, 23). Changes in these recommended genes will be amended at the time of annual renewal of the protocol. Estimated yield as of 2014 is that 1-4% of participants may have such a finding (24). If an incidental finding is found and meets the above criteria, then that mutation will be verified in a CLIA certified laboratory (if original testing was in a non-CLIA lab), entered into the patient's NIH medical record, and returned to the patient by the research team, provided that the patient did not opt-out of receiving incidental findings (by signing the opt-out section of the consent document) and the team is able to get in contact with the patient. The consent document informs the patient that it is his/her responsibility to keep the research team informed of any changes to contact information, that an incidental finding could be life saving information, and that the patient may change his or her decision about receiving/opting-out of receiving incidental findings in the future by contacting the investigators and being re-consented to the study. This information, including the nature, probability, and potential importance of medically actionable incidental findings, will also be discussed during the consent session to be sure that participants fully understand the consequences of their decision as well as their right to change their minds about this decision at any time in the future.

The participant may specify in the provided spaces on the consent form those relatives with whom we are authorized to share genetic test results in the event that the participant is deceased or permanently incapacitated.

Outcome parameters: The principal outcome to be monitored is cure of hyperparathyroidism. This is monitored by standard parameters (blood calcium and parathyroid hormone). Since this is a natural history protocol, description of other outcome parameters, such as definition of the regions of allelic loss in parathyroid tumors, is not appropriate.

Monitoring and follow-up: Most patients without prior neck surgery will have all their testing completed prior to planning for parathyroid surgery. Patients with prior neck surgery will generally require both diagnosis and tumor localization prior to surgical intervention. Following treatment, patients may be followed if they develop recurrence of hyperparathyroidism or if they have end-organ sequelae that requires continued follow up care. Many patients will be referred back to local Endocrinologists if no further research is planned. For familial causes of hyperparathyroidism, including MEN1, patients will be followed as per standard of care. Some patients may be followed in the NIH outpatient clinic.

Benefits: Patients will benefit from diagnosis of their endocrine-metabolic disorder. Most patients will benefit from treatment of primary hyperparathyroidism.

Risks and complications and consent procedures: These are listed below with the same paragraph numbers as in the section on Study Design (see above). All tests and procedures that involve greater than minimal risk will be separately explained and documented by additional signed consent as indicated in parentheses below. A pregnancy test will be done on all potentially fertile women. No diagnostic or therapeutic procedure will be done on a pregnant woman unless clinically justified. In the rare situation where the patient is a small child or infant, appropriate precautions will be taken. For example, general anesthesia may be indicated in a young child for a clinically necessary procedure, such as arteriography.

RISKS FROM GENERAL EVALUATION OF DIAGNOSIS AND SEVERITY

l) Serum or plasma. Standard inconvenience of diagnostic phlebotomy.
2) Urine specimens. Minor inconvenience of collecting timed urines.
3) Blood and clotting. Standard inconvenience of diagnostic phlebotomy.
4) EKG. Minimal inconvenience.
5) Radiographic noninvasive imaging Skeletal x rays. No risk. Pyelographic x-rays. Risks and precautions for intravenous contrast agents as for computerized tomography. (Standard NIH consent for contrast) Bone mass - minimal risk.
6) Isotope tests. Inconvenience of venipuncture to administer isotope(s). Minimal risk from isotope. Separate consent for 68-Gallium DOTATATE scan and 18F-DOPA (Appendix C)
7-8) Ophthalmologic and Dental evaluations. No risk.

RISKS FROM PARATHYROID TUMOR LOCALIZATION TESTS

9) Parathyroid noninvasive imaging Ultrasound - no risk. Parathyroid isotope scan - inconvenience of venipuncture. Computerized tomography (CT) - intravenous contrast agents

may cause renal damage or allergy. To avoid exacerbation of any renal disease, no patient will have radiologic studies requiring intravenous contrast (i.e. CT, pyelogram, arteriogram, venous sampling) on two successive days. Patients with history of dye-associated anaphylaxis will not receive dye. Patients with less severe allergy will be premedicated by standard methods. (Standard NIH permit for procedure with intravenous contrast). Magnetic resonance imaging - inconvenience of being in small chamber with loud noise. Magnetic field can disturb objects such as pacemakers. Patients with pacemakers or other metal objects at risk will not undergo this procedure. (Standard NIH permit for MRI).

10) Fine needle aspiration to locate parathyroid hormone (PTH) in a lesion. Discomfort of needle after local anesthesia. Needle might compromise nearby structure such as carotid artery. This non-research procedure is done according to clinical indications under guidance of ultrasound or computerized tomography depending on which imaged the mass better. (Standard NIH consent).
11) Selective parathyroid arteriogram - Risks of intravenous dye, arterial puncture, inadvertent injection or dissection of critical vessels (including those feeding the spinal cord and brain). (Standard NIH permit). Selective venous sampling for PTH - Hazards of intravenous contrast, hazards of femoral vein catheter insertion (bleeding or thrombosis). (Standard NIH permit).

RISKS FROM TREATMENT

12) Treatment. Parathyroid surgery - Risks of recurrent nerve damage, hypoparathyroidism, persistent hyperparathyroidism, anesthetic problems, recurrent hyperparathyroidism more than 6 months after surgery. (Standard NIH consent) Angiographic ablation of tumor - Risks of intravenous contrast, compromise of another critical structure, parathyroid disruption with bleeding, persistent or recurrent hyperparathyroidism, hypoparathyroidism. Also lack of excised parathyroid tumor for pathology and for cryopreservation. (Standard NIH consent). Medical treatment including calcimimetics (risks of nausea, hypocalcemia), bisphposphonate (risks of atypical jaw or femur fracture). - estrogens given at high dose to women will exacerbate hypophosphatemia. Phosphates to control calcium increase the risk of soft tissue (including renal) calcification. Phosphates are contraindicated in patients with chronic hyperphosphatemia (i.e. uremia).
13) Management of hypocalcemia - hypocalcemia causes paresthesias, muscle cramps, and, if severe, seizure. Long-term treatment of hypoparathyroidism is usually with combinations of calcium and a vitamin D analog. These carry risks of calcium overload with hypercalcemia and renal damage (temporary or permanent). Long term treatment of hypoparathyroidism by self-injection with synthetic 1-84 PTH is now possible, for adult patients only, following approval by the Food and Drug Administration
15) Parathyroid autografts carry risk of graft failure, infection, and graft dependent recurrent hyperparathyroidism. (Standard NIH consent).

SPECIMENS FOR RESEARCH

16) Additional blood and tissue. Minimal inconvenience of phlebotomy. Will not be taken from patient with severe anemia (Hematocrit below 30 %). Blood volume for research will be limited or omitted if total blood withdrawal approaches the NIH guideline of no more than 5 mL/kg in a single day, and no more than 9.5 mL/kg over any eight week period for subjects less than 18 years old, or of 450 mL over 6 weeks in adults. DNA or RNA may be extracted from blood or tumor for frozen storage indefinitely (see Research Tests). Whole blood may also be frozen and stored indefinitely. Tumor tissue will also be cryopreserved indefinitely.

17) Risks from DNA and RNA testing. There is a risk for the discovery of unexpected information such as misidentified paternity from an associated protocol (93-DK-0127) on family testing. Only information which directly affects an individual's health, health-care choices, or reproductive choices will be imparted to him/her. Specifically, families and individuals will not be confronted with issues of mis-specified paternity or adoption. In the case where a pedigree must be published to support the research findings, all identifying information regarding the issue of mis-specified parenthood will be excluded, without changing the scientific information. In all such cases a bioethics consultation will be sought to resolve specifically how the issue should be handled.

There is a possibility of an incidental or "unexpected" genetic finding when genome-scale testing is performed as well as the risk of emotional or psychological harm resulting from the discovery of a gene mutation that causes or contributes to a disorder. We will provide patients with information about incidental mutations in the selected important genes recommended for return by authorities (22, 23).

There is a risk to the insurability of the participating subject.

Data Sharing Policy: The investigators will comply with the NIH Genomic Data Sharing (GDS) policy by submitting the required data and clinical information to dbGaP for any patient on whom genomic data is produced under this protocol, such as through exome sequencing, whole genome sequencing, or genome-wide copy number analysis (25). The deposited data can be used by other researchers for studies outside of the scope of this protocol; this is a controlled-access database and researchers must promise to keep the information confidential, and the information will not include the patient's name or similar identifiers.

We may share de-identified data or samples collected under this protocol with other researchers who would first be added as collaborators to the protocol.

Current Non-NIH Collaborations:

- Nancy Perrier, M.D., MD Anderson Cancer Center
    - We are sharing de-identified clinical and research data from 30 patients with parathyroid cancer to help validate a staging system for parathyroid cancer. This collaboration is described further in the waiver of consent earlier in this document.

    - We are also sharing de-identified clinical data and research samples from 30 patients with multiple endocrine neoplasia type 1 (MEN1). This research project aims to further identify blood-based biomarkers for the detection of patients with metastatic gastrointestinal neuroendocrine tumors (dpNETs). The aim of this collaboration is to (1) test the potential of plasma-derived metabolite biomarkers for early detection of patients with MEN1-related dpNETs with distant metastases (2) concomitantly, perform in-depth metabolomic, proteomic and immune complex profiling of plasma- and plasma-derived exosomes to facilitate identification of novel protein and autoantibody biomarker candidates for patients with MEN1.

Withdrawal from study: Most patients will be released from the study after discharge from the admission at which they received treatment for hyperparathyroidism or at the time it is decided that they are not currently appropriate for attempts (surgical or angiographic) to ablate parathyroid tumors. Some uncured patients and some cured patients will have return visits in the outpatient or inpatient service.

The subject may withdraw from the study at any time and refuse further study procedures or further contact initiated by investigators associated with this study. However, any information already obtained from the samples provided will be kept by the investigator. In addition, remaining samples will be retained by NIH for potential future studies unless the subject specifically indicates to us in writing that he or she wishes for us to destroy their samples. In this case we will destroy all samples (original specimen and derived materials) in our possession and will make every effort to have materials in the possession of outside collaborators destroyed as well. In the unlikely event that a subject's sample, which he or she has requested to have destroyed, must be retained in order to protect the research (such as a sample that would be required so the investigators could confirm research results), then the sample would be anonymized so that no personal identifying information would be associated with it; the sample would then be destroyed as soon as its retention was no longer necessary. Data uploaded to a

genomic data-sharing database may not be able to be removed or destroyed, but such data will have already been de-identified.

Analysis of study: Not applicable as this is a natural history protocol.

Data and Safety Monitoring: The Principal Investigator will function as the data and safety monitor and report any adverse events to the IRB.

Study procedures will be subject to audits and/or monitoring visits to ensure compliance with the protocol and applicable regulatory requirements consistent with the NIDDK quality assurance program plan. Audit and/or monitoring visits results will be reported to the Principal Investigator for further reporting as appropriate. Study documents and pertinent hospital or clinical records will be reviewed to verify that the conduct of the study is consistent with the protocol plan.

Reporting of Adverse Events:
Adverse events, non-compliance both serious or continuing, protocol deviations both major and minor, as well as unanticipated problems are defined & described by the NIH Office of Human Subjects Research Protection policy #801 and will be reported in accordance with this policy.

Research Use, Storage and Disposition of Human Subject's Samples and Data

Only DNA samples and the data derived from testing of DNA samples will be stored. All samples will be coded per the current Core Laboratoy practices . Samples that go to another lab may have these codes, but identifying information such as patient name or date of birth will only be given if the lab requires the information and is a CLIA-approved genetics lab bound by HIPAA . The laboratory code is retained indefinitely because newly discovered hyperparathyroid genes may be analyzed in the future and the analysis should be related to the patient and family.

Samples are stored in a freezer in or near the MDB lab under direct supervision of Dr. Mary Walter of NIDDK. The freezer has an alarm to detect malfunction of the freezer.

Stored data generated from genome-scale testing will be held on encrypted hard drives which will be stored securely in or near the MDB lab under the supervision of the PI or an associate investigator.

Since the study has no set termination date, no finishing date for sample storage analysis has been set.

If any sample is lost, emptied, or destroyed, the PI will report the occurrence to the IRB.

REFERENCES

1. Aurbach GD, Marx SJ, Spiegel AM. Parathyroid hormone, calcitonin, and the calciferols. In Williams Textbook of Endocrinology: Eighth Edition. Eds Wilson JD and Foster DW WB Saunders Co. 1992, pp 1397-1476.

2. Bilezekian JP, Khan AA, Potts JT jr on behalf of the Third International Workshop on Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the Third International Workshop. J Clin Endocrinol Metab 94: 335-39, 2009.

3. Eastell E, Arnold A, Brandi ML, Brown E, D'Amour P, Hanley DA, Rao DS, Rubin M, Goltzman D, Silverberg S, Marx SJ, Peacock M, Moselikde L, Bouillon R, Lewiecki EM. Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the third international workshop. J Clin Endocrinol Metab 94: 340-50, 2009.

4. Arnold A, Marx SJ. Familial hyperparathyroidism (Including MEN, FHH, and HPT-JT). Primer on the Metabolic Bone Diseases and Mineral Metabolism 8th Edition. Ed Rosen C, et al. John Wiley & Sons, Inc. 553-561, 2013

5. Marx SJ and Wells SA Jr. Multiple Endocrine Neoplasia. Chapter 41. Williams Textbook of Endocrinology 12th Edition. Ed by Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Elsevier Saunders. Philadelphia. 1728-67, 2011

6. Norton J, Aurbach GD, Marx SJ, Doppman JL. Surgical management of hyperparathyroidism. In DeGroot U Ed. Endocrinology Vol 2. Saunders, Philadelphia. 1989, 1013-31.

7. Powell AC, Alexander HR, Chang R, Marx SJ, Skarulis MC, Pingpank JF, Simonds WF, Collins MF, Shawker T, Chen CC, Reynolds J, Cochran C, Steinberg SM, Libutti SK. Re-operation for parathyroid adenoma: A contemporary experience. Surgery 146: 144-55, 2009.

8. Nilubol N, Weinstein L., Simonds WF., Jensen RT., Phan GQ., Hughes MS., K. Libutti SK., Marx S., Kebebew E. Preoperative localizing studies for initial Parathyroidectomy in MEN1 syndrome: Is there any benefit? World J Surg 36:1368-74, 2012.

9. Agarwal S, Mateo CM, Marx SJ. Rare Germline Mutations in Cyclin-Dependent Kinase Inhibitor Genes in Multiple Endocrine Neoplasia Type 1 and Related States. J Clin Endocrinol Metab 2009 94: 1826-1834

10. Marx SJ Hyperparathyroid genes: Sequences reveal answers and questions. Endocrine Practice. Suppl 3, 18-27, 2011.

11. Chang R, Marx SJ. Role of preoperative localization and intraoperative localization maneuvers including intraoperative PTH assay determination for patients with persistent or recurrent hyperparathyroidism. J Bone Min Res 17 (Suppl 2): N133-N140, 2002.

12. MacFarlane MP, Fraker DL, Shawker TH, Norton JA, Doppman JL, Chang RA, Skarulis MC, Marx SJ, Spiegel AM, Alexander HR. Use of preoperative fine-needle aspiration in patients undergoing reoperation for primary hyperparathyroidism. Surgery 116:959-965, 1994

13. Powell, AC; Alexander, HR; Pingpank, JF, et al. The utility of routine transcervical thymectomy for multiple endocrine neoplasia 1-related hyperparathyroidism . Surgery 144: 878-83, 2008.

14. Yavuz S, Simonds WF, Weinstein LS, Collins MT, Kebebew E, Nilubol N, Phan GQ, Libutti SK, Remaley AT, Van Deventer M, Marx SJ. Sleeping parathyroid tumor: rapid hyperfunction after removal of the dominant tumor. J Clin Endocrinol Metab. 97: 1834-41, 2012

15. Miller DL, Doppman JL, Chang R, Simmons JT, O'Leary TJ, Norton, JA, Spiegel AM, Marx SJ, Aurbach GD. Angiographic ablation of parathyroid adenomas: lessons from a 10-year experience. Radiology 165: 601-7, 1987.

16. Ward DT and Riccardi D. New concepts in calcium-sensing receptor pharmacology and signaling. Brit J Pharmacol 165: 35-48, 2012

18. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML Clinical practice guidelines for multiple endocrine Neoplasia type 1 (MEN1). J Clin Endocrinol Metab 97: 2990-3011, 2012

19. Cooper GM and Shendure J. Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data. Nat Rev Genet. 12(9): 628-40, 2011.

20. Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. Genet Med. 14(4): 393-8, 2012.

21. Deo RC, Musso G, Tasan M, Tang P, Poon A, Yuan C, et al. Prioritizing causal disease genes using unbiased genomic features. Genome Biol.15(12): 534, 2014.

22. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 15(7): 565-574, 2013.

23. ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med. 17(1): 68-9, 2015.

24. Dorschner MO, Amendola LM, Turner EH, Robertson PD, Shirts BH, Gallego CJ, et al. Actionable, pathogenic incidental findings in 1,000 participants' exomes. Am J Hum Genet. 93(4): 631-40, 2013.

25. National Institutes of Health Genomic Data Sharing Policy. August 27, 2014. See http://gds.nih.gov/PDF/NIH_GDS_Policy.pdf.

Appendix A: Re-Contact Letter/Email Template (approved in 2015 Amendment U)

[DATE]

[PARTICIPANT'S NAME AND ADDRESS]

Dear [PARTICIPANT'S NAME],

I am a medical researcher working on a study that you have participated in at the National Institutes of Health (NIH) in Bethesda, Maryland. We are hoping to get back in touch with you to check in about your health, update your family medical history, and discuss the possibility of doing a new gene test on a stored specimen of yours as part of our research. This new test increases our chance to make discoveries, which could help us provide answers to patients like you, but it was not included in the original research consent form (that you previously signed) since it was not available at that time. We would do this test for exactly the same purpose as the previous gene testing that was in your consent (to learn about the condition being studied), but it is a new technology that merits its own discussion; therefore, before proceeding with the test, we would like to have a conversation with you to discuss your preferences and ask your permission. Please give me a call or e-mail back when you can, even just to schedule a convenient time to talk in the future. Thank you very much and have a great day.

Sincerely,
[INVESTIGATOR'S NAME]
[INVESTIGATOR'S CONTACT INFORMATION]

Appendix B: Re-Contact Call/Voicemail Script (approved in 2015 Amendment U)

Call Script

Calling number for subject:

Hello, this is [CALLER'S NAME] calling from the National Institutes of Health in Bethesda, Maryland. May I please speak with [PARTICIPANT'S NAME]?

If explanation is needed:
I work on a medical research study that [PARTICIPANT'S NAME] is a participant in. I am hoping to get in contact with [HIM/HER]. Is [HE/SHE] available to speak?

Participant not available:
I'm sorry I missed [HIM/HER/NAME]. What is the best time to reach [HIM/HER/NAME]?
Record: Time/Date
Thank you for your time, and may I ask who I'm speaking with?
[Record Initial Call Recipient]
Thanks again, [SPEAKER'S NAME]. I will try to reach [HIM/HER/NAME] again at [RECORDED TIME AND DATE].

Knows the participant but this is not the correct contact information:
Okay, well thank you for your time. Do you happen to have new contact information for [HIM/HER/NAME]? While it's by no means an emergency, it would be helpful for our research, and potentially helpful for [PARTICIPANT'S NAME] as well, if we could speak with [HIM/HER] as soon as possible.
Wrong number:
Thank you for your time and I'm sorry for the inconvenience.

Voicemail:
Hello, this is [CALLER'S NAME] calling from the National Institutes of Health in Bethesda, Maryland. I am hoping to get in contact with [PARTICIPANT'S NAME], who is a participant in our medical research study. We wanted to check in about [HIS/HER] health, ask about any updates to the family medical history, and discuss the possibility of doing a new test on a specimen that we have stored from [PARTICIPANT'S NAME] as part of our research. Please give me a call back whenever you can, even just to schedule a convenient time to talk in the future. My number is [CALLER'S NUMBER], and again my name is [CALLER'S NAME]. Thank you very much and have a great day.

Calling number of next of kin, emergency contact, or physician to receive records:

Hello, this is [CALLER'S NAME] calling from the National Institutes of Health in Bethesda, Maryland. I work on a medical research study that [PARTICIPANT'S NAME] is a participant in. We are trying to get in contact with [HIM/HER/NAME], but unfortunately we've been unsuccessful so far using the contact information we have on file. I'm calling you because this number was listed as [HIS/HER] [NEXT OF KIN/EMERGENCY CONTACT/PHYSICIAN TO RECEIVE RECORDS]. Do you know how we might be able to get in touch with [PARTICIPANT'S NAME]?

Voicemail:
Hello, this is [CALLER'S NAME] calling from the National Institutes of Health in Bethesda, Maryland. I work on a medical research study that [PARTICIPANT'S NAME] is a participant in. We're trying to get in contact with [HIM/HER/NAME], but unfortunately we've been unsuccessful so far using the contact information we have on file. I'm calling you because this number was listed as [HIS/HER] [NEXT OF KIN/EMERGENCY CONTACT/PHYSICIAN TO RECEIVE RECORDS], so I'm hoping you might have updated contact information for [HIM/HER/NAME]. While it's by no means an emergency, it would be helpful for our research, and potentially helpful for [PARTICIPANT'S NAME] as well, if we could speak with [HIM/HER] as soon as possible. Please give us a call back when you get a chance, even if you don't have new contact information because just knowing that could be helpful for us. My number is [CALLER'S NUMBER], and again my name is [CALLER'S NAME]. Thank you very much and have a great day.

Appendix C: Research Imaging Substudy – 68GALLIUM-DOTATATE versus 18F-DOPA (approved in 2018 Amendment AA) (Completed Enrollment on 7/29/2019)

The role of ^{68}GALLIUM-DOTATATE PET/CT versus ^{18}F-DOPA PET/CT in the imaging of neuroendocrine neoplasms in patients with Multiple Endocrine Neoplasia Type 1 (MEN1)

Précis

This amendment requests the addition of a study in the MEN1 subpopulation of the full protocol. This study is designed to compare the efficacy of ^{68}Ga-Dotatate PET/CT scan versus ^{18}F-DOPA PET/CT, MRI and CT scan in detecting known and occult primary and metastatic neuroendocrine tumors. Further research into identifying the best imaging modalities is important in this rare disease because (1) duodenal and pancreatic neuroendocrine tumors are the most important determinant of MEN1-related survival – and treatment (surgical or medical) is based on the accurate localization and size of primary and metastatic lesions; (2) there is no clear evidence to suggest that MEN1 patients have a phenotype-genotype correlation, thus limiting the ability to predict tumor location and/or progression, (3) there are no adequate or sensitive serum tumor markers for the detection and surveillance of non-functional neuroendocrine tumors, thus requiring yearly functional and anatomical tumor screening for all MEN1 patients, and (4) the multiplicity and heterogeneity of neuroendocrine tumors in this disease can make detection using anatomical imaging challenging, thus requiring the addition of sensitive functional imaging. Using various standard-of-care imaging modalities (CT and MRI), the comparison of ^{68}Ga-Dotatate and ^{18}F-DOPA offers the opportunity to further characterize NETs based on molecular transporters, delineate molecular tumor characteristics, and offer insights into promising therapeutic targets in the future.

Background

The Metabolic Disease Branch has studied patients with Multiple Endocrine Neoplasia type 1 (MEN1) for over four decades, with important discoveries and contributions to the field, most notably the discovery of the *MEN1* gene to 11q13.[1] This rare disease has an estimated prevalence of three to four per 100,000, and currently the MDB branch is actively following ~350 patients including multiple kindreds with MEN1. This disease manifests typically with parathyroid (90-95%), enteropancreatic neuroendocrine (30-70%) and anterior pituitary tumors (30-40%).[2] Other recognized features include thymic and bronchial carcinoids (2-8%)[3], adrenocortical tumors (40%), and cutaneous lesions (30-85%).[2]

The introduction of proton pump inhibitors has greatly reduced the mortality from gastrinoma-induced Zollinger Ellison syndrome.[4] Currently, the cause of death in 50-70% of MEN1 patients is a malignant tumor process, or is directly related to manifestations of MEN1.[5] Patients with neuroendocrine thymic tumors and secretory NETs (neuroendocrine tumors) have over four-times the risk of death, while non-functional pancreatic tumors have over three times the risk of death as compared to other tumor types in MEN1.[6] Factors that determine the clinical course and outcome of NETs in MEN1 are complex and include the site of origin, hormone secretory properties, the size of the primary tumor, the extent of disease, and the grade (based on Ki-67 staining).[7] Characteristics of both sporadic and familial neuroendocrine tumors as described by the European Neuroendocrine Tumor Society and the WHO guidelines distinguish the differences between well- and poorly-differentiated NET (Table 1). Well-differentiated neuroendocrine tumors typically have an indolent course, while

poorly differentiated tumors are often difficult to detect and rapidly progressive. In MEN1, most neuroendocrine tumors are slow growing, and have low oncologic properties such as low Ki67 index (%) and/or mitotic count.

Identification of primary and metastatic disease represents the most important prognostic factor after tumor grading for NETs.[8,9]As such, clinical and pre-operative management decisions are dependent on the localization, assessment and accurate monitoring of functional and non-functional NETs and their metastases. Tumors arise from neuroendocrine cells, which are the largest group of hormone-producing cells in the body and metastasis may occur at any location. At least thirteen types of distinct gut neuroendocrine cells exist, all of which may oversecrete various bioactive peptides or amines or may be biochemically silent. Secreted peptides and biogenic amines include serotonin, somatostatin, histamine, bradykinin, gastrin, insulin, glucagon, pancreatic polypeptide, and vasoactive intestinal polypeptide. In MEN1 patients, the reported most common manifestations are gastrinoma (40%), insulinoma (10%), non-functional pNET and pancreatic polypeptidioma (20-55%), and glucagonoma and VIPoma (<1%). [2,10]

A tumor's malignant potential is often related to the rate of growth and size of the tumor. Retrospective data demonstrates that patients with non-functional pancreaticoduodenal tumors with increased tumor size (>30 mm vs. 10 mm – 30 mm vs <10 mm) have shorter survival times.[11] Early surgical intervention for non-functional pancreatic neuroendocrine tumors with a size of ≥ 20 mm has become standard of care.[2] Functional tumors, on the other hand, have potential to cause severe clinical sequelae and therefore surgical resection is recommended regardless of tumor size. In these situations, biochemical monitoring helps identify the type of tumor, which may be a microadenoma, and imaging is critical to localize the lesion.

Table 1. Characteristics of sporadic and familial neuroendocrine tumors (adapted from [12])

Characteristic	Well-differentiated neuroendocrine tumor or carcinoma		Poorly differentiated neuroendocrine carcinoma
Tumor grade[#]	1 (low)	2 (intermediate)	3 (high)
Ki67 index (%) and/or mitotic count (per 10 HPF)	Ki67 <3% and <2 mitoses	Ki67 3–20% or 2–20 mitoses	Ki67 >20% or >20 mitoses
Clinical course and findings on CT or MRI	Indolent course	Intermediate	Rapid growth
Incidence FDG-PET-positive lesions[‡]	Lower	Intermediate	Higher
Somatostatin receptor expression[‡]	Higher	Intermediate	Lower
Prognosis	Relatively good	Intermediate	Poor
First-line therapy	Curative surgery	Curative surgery	Curative surgery
Second-line therapy	Surgery (debulking of primary tumor and/or metastases) SSA Sunitinib[§] Everolimus[§] Radiolabelled SSA (PRRT) Chemotherapy for pNET Interferon HA(C)E, radioembolization or radiofrequency ablation	Surgery (debulking of primary tumor and/or metastases) SSA Sunitinib[§] Everolimus[§] Radiolabelled SSA (PRRT) Chemotherapy for pNET Interferon HA(C)E, radioembolization or radiofrequency ablation	Chemotherapy

[#]According to the European Neuroendocrine Tumor Society and WHO guidelines
[‡]Findings on functional imaging.
[§]Registered for pNET.
Abbreviations: HA(C)E, hepatic artery (chemo)embolization; HPF, high power field; pNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.

Detection methods for NETs in MEN1

Many diagnostic recommendations, as well as data about surgery and chemotherapy, are derived from long-term experiences of specialists in the area, from clinical work of numerous specialist referral centers worldwide, and from trials performed on sporadic counterparts of MEN1-associated tumors. However, routine clinical practice incorporates a combination of anatomical imaging and functional or molecular imaging, most notably somatostatin receptor imaging, that has improved detection of NETs.[13] In order to track and monitor these tumors, chest and abdominal imaging is recommended starting at diagnosis and every 1-2 years thereafter.[2,14]Anatomic imaging is important for localization of tumors (and their metastasis), and to evaluate vascularization, attenuation, invasion into local structures, and other characteristics like Hounsfield Units (MRI) or calcifications (CT). Cross-sectional imaging with CT or MRI scan is recommended yearly for pancreatic NET, and every 1-2 years for thymic or bronchial NET.[2] Non-functional pancreatic neuroendocrine tumors (pNETs), one of the main features of MEN1, have reported CT and MRI detection rates of 73% and 93% and specificity of 96% and 88%, respectively.[12]

Conventional imaging modalities can be limited by tumor size, the location and tissue contrast, resulting in some tumors escaping detection. For example, MRI is generally superior to CT for liver lesions, but CT may be able to detect pancreatic lesions with more accuracy.[15] As a result, nuclear imaging augments anatomic imaging and is based on the fact that most well-differentiated neuroendocrine tumors express somatostatin receptors (SSTR), making radiolabeled somatostatin analogs an agent of choice.[16] More than 70% of NETs in both the GI tract and pancreas express multiple subtypes, with a predominance of receptor subtypes 2 (SSTR2) and 5 (SSTR5).[17,18] Octreotide, an SSTR2 analog, is widely available as ^{111}In-pentetreotide scintigraphy (also known as ^{111}In-diethylene triamine penta-acetic acid-D-Phe^{1}-octreotide or ^{111}In-DTPA-octreotide) and has an overall sensitivity of detecting abdominal NETs of 78% (46% - 100%).[19] However, this imaging modality fails to identify one-third of lesions identified at surgery, even in the case of sporadic gastrinomas.[20]

^{68}Ga-Dotatate in the detection of NETs in MEN1

A newer agent, ^{68}Ga-Dotatate (DOTA-0-Tyr3-Octreotate) PET combined with CT imaging (PET/CT) was FDA approved in June 2016 for clinical imaging in patients with neuroendocrine tumors. The half maximal inhibitory concentration (IC50 ± SEM in nmol/l) for ^{68}Ga-Dotatate at SSTR2 is 0.2 ± 0.04 compared to 22 ± 3.6 for ^{111}In-pentetreotide scintigraphy, demonstrating a ~100 fold higher affinity for SSTR2, and about an equal affinity for SSTR5.[21] Superiority of localization compared to ^{111}In-pentetreotide scintigraphy may be due to these higher binding affinity of the ligand for the SSTR2 and 5 receptors, higher spatial resolution allowing detection of microadenomas < 10mm, and better target-to-background ratios.

^{68}Ga Dotatate PET/CT for neuroendocrine tumors has been well documented in clinical trials for NETs[22-24]. However, to date, only a small number of studies in patients with MEN1 are available: two with ^{68}Ga-Dotatate and two with ^{68}Ga Dotatoc (the affinity of ^{68}Ga-Dotatate is approximately 10-fold higher than that of 68Ga-Dotatoc in binding to SSTR2). The findings are summarized as follows:[25-28]

(1) Lastoria et al[25] compared ^{68}Ga Dotatate PET/CT with relevant conventional imaging (comprised of CT, MRI, duodeno-pancreatic endoscopic ultrasound, ^{111}In-pentetreotide scintigraphy) in MEN1 patients (n=18).
    - ^{68}Ga Dotatate PET/CT identified 11/11 patients with pancreatic lesions, 9/12 patients with pituitary adenoma, 5/15 patients with parathyroid enlargements, and 5/7 patients with adrenal lesions.

- ^{68}Ga Dotatate PET/CT showed sensitivity and specificity of 100% and 100% in pancreas, 75% and 83% in pituitary, 28% and 100% in parathyroids, and 62.5% and 100% in adrenals, respectively.
- There was no mention of metastatic lesions, functional status of pancreatic lesions, and all patients were newly diagnosed.

(2) Sadowski et al[26] compared ^{68}Ga Dotatate PET/CT with ^{111}In-pentetreotide scintigraphy and anatomic imaging with triphasic CT scan in MEN1 patients as part of a larger NET cohort and active surveillance program (n=26).

- ^{68}Ga Dotatate PET/CT detected 107 lesions, of which 33 were also detected by ^{111}In-pentetreotide scintigraphy and 43 were also detected by CT scan. In total, there were 18 patients who had additional lesions detected by ^{68}Ga Dotatate PET/CT.
- ^{68}Ga Dotatate PET/CT identified additional lesions in the pancreas, duodenum, gastric body, metastasis to the liver, lymph nodes, primary tumors in the appendix and lung.
- In an analysis based on available histology, 23 lesions were true positive and 5 lesions were false positive. It is not clear if any lesions were detected on MRI/CT that were not detected on ^{68}Ga Dotatate.

(3) Froeling et al[28] (n=21 total, 19 MEN1) evaluated Ga-68 DOTATOC PET/CT compared to PET, CT contrast vs non-contrast and evaluated changes in treatment recommendations were recorded per a NET consensus

- Management alterations occurred in 10 of 21 (47.6 %) patients
- ^{68}Ga-DOTATOC PET/CT conferred an overall sensitivity and specificity of 91.7 and 93.5 %, respectively, in detecting NET lesions
- However, this study had a particularly low CT (contrast and non-contrast) sensitivity/specificity of 43.4%/61.3% and there was no mention of the location of the lesions that were not found on Dotatoc that were localized by other methods.
- Likewise, this study had a low detection rate of 89.2% in the contrast-enhanced Ga-68 Dotatoc, lower than previously reported rate of 92% in NET[29], and an unusually higher detection rate in non-contrast CT.

(4) Albers et al[27] (n=33 MEN1) evaluated ^{68}Ga Dotatoc PET/CT as compared with conventional imaging (endoscopic ultrasound (EUS), MRI, CT and EGD) and found:

- ^{68}Ga Dotatoc failed to detect bronchial carcinoids (0/6; 6 detected by CT thorax), as well as a lower rate of detection of pancreatoduodenal NETs (44/117 detected by EUS).
- Conventional imaging (MRI, EUS, EGD and thoracic CT) detected 145 NETs in 27 (82%) of 33 patients whereas ^{68}DOTATOC PET/CT detected only 55 lesions in 23 (70%) of 33 patients ($p<0.001$).
- The smallest NET visualized by ^{68}DOTATOC PET/CT was 7 (range 7–50) mm in size, whereas conventional imaging, especially EUS, detected lesions as small as 2 (range 2–50) mm.
- The sensitivity of ^{68}DOTATOC PET/CT for NETs <5, 5–10, 10–19 and >20 mm was 0, 29, 81 and 100%, respectively, when using findings of all other imaging techniques as reference standard.

In summary, the available data strongly support a role for the use of ^{68}Ga-Dotatate PET/CT in neuroendocrine tumors in MEN1, even though the accumulation of evidence in this rare disease is limited. Nonetheless, there is discrepancy in the results in this cohort, suggesting that there may be (1) additional heterogeneity in tumor SSTR expression in MEN1 tumors, (2) unknown factors related to the location of the NET which may play a role in SSTR2 expression or that (3) differences or changes occur in SSTR expression in metastatic NET lesions compared to primary tumors.

Tumor multiplicity, heterogeneity, location and metastasis: A call for further investigation

Koopmans et al[19] have demonstrated that radionuclide tracer uptake may differ even within a single NET (Figure 1). In this example, a carcinoid tumor demonstrates uptake in one portion of the tumor based on ^{18}F-DOPA, while another area of the tumor has SSTR receptors that demonstrate uptake with octreotide scan. Metastatic NET lesions may require a multi-pronged approach as intra-individual heterogeneity may account for variations in detection, including de-differentiation.

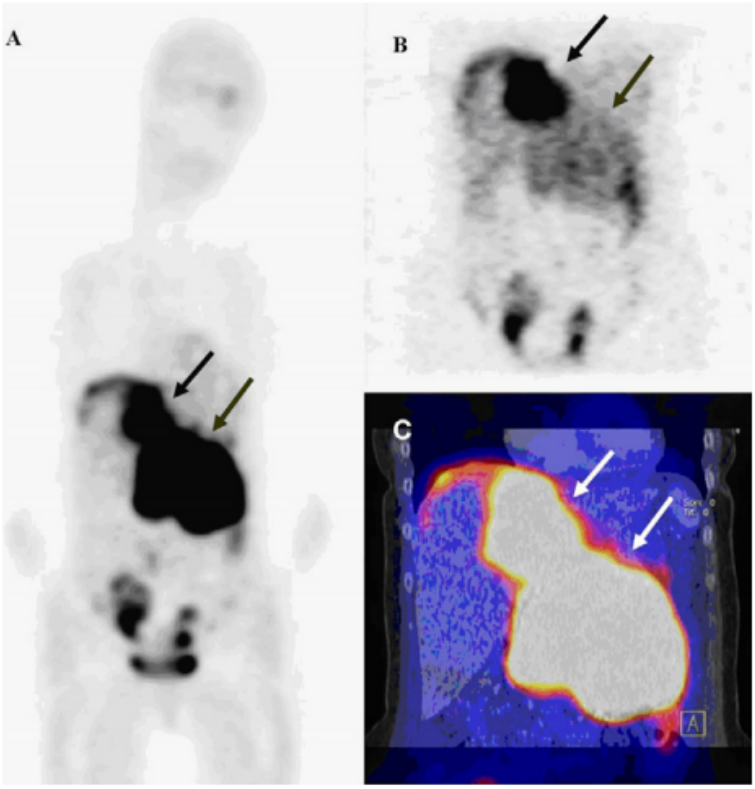

Figure 1. Intra-individual heterogeneity in the uptake of different tracers in a metastatic carcinoid patient (A: ^{18}F-DOPA PET, B: Octreotide scan, C: fusion image). From Koopmans et al[19]

Albers et al.[27] demonstrated that as many as 62% of neuroendocrine tumors detected by conventional imaging were missed by ^{68}Ga Dotatoc PET/CT. These tumors were typically small (0-10mm) and frequently located in the lung. While the above studies report improved sensitivity in the detection of NETs in MEN1 as

compared to conventional ^{111}In-Pentetreotide SPECT/CT, lesions that do not highly express SSTR may escape detection (estimated anywhere from 3-10% based on the available literature).

In an NIH analysis[30] of all-inclusive NET (n=131; sporadic and familial inclusive of Von Hippel-Lindau and MEN1), 16% (4/25 patients) with biochemical evidence of hormone excess symptoms failed to localize on all imaging modalities (^{68}Ga-Dotatate PET/CT, ^{111}In-Pentetreotide SPECT/CT, and CT/MRI). In addition, an analysis of the lesions detected by anatomic imaging demonstrated that ^{68}Ga-Dotatate missed 25% of lung and mediastinum NETs that were detected by CT/MRI. The accumulation of this data suggests that additional imaging modalities would be helpful to detect small, sometimes functional, lesions, which occur in up to 5-10% in MEN1[31].

Additionally, NETs may have different expression of SSTR subtypes and this expression many limit the ability to localize these tumors. Mizutani et al[32] used RT-PCR and immunohistochemistry to analyze SSTR expression in 32 NETs (9 Grade 1 carcinoids: duodenum, colon, appendix, rectum and lung; 2 Grade 2: lung and stomach; 18 Grade 3: multiple locations including esophagus, lung, thymus, stomach, breast, etc). Interestingly, expression of SSTR2 was significantly high in the NETs located in the GI tract (Grade 1,2) but not in the lung (Figure 2). Likewise, expression of SSTR was lower in the hindgut carcinoids. While MEN1 most commonly manifests with foregut carcinoids,[33] there are infrequently manifestations of hindgut carcinoids.[26] Another analysis using *in vitro* receptor autoradiography demonstrated the variable presence of SSTR2 among various neuroendocrine tissues: 100% in gastrinomas (n=11), 70% incidence in insulinomas (n=27), and 60% in bronchial carcinoids (n=29).[34] This data may suggest that treatment modalities with cold or 'hot' somatostatin analogs (e.g. peptide receptor radionuclide therapy [PRRT]) may have preferential benefit based on tissue of origin.

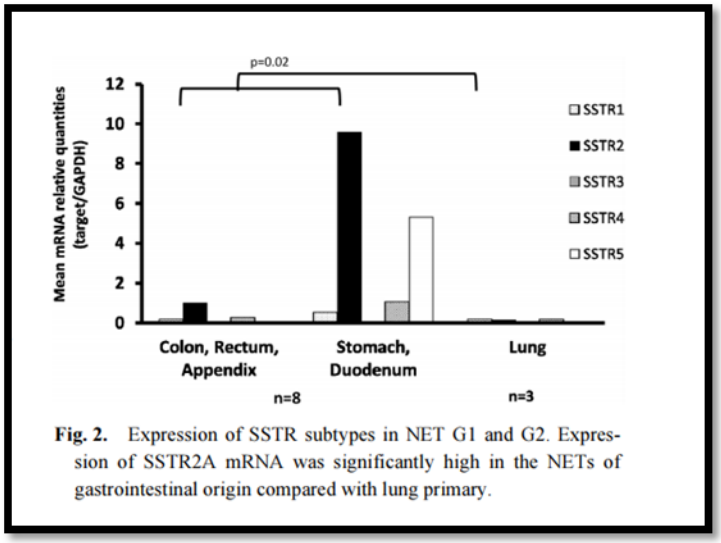

Fig. 2. Expression of SSTR subtypes in NET G1 and G2. Expression of SSTR2A mRNA was significantly high in the NETs of gastrointestinal origin compared with lung primary.

Figure 2. SSTR expression in a variety of NET, as published by Mizutani et al.[32]

Detection of NETs in MEN1 are important for a variety of reasons, including: (1) detecting functional symptomatic NETs, or nonfunctional NETs at or exceeding the 20 mm size threshold, makes a surgical cure possible, (2) localizing metastatic disease prior to surgical resection is critical for staging, surgical plan, and follow-up and (3) documenting the presence of NETs by imaging techniques utilizing SSTR expression has implications for the therapy of NETs, particularly with respect to the possible use of PRRT with radiolabeled SST analogues.[35]

^{18}F-DOPA for the detection of NET in MEN1

Another agent, 6-18F-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) has been investigated in NET. Particularly for MEN1, it shows promising results in both carcinoids as well as functional pancreatic NETs.[19,36-43] ^{18}F-DOPA is taken into the cells by L-Type Amino Acid Transporter 1 and 2 (LAT1 and LAT2), and has been useful in the diagnosis of pheochromocytoma/paraganglioma and suggested for use in medullary thyroid carcinoma.[44-46] More recently, the use of ^{18}F-DOPA has been evaluated in hyperinsulinemic hypoglycemia, with carbidopa.[38-40]

In serotonin-secreting tumors (no mention if familial or sporadic), a head to head study by Haug et al[37] of ^{68}Ga-Dotatate vs ^{18}F-DOPA PET found that overall, ^{68}Ga-Dotatate was superior to ^{18}F-DOPA in 13 patients, but comparable in 12. However, for 13 patients with increased serotonin, 85% had localizing uptake with ^{18}F-DOPA. While the overall sensitivity of localizing carcinoids was superior in ^{68}Ga-Dotatate, ^{18}F-DOPA PET demonstrated evidence of more metastatic lesions in two patients as compared to ^{68}Ga Dotatate, particularly in the liver.

In unpublished data made available from by Dr. Stephen Wank from protocol 08-DK-0098, which includes the evaluation of the detection of familial carcinoids with ^{68}Ga Dotatate as compared to ^{18}F-DOPA with premedication carbidopa (an efficient inhibitor of the peripheral aromatic amino acid decarboxylase, significantly reducing the physiological pancreatic FDOPA uptake, and has been shown to be beneficial in other NETs[38,39,44-47]) there are case detections as demonstrated below that highlight the utility of this added detection method (Figure 3-6) in the detection of serotonin-secreting tumors.

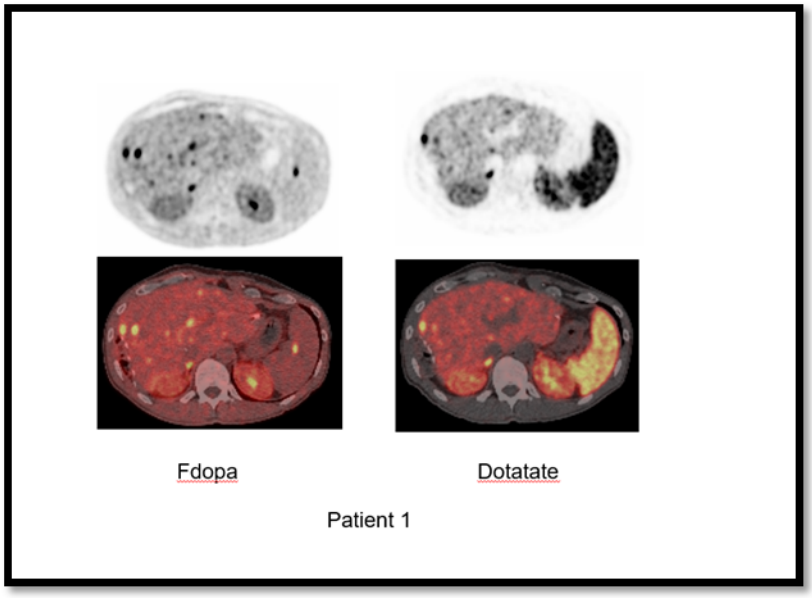

Figure 3. Patient example 1

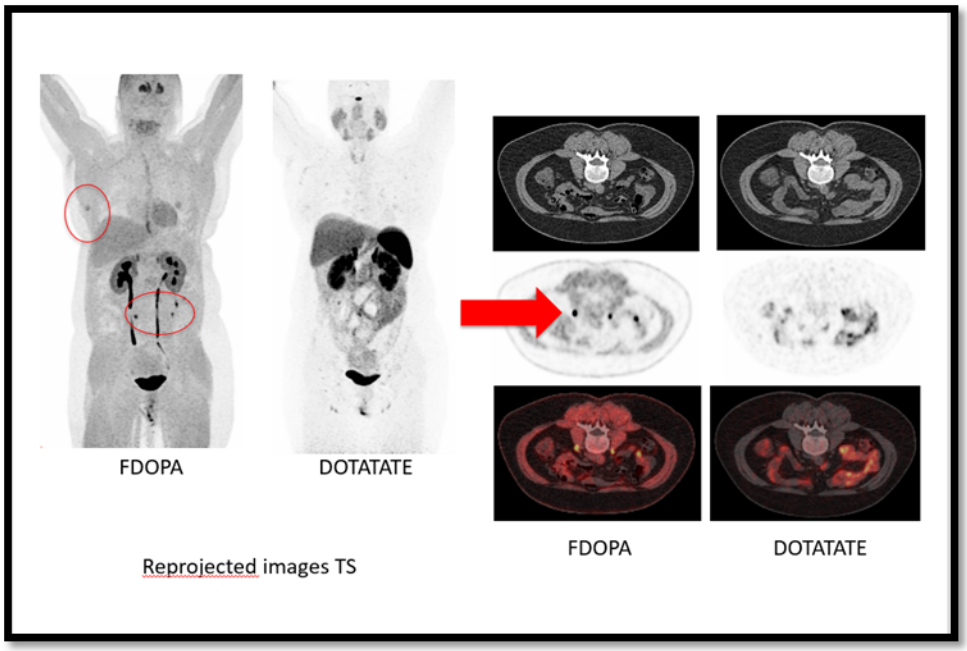

Figure 4. Patient example 2

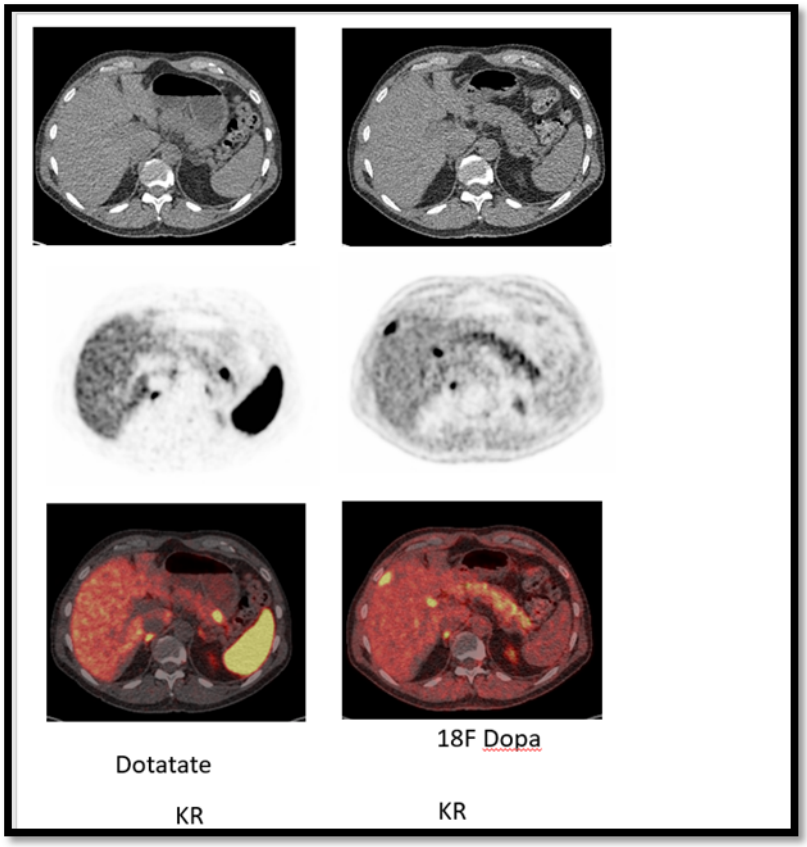

Figure 5. Patient example 3

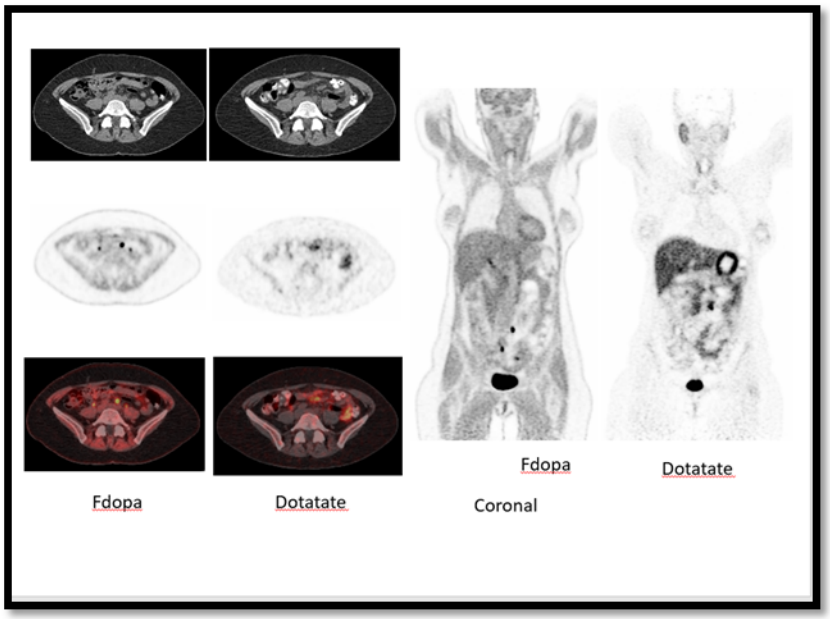

Figure 6. Patient example 4

While the carcinoids that are present in MEN1 are typically foregut carcinoids, which is a different population that those studied above, the detection of these lesions especially in the liver and lung may be of utility as the sensitivity of detection for those locations in the available MEN1 data have a lower detection rate in ^{68}Ga-Dotatate. Reports of mid- and hindgut MEN1 related carcinoids have been reported[26,48-50] and could be detected by ^{18}F-DOPA if they escape detection by ^{68}Ga-Dotatate. In summary, MEN1 offers a unique patient population because of tumor multiplicity in distinct anatomical sites[51,52], the simultaneous presence of (often small) functional tumors that may oversecrete various bioactive peptides or amines (including insulin, serotonin, somatostatin, histamine, and gastrin, among others), and the heterogeneity of tumor presentation and malignant potential. Interestingly, it should be noted that the MEN1 mutation is not only found in hereditary syndromes. Somatic inactivating mutations in the MEN1 gene have been reported in sporadic tumors like those that are present in MEN1 syndrome. Unlike the 'first hit – second hit' hypothesis for inactivating mutations (germline -> somatic) in inherited familial conditions, in sporadic tumors, the 2-hits occur in the MEN1 gene for biallelic inactivations. Using targeted sequencing of *MEN1* exons or whole-exome sequencing approaches, the frequency of somatic *MEN1* mutations reported in sporadic tumors is as follows: glucagonoma (60%), VIPoma (57%), non-functioning PNETs (44%), gastrinoma (38%), bronchial carcinoid (35%), parathyroid adenoma (35%), lipoma (28%), insulinoma (2–19%), angiofibroma (10%), anterior pituitary tumor (3.5%) and adrenocortical tumor (2%).[53] Similar to the distribution of mutations occurring in MEN1 hereditary germ line mutations, the somatic mutations are also spread over the entire coding region of *MEN1* with no hot spots. This finding may have relevance in the future as we continue to explore the role of MEN1 mutations in tumorigenesis.

Without a clear phenotype-genotype correlation nor adequate serum tumor markers for the detection and surveillance of non-functional NETs, tumor screening and detection is necessary for all patients.[54] Using various standard-of-care imaging modalities (CT and MRI), the comparison of ^{68}Ga-Dotatate and ^{18}F-DOPA offers the opportunity to further characterize NETs based on molecular transporters, further delineate molecular tumor characteristics, and offer insights into promising therapeutic targets in the future.

Study Design

Study Objectives

- *Primary Objective*: To compare the efficacy of ^{68}Ga-Dotatate PET/CT scan versus ^{18}F-DOPA PET/CT, MRI and CT scan in detecting known and occult primary and metastatic bronchial, gastrointestinal and pancreatic neuroendocrine tumors.
- *Secondary Objectives*: (1) To evaluate ^{68}Gallium-Dotatate versus ^{18}F-DOPA PET/CT uptake in NETs and its association with tumor differentiation. (2) To determine whether ^{68}Gallium-Dotatate and/or ^{18}F-DOPA PET/CT uptake value is predictive of tumor growth and/or disease progression and of its differentiation state.

Inclusion Criteria

- Patients who have genetically confirmed MEN1 or have clinical criteria of MEN1 as per guidelines[2]
- Age ≥ 18 years of age
- For females: Negative urine pregnancy test OR post-menopausal for at least 2 years OR patient has had a hysterectomy.

Exclusion Criteria

- Serious underlying medical conditions that restrict diagnostic testing or therapy such as renal failure or congestive cardiac failure
- Patients unable or unwilling to give informed consent
- Pregnant or lactating women: Pregnant women are excluded from this study because the effects of ^{68}Ga-DOTATATE in pregnancy are not known. Because there is an unknown but potential risk for adverse events in nursing infants secondary to administration of ^{68}Ga-DOTATATE in the mother, women who are breastfeeding are also excluded from this study
- Patients that have recognized concurrent active infection
- Patients with known hypersensitivity to carbidopa, or who are concurrently taking a nonselective monoamine oxidase (MAO) inhibitor.

Patient Registration and Consent

See page 3 of the protocol for consent procedures. Patients with MEN1 will be identified from the standard protocol by the investigators and consented to this additional substudy if they choose to participate. The potential candidates for the study will be screened for the eligibility criteria by the Principal Investigator and/or Associate Investigators, and research team. The patients who are eligible and sign the Research Imaging Substudy informed consent form in addition to the standard consent form.

Study Implementation and Methods

A ^{68}Ga-DOTATATE PET/CT scan will be done per the standard FDA approved protocol.[55] The ^{68}Ga-DOTATATE PET/CT will be compared to the ^{18}F-DOPA and CT and MRI as outlined in the full amendment description. From the original protocol, ^{111}In-Pentetreotide SPECT/CT will no longer be performed. All other testing (blood sampling, parathyroid testing, and other localization studies as required per patient's biochemical evaluation) will continue as per the original protocol, on a yearly basis.

For both scans, the subject reports to the PET scanning facility. All patients should fast for at least 4 hours prior to the PET examination, oral water is permitted. An intravenous line is inserted into an arm vein for administration of radiopharmaceutical. The subject then is placed in the PET/CT scanner, with the head, neck, chest, abdomen, pelvis, or extremities in the field of view. CT scanning is done to correct for attenuation of emitted radiation and localize the potential abnormalities. The tracer is prepared and tested for purity just prior to use.

Scans are performed with the Siemens mCT (PET/CT) tomograph-scanner. Scans will be acquired in 3D mode, producing a reconstructed resolution of ~7 mm in all directions. Although at this point the CT portion of the PET scan is not considered diagnostic (because it is performed at a lower energy and without i.v. or oral contrast) in the future we may have the capability to perform a diagnostic quality CT in which case it could be substituted for conventional diagnostic CT that the patients currently undergo.

The two scans will typically be performed at least one day apart, but in extenuating circumstances, the scans may be performed on the same day, at least 7 hours apart. In these situations, the ^{68}Ga-DOTATATE scan must be done first, in the morning, followed by ^{18}F-DOPA in the late afternoon, due to the half-lives of the agents (68min for ^{68}Ga-DOTATATE, and there must be 6 half-lives between scans.)

Standardized ^{68}Ga-Dotatate Protocol

Using the established IV line and, with the patient supine, around 5mCi of ^{68}Ga-DOTATATE will be administered intravenously, followed by incubation for approximately 60 minutes. Then the patient will be positioned in a PET/CT scanner and images from the upper thighs to the base of the skull will be obtained. To date, there are no known allergic reactions to ^{68}Ga-DOTATATE.

Standardized 18-Fluorodopa ([^{18}F]-DOPA) PET Scan Protocol

Carbidopa (200 mg) is given p.o. one hour before the injection of [^{18}F]-DOPA. A dose of 12 mCi of [^{18}F]-DOPA is injected i.v. over 1-3 minutes. The whole-body scan is started approximately 60 minutes after [^{18}F]-DOPA is administered. [^{18}F] DOPA is produced by using a standard procedure as indicated in the IND. Altogether, the [^{18}F]-DOPA PET scanning will proceed for up to 2 hours on the Siemens mCT. Typically scans will extend from the top of the skull to the upper thighs.

Clinical Evaluation

As per the natural history protocol, patients will be evaluated based on the manifestations of their disease. The current lab testing as outlined in the protocol will continue, and the addition of ^{18}F-DOPA and ^{68}Ga-Dotatate will be added to the protocol based on availability during the week of testing. However, Octreotide scanning will no longer be utilized.

Example of Calendar

Day 0 (Sunday)	Day 1 (Monday)	Day 2 (Tuesday)	Day 3 (Weds)	Day 4 (Thrs)	Day 5 (Friday)	Day 6 (Sat)
Admission	History/Physical exam Blood work Pregnancy test if appropriate	CT C/Ab/Pelvis Consults as needed	MRI C/Ab/Pelvis And MRI Pituitary	^{18}F-DOPA	^{68}Ga DOTATATE	D/C

HUMAN SUBJECTS PROTECTIONS

Rationale For Subject Selection

Patients with MEN1, with unknown primary tumor or metastatic neuroendocrine disease found on anatomic imaging (CT/MRI) or patients with biochemically active disease will be selected for this study. Both functional and non-functional solid tumors will be included in this study. Furthermore, asymptomatic and symptomatic, and both sporadic and familial cases of NETs in the setting MEN1 will be included. Patient selection for this protocol will not be based on gender, race or ethnic background.

Participation of Children

Children below the age of 18 will not be included on this protocol. Only patients age 18 and older will be eligible for this substudy because the research PET/CT scans are being investigated to their potential to characterize and identify neuroendocrine tumors and metastasis which are uncommon manifestations in children under the age of 18. Thus, the risk:benefit ratio of this additional research radiation may not be justified at this time in this population. Children will still be able to receive clinically indicated ^{68}Ga-Dotatate scans in the standard natural history protocol.

Evaluation of Benefits and Risks/Discomforts

There is the potential for direct benefit for patients participating in this study if the study results show ^{18}F-DOPA PET/CT imaging to be more accurate than the current standard ^{68}Gallium-DOTATATE at detecting primary lesions or metastasis. The future application of ^{18}F-DOPA imaging modality in other patients could lead to early detection of solid gastrointestinal or pancreatic lesions and metastatic lesions, which would improve early management of these lesions and potentially have an impact on the overall course of the disease.

Most complications are expected to be minor and require no treatment. There may be some discomfort associated with lying on the hard imaging table for the duration of the study. Risks and discomforts include the discomfort of an IV placement and the theoretical effects of the amount of additional radiation

exposure. However, exposure to ionizing radiation is considered by the radiation safety committee (RSC) and quantified in the accompanying NIH Form 88-23. The RSC has determined that this substudy involves greater than minimal risk to the subject due to the research-related radiation of the ^{68}Ga-DOTATATE, ^{18}F-DOPA and PET/CT imaging.

[^{18}F]-DOPA and ^{68}Ga-DOTATATE has been used at the NIH in several clinical protocols. They are investigational agents approved by the FDA for use under IND #35513 and 119098, respectively (IND Sponsor is NIH Clinical Center). Carbidopa is a peripheral decarboxylase inhibitor with little or no pharmacological activity when given alone as a single dose of 200 mg as indicated for this procedure.

The effective radiation dose for adults per PET/CT scan with 5.0 mCi of ^{68}Ga-DOTATATE administered is 0.91 rem per year. The effective radiation dose for adults per PET/CT scan with 12.0 mCi of ^{18}F-DOPA is administered is 1.4 rem per year. The cumulative research dose is below the maximum of 5.0 rem per year recommended by the radiology safety guidelines for adult research subjects. In this study, the subject will be required to lie still on his back for around 30 minutes during image acquisition in the PET/CT scanner, and this might produce some discomfort.

Data Sharing, Use, and Storage:
The same policies and procedures for data sharing, use, and storage described in the main protocol pages 20-22 will apply to this substudy.

Reporting of Adverse Events
IRB reporting will follow the same guidelines as the original protocol. In addition, if either the ^{68}Ga-DOTATATE or ^{18}F-DOPA radiotracer does not pass quality control by the manufacturer (external or NIH facility) and the scan needs to be cancelled, this information will be relayed to the IRB at the time of the continuing review.

IND SPONSOR REPORTING CRITERIA

Unanticipated problems, adverse events and protocol deviations will also be reported to the IRB and the Clinical Director as outlined in the main protocol on page 21, consistent with SOP 16.
Expedited Adverse Event Reporting Criteria to the IND Sponsor
An investigator must **immediately** report to the sponsor using the mandatory MedWatch form 3500a, any serious adverse event whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.
Study endpoints that are serious adverse events (e.g. all-cause mortality) will be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Expedited Adverse Event Reporting Criteria to the IND Manufacturer.

Investigators will submit reports of all SAEs, regardless of attribution to RPS within 24 hours of learning of the events. For initial SAE reports, Investigators should record all case details that can be gathered within 24 hours on a SAE Report Form and submit the report via fax to:

Research Pharmaceutical Services (RPS) Drug Safety
Fax Number: (800) 516-5542 or (+ 1) 484 533-2817
Relevant follow-up information should be submitted to RPS's Drug Safety Department as soon as it becomes available and/or upon request.
IND Safety Reports to the FDA (Refer to 21 CFR 312.32)
The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.
The Sponsor is responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendar days after receiving the request.
FDA Annual Reports (Refer to 21 CFR 312.33)
The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

STATISTICAL CONSIDERATIONS

Sample size

The primary goal of this study is to identify patients whose primary, unknown or metastatic lesions are characterized by SSTR2 expression documented by ^{68}Ga-DOTATATE uptake compared to ^{18}F-DOPA PET/CT. The anticipated recruitment time for the study will be 5 years. The total number of patients per year is expected to be 250.

Bibliography

1. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science (New York, NY) 1997;276:404-7.
2. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). The Journal of clinical endocrinology and metabolism 2012;97:2990-3011.
3. Gibril F, Chen YJ, Schrump DS, et al. Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. The Journal of clinical endocrinology and metabolism 2003;88:1066-81.
4. Norton JA, Krampitz G, Zemek A, Longacre T, Jensen RT. Better Survival But Changing Causes of Death in Patients With Multiple Endocrine Neoplasia Type 1. Annals of surgery 2015;261:e147-8.
5. Goudet P, Murat A, Binquet C, et al. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World journal of surgery 2010;34:249-55.
6. Goudet P, Dalac A, Le Bras M, et al. MEN1 disease occurring before 21 years old: a 160-patient cohort study from the Groupe d'etude des Tumeurs Endocrines. The Journal of clinical endocrinology and metabolism 2015;100:1568-77.
7. Scoazec JY, Couvelard A. [The new WHO classification of digestive neuroendocrine tumors]. Annales de pathologie 2011;31:88-92.
8. Pape UF, Jann H, Muller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer 2008;113:256-65.
9. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:3063-72.
10. Ito T, Jensen RT. Molecular imaging in neuroendocrine tumors: recent advances, controversies, unresolved issues, and roles in management. Current opinion in endocrinology, diabetes, and obesity 2017;24:15-24.
11. Triponez F, Dosseh D, Goudet P, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Annals of surgery 2006;243:265-72.
12. van Essen M, Sundin A, Krenning EP, Kwekkeboom DJ. Neuroendocrine tumours: the role of imaging for diagnosis and therapy. Nature reviews Endocrinology 2014;10:102-14.
13. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2014;55:1598-604.
14. de Laat JM, Tham E, Pieterman CR, et al. Predicting the risk of multiple endocrine neoplasia type 1 for patients with commonly occurring endocrine tumors. European journal of endocrinology 2012;167:181-7.
15. Dromain C, de Baere T, Lumbroso J, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:70-8.
16. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. European journal of nuclear medicine 2001;28:836-46.
17. Veenstra MJ, de Herder WW, Feelders RA, Hofland LJ. Targeting the somatostatin receptor in pituitary and neuroendocrine tumors. Expert opinion on therapeutic targets 2013;17:1329-43.
18. de Herder WW, Hofland LJ, van der Lely AJ, Lamberts SW. Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. Endocrine-related cancer 2003;10:451-8.
19. Koopmans KP, Neels ON, Kema IP, et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. Critical reviews in oncology/hematology 2009;71:199-213.

20. Alexander HR, Fraker DL, Norton JA, et al. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. Annals of surgery 1998;228:228-38.
21. Reubi JC, Schar JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. European journal of nuclear medicine 2000;27:273-82.
22. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. Journal of medical imaging and radiation oncology 2012;56:40-7.
23. Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2010;51:875-82.
24. FDA. NETSPOT Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf2016.
25. Lastoria S, Marciello F, Faggiano A, et al. Role of (68)Ga-DOTATATE PET/CT in patients with multiple endocrine neoplasia type 1 (MEN1). Endocrine 2016;52:488-94.
26. Sadowski SM, Millo C, Cottle-Delisle C, et al. Results of (68)Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1. Journal of the American College of Surgeons 2015;221:509-17.
27. Albers MB, Librizzi D, Lopez CL, et al. Limited Value of Ga-68-DOTATOC-PET-CT in Routine Screening of Patients with Multiple Endocrine Neoplasia Type 1. World journal of surgery 2017;41:1521-7.
28. Froeling V, Elgeti F, Maurer MH, et al. Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia. Annals of nuclear medicine 2012;26:738-43.
29. Schraml C, Schwenzer NF, Sperling O, et al. Staging of neuroendocrine tumours: comparison of [(6)(8)Ga]DOTATOC multiphase PET/CT and whole-body MRI. Cancer imaging : the official publication of the International Cancer Imaging Society 2013;13:63-72.
30. Sadowski SM, Neychev V, Millo C, et al. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:588-96.
31. Singh Ospina N, Thompson GB, C. Nichols F r, Cassivi SD, Young WF, Jr. Thymic and Bronchial Carcinoid Tumors in Multiple Endocrine Neoplasia Type 1: The Mayo Clinic Experience from 1977 to 2013. Hormones & cancer 2015;6:247-53.
32. Mizutani G, Nakanishi Y, Watanabe N, et al. Expression of Somatostatin Receptor (SSTR) Subtypes (SSTR-1, 2A, 3, 4 and 5) in Neuroendocrine Tumors Using Real-time RT-PCR Method and Immunohistochemistry. Acta histochemica et cytochemica 2012;45:167-76.
33. Leotlela PD, Jauch A, Holtgreve-Grez H, Thakker RV. Genetics of neuroendocrine and carcinoid tumours. Endocrine-related cancer 2003;10:437-50.
34. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. European journal of nuclear medicine and molecular imaging 2003;30:781-93.
35. Kwekkeboom DJ, Krenning EP, Lebtahi R, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology 2009;90:220-6.
36. Addeo P, Poncet G, Goichot B, et al. The Added Diagnostic Value of (18)F-Fluorodihydroxyphenylalanine PET/CT in the Preoperative Work-Up of Small Bowel Neuroendocrine Tumors. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2017.

37. Haug A, Auernhammer CJ, Wangler B, et al. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. European journal of nuclear medicine and molecular imaging 2009;36:765-70.
38. Nakuz TS, Berger E, El-Rabadi K, et al. Clinical Value of (18)F-FDOPA PET/CT With Contrast Enhancement and Without Carbidopa Premedication in Patients with Insulinoma. Anticancer research 2018;38:353-8.
39. Imperiale A, Bahougne T, Goichot B, Bachellier P, Taieb D, Namer IJ. Dynamic 18F-FDOPA PET Findings After Carbidopa Premedication in 2 Adult Patients With Insulinoma-Related Hyperinsulinemic Hypoglycemia. Clinical nuclear medicine 2015;40:682-4.
40. Imperiale A, Sebag F, Vix M, et al. 18F-FDOPA PET/CT imaging of insulinoma revisited. European journal of nuclear medicine and molecular imaging 2015;42:409-18.
41. Koopmans KP, de Vries EG, Kema IP, et al. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. The Lancet Oncology 2006;7:728-34.
42. Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:1489-95.
43. Putzer D, Gabriel M, Kendler D, et al. Comparison of (68)Ga-DOTA-Tyr(3)-octreotide and (18)F-fluoro-L-dihydroxyphenylalanine positron emission tomography in neuroendocrine tumor patients. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So 2010;54:68-75.
44. Minn H, Kemppainen J, Kauhanen S, Forsback S, Seppanen M. 18F-fluorodihydroxyphenylalanine in the diagnosis of neuroendocrine tumors. PET clinics 2014;9:27-36.
45. Amodru V, Guerin C, Delcourt S, et al. Quantitative (18)F-DOPA PET/CT in pheochromocytoma: the relationship between tumor secretion and its biochemical phenotype. European journal of nuclear medicine and molecular imaging 2018;45:278-82.
46. Castinetti F, Kroiss A, Kumar R, Pacak K, Taieb D. 15 YEARS OF PARAGANGLIOMA: Imaging and imaging-based treatment of pheochromocytoma and paraganglioma. Endocrine-related cancer 2015;22:T135-45.
47. Santhanam P, Taieb D. Role of (18) F-FDOPA PET/CT imaging in endocrinology. Clinical endocrinology 2014;81:789-98.
48. Agarwal R, Szalkiewicz ER, Warner RR, et al. Multiple endocrine neoplasia type 1 associated with a new mutation in the menin gene and a midgut neuroendocrine tumor. Pancreas 2014;43:145-6.
49. Gortz B, Roth J, Krahenmann A, et al. Mutations and allelic deletions of the MEN1 gene are associated with a subset of sporadic endocrine pancreatic and neuroendocrine tumors and not restricted to foregut neoplasms. The American journal of pathology 1999;154:429-36.
50. Duh QY, Hybarger CP, Geist R, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. American journal of surgery 1987;154:142-8.
51. Simonds WF, Varghese S, Marx SJ, Nieman LK. Cushing's syndrome in multiple endocrine neoplasia type 1. Clinical endocrinology 2012;76:379-86.
52. Marini F, Giusti F, Fossi C, et al. Multiple endocrine neoplasia type 1: analysis of germline MEN1 mutations in the Italian multicenter MEN1 patient database. Endocrine 2018.
53. Agarwal SK. The future: genetics advances in MEN1 therapeutic approaches and management strategies. Endocrine-related cancer 2017;24:T119-t34.
54. de Laat JM, Pieterman CR, Weijmans M, et al. Low accuracy of tumor markers for diagnosing pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 patients. The Journal of clinical endocrinology and metabolism 2013;98:4143-51.
55. Virgolini I, Ambrosini V, Bomanji JB, et al. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. European journal of nuclear medicine and molecular imaging 2010;37:2004-10.