Flurpiridaz F-18 PET/CT Imaging for detecting Parathyroid Adenomas in patients with Primary Hyperparathyroidism

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Study Summary

Title	Flurpiridaz F-18 PET/CT Imaging for detecting Parathyroid Adenomas in patients with Primary Hyperparathyroidism
Short Title	Flurpiridaz F-18 PET/CT for Parathyroid Imaging
Protocol Number	*859544 (25-1796)*
Study Design	Study of Flurpiridaz F-18 PET/CT as a diagnostic imaging tool to detect abnormal parathyroid glands in patients with primary hyperparathyroidism, prior to multi-parathyroid gland surgical exploration. Patients with known or suspected parathyroid adenomas will be eligible for this study. Comparisons of diagnostic performance using Flurpiridaz F-18 PET/CT versus standard of care dual time point sestamibi SPECT/CT imaging will be tested.
Study Center(s)	University of Pennsylvania
Objectives	**Primary Objective:** To estimate and compare sensitivity of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT **Secondary Objective:** To estimate and compare specificity, NPV, PPV of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT. **Tertiary Objectives** • To measure the uptake of F-18 Flurpiridaz in parathyroid adenomas . • To evaluate the safety of Flurpiridaz F-18 by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 during study reporting period. • To compare imaging quality and lesion detectability across multiple PET/CT acquisition and reconstruction conditions, including: (1) imaging data from long-axis field-of-view PET/CT scanners versus simulated standard field-of-view scanners using subsampled datasets; and (2) reconstructed datasets acquired in ultra-high-sensitivity mode versus high-sensitivity mode.
Number of Subjects	Up to 20 evaluable subjects

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Diagnosis and Main Inclusion Criteria	**Inclusion Criteria** 1. Adult patients, at least 18 years of age 2. History of primary hyperparathyroidism as clinically confirmed by serum laboratory values of elevated calcium levels (>10.2 mg/dl) and abnormal or inappropriately normal parathyroid hormone concentrations (normal range: 15 to 65 pg/ml). 3. Participants must be informed of the investigational nature of this study and provide written informed consent in accordance with institutional and federal guidelines prior to study-specific procedures. 4. Participants must have had prior SPECT/CT sestamibi parathyroid imaging within 6 months of this investigational study or planned SPECT/CT sestamibi parathyroid imaging scheduled prior to this investigational study. 5. Planned surgery within 6 months following this investigational study. **Exclusion Criteria** 1. Females who are pregnant or breast feeding at the time of the PET/CT scan will not be eligible for this study; a urine pregnancy test will be performed in women of child-bearing potential (as self-reported by menstrual history) before the injection of radiotracer. 2. Inability to tolerate imaging procedures, including but not limited to claustrophobia, inability to remain still during scanning, or any other condition that, in the judgment of the investigator or treating physician, would interfere with safe or adequate imaging. 3. Serious or unstable medical or psychological conditions that, in the opinion of the investigator would compromise the subject's safety or successful participation in the study.
Study Product	Flurpiridaz F-18 also known as FLYRCADO™
Statistical Methodology	This is an exploratory study of 20 patients. For continuous variables, we will generate graphs and descriptive statistics (e.g., means, standard deviations, medians and inter-quartile range). Categorical variables will be described by frequencies, proportions and 95% exact confidence intervals. Wilcoxon matched pairs signed rank test will be used to compare SUVs at various imaging time points. Spearman correlation will be used to evaluate the association between radiotracer uptake and histologic, laboratory variables.

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STUDY SCHEMA

Screening (Day-180 to 0)	Recruitment (in-person or via phone), Screen potential participants by inclusion and exclusion criteria; Obtain medical history including history of prior or planned dual-time point sestamibi SPECT/CT imaging within 6 months of enrollment.
Enrollment (Day 0)	Obtain Informed consent after confirming eligibility
Day 0 to Day 90	F-18 Flurpiridaz Parathyroid PET/CT imaging
Day 91 to Day 270	Surgery: Parathyroid Gland Exploration within 6 months following PET/CT imaging
Day 271 to Day 360	Histopathologic results and Postoperative serum parathyroid hormone and calcium level 8-12 weeks after surgery

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Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1 Background

1.1 Rationale

Primary hyperparathyroidism (PHPT) is a prevalent endocrine disorder characterized by elevated calcium levels and abnormal or inappropriately normal parathyroid hormone concentrations. The leading cause of PHPT is a single parathyroid adenoma (80-85%), followed by multiple adenomas (10-15%). Parathyroidectomy is the definitive treatment, yet preoperative localization remains challenging, particularly with the increasing prevalence of subclinical or asymptomatic PHPT, often associated with small or mildly hyperfunctioning glands. Precise pre-surgical localization of pathologic parathyroid tissue, including ectopic and supernumerary parathyroid tissue, has become increasingly crucial due to the shift from bilateral neck exploration to minimally invasive or focused parathyroidectomy in recent decades.

Imaging studies commonly used for localizing hyperfunctioning parathyroid tissue include ultrasound, dynamic contrast enhanced ("4D") CT/MRI, and 99mTc-sestamibi parathyroid scintigraphy. However, these techniques often fail to accurately locate the adenoma, potentially delaying access to curative surgery and increasing the risk of surgical failure. In some cases, up to 20% of cases may have a pathologic parathyroid gland undetected by conventional sonography or scintigraphy[1]. Recently, PET/CT imaging with 18F-fluorocholine has gained traction in the detection and correct localization of hyperfunctioning parathyroid glands. A growing body of evidence demonstrates multiple advantages of PET/CT imaging over conventional imaging techniques[2,3,4]. These advantages include higher spatial resolution, which enhances the detectability of small parathyroid lesions[5]. Furthermore, PET/CT demonstrates superior accuracy in detecting lesions in challenging scenarios, such as in patients with prior failed localization by conventional imaging[6,7], recurrence after surgery[8], normocalcemic PHPT[9], MEN-1-related PHPT[10], and coexisting thyroid disease[5]. A significant advantage of PET/CT is shorter imaging time accompanied with workflow efficiency, which can save as much four hours per patient[11]. Another notable benefit of PET is the lower radiation exposure, with an estimated effective dose of 2.8 mSv compared to 6.8 – 7.4 mSv for planar and SPECT imaging[12]. These factors translate to improved patient access and outcomes including potentially higher surgical success rates.

Conventional SPECT/CT parathyroid imaging leverages the fact that Tc-99m sestamibi is taken up by cells with high concentration of mitochondria, including in myocardial tissue and parathyroid adenomas[13]. Similarly, a relatively new PET tracer, Flurpiridaz F-18 PET/CT, binds to mitochondrial complex 1, located at the mitochondrial membrane of cardiomyocytes, providing excellent imaging of myocardial blood flow in the detection and evaluation of coronary artery disease[14,15]. Flurpiridaz F-18 PET/CT was approved by the FDA for myocardial perfusion imaging in 2024.

Given the similar mechanistic binding and action of both Tc-99m sestamibi and Flurpiridaz F-18 within mitochondrial rich cells, Flurpiridaz F-18 could be a potential radiotracer to detect parathyroid adenomas. Histologically, parathyroid adenomas are composed of primarily chief cells, and to a lesser extent oxyphil cells[16]. Oxyphil cells, rich in mitochondria, accumulate

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mitochondrial DNA mutations affecting mitochondrial complex 1 genes, particularly in parathyroid adenomas[16]. Altogether, data from literature indicate that Flurpiridaz F-18 uptake in oxyphil cells may provide a method to molecularly target and image parathyroid adenomas. Recent developments have shown promising results. The only publication on this topic demonstrated successful localization of parathyroid adenomas using Flurpiridaz F-18 PET/CT imaging[17]. In this retrospective study, the authors reported that Flurpiridaz F-18 PET/CT identified parathyroid adenomas in 91% of patients with primary hyperparathyroidism and allowed for successful localization of adenomas in 80% of patients with negative conventional Tc-99m sestamibi SPECT/CT scans[17.]

In this study, we propose estimating the sensitivity of Flurpiridaz-18 PET/CT in detecting parathyroid adenomas in patients with primary hyperparathyroidism in comparison with standard of care dual time-point 99mTc sestamibi SPECT/CT imaging. In addition, we will measure the uptake of Flurpiridaz F-18 in parathyroid adenomas . We hypothesize that Flurpiridaz F-18 PET/CT imaging will be able to detect parathyroid adenomas in patients with primary hyperparathyroidism, and with higher sensitivity compared to 99mTc sestamibi SPECT/CT imaging.

1.2 Dose Rationale and Risk/Benefit Assessment

Flurpiridaz F-18 (FLYRCADO™) is an FDA approved radiopharmaceutical approved for use in adult patients with known or suspected coronary artery disease (CAD) to evaluate for myocardial ischemia and infarction. The safety, tolerability, pharmacokinetic (PK) properties and radiation dosimetry of Flurpiridaz F-18 have been investigated in a phase 1 first in human study of 12 adult patients[18]. In that study, each subject received from 1 to 3 mL IV bolus injection targeted to deliver approximately no more than 8 mCi. The doses were administered in less than 10 seconds, followed immediately by a 3 to 5 mL saline flush. All dose levels were found to be safe. No drug-related adverse events were reported in any of the 12 subjects. Dosimetry was performed on all 12 subjects, with an effective radiation dose (ICRP 103) ranging from 0.015-0.024 mSv/MBq with a mean of 0.019 mSv/MBq. In this study, we will administer a dose of 2.5mCi (± 20%) of Flurpiridaz F-18 to each patient. This dosing is consistent with commercially available doses and dosimetry data.

Risk/Benefit

Participants will undergo a single intravenous injection of Flurpiridaz F-18 and one PET/CT scan for the purposes of this study. Flurpiridaz F-18 is a positron emitting radiopharmaceutical. As such, it poses an intrinsic radiation exposure risk. However, when administered in low tracer doses as a PET imaging agent, as described in this protocol, this risk is felt to be small.

Flurpiridaz F-18 is a PET imaging agent approved for use in cardiac perfusion imaging. The potential side effects and adverse reactions reported in the drug package insert are primarily related to the fact that this agent is used as part of cardiac stress imaging. The side effects and adverse reactions include dyspnea, headache, angina pectoris, chest pain, fatigue, ST segment changes, flushing, nausea, abdominal pain, dizziness, arrhythmia, diarrhea, palpitations, back pain, cardiac conduction disturbance, rash, dysgeusia, cough, hypotension, anxiety, vomiting, pruritus, bronchospasm, dry mouth, blood pressure elevation, syncope, and wheezing. Previous safety analysis of Flurpiridaz F-18 has reported that all adverse reactions were unrelated to the drug itself and were instead related to the cardiac stress imaging agent. No cardiac stress

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imaging will be performed as part of this study. Hence, these risks are not applicable to our current study

In addition to the radioactive Flurpiridaz F-18 tracer, a low-dose CT from the skull-base, neck chest, abdomen, pelvis and thighs is typically performed with the PET/CT scan for the purpose of anatomical registration and attenuation correction of PET images; the risk from this low-dose CT is also felt to be small. The organ and total body doses associated with Flurpiridaz F-18 PET/CT imaging are felt to be comparable to those associated with other clinical F-18 labeled diagnostic agents.

PET/CT imaging
This research involves exposure to radiation that could affect a fetus or pregnant woman, or breast-feeding baby. Due to this risk, menopausal status, pregnancy and breast-feeding status will be queried prior to scheduling of the scan and on the day of the scan prior to injection. Women of childbearing potential will have a urine pregnancy test performed prior to injection on the day of the scan. This is a short-lived radiotracer that has very low risk of any risk to a fetus conceived more than a day after administration. No specific contraception is required, and incidental pregnancies will not be tracked or followed.

There is potential with intravenous injections, including Flurpiridaz F-18, for allergic reactions. The dose will be delivered intravenously by skilled clinical professionals and subjects will be monitored for any signs or symptoms of allergic reaction by trained personnel during the PET procedure. Symptoms of an allergic reaction could include hives, shortness of breath or difficulty breathing.

Venous cannulation is a routine clinical procedure that carries minimal risks when performed by trained personnel. It is possible that bruising, dizziness or fainting could occur in some subjects. There is a risk of phlebitis or infection, which is very remote.

The PET/CT scan takes place in a small, enclosed space and therefore can be uncomfortable for some people with claustrophobia or musculoskeletal disorders (such as arthritis). Subjects will be made as comfortable as possible and PET technologists and study personnel will be available throughout the imaging to address any discomfort. The subject will be allowed to get off the table between the described imaging segments as necessary. No psychological, social or legal risk is expected. While loss of confidentiality is possible, it is felt to be very unlikely due to the small number of professionals involved in the study with knowledge of this information. All clinicians and research staff involved are well trained in HIPAA practices.

Incidental Findings
It is possible that during the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel, and the PI will determine if the patient and referring physician should be informed. These possible finding(s) may or may not be significant and may lead to anxiety about a condition and to further work-up by the subject's physician.

There is no anticipated benefit to study subjects because of their participation in this study. There is potential benefit to general society if Flurpiridaz F-18 PET/CT proves to be a useful imaging agent for detecting parathyroid adenomas.

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2 Study Objectives

Primary Objective:

To estimate and compare sensitivity of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT

Secondary Objective:

To estimate and compare specificity, NPV, PPV of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT.

Tertiary Objectives

• To measure the uptake of F-18 Flurpiridaz in parathyroid adenomas .
• To evaluate the safety of Flurpiridaz F-18 by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 during study reporting period.
• To compare imaging quality and lesion detectability across multiple PET/CT acquisition and reconstruction conditions, including: (1) imaging data from long-axis field-of-view PET/CT scanners versus simulated standard field-of-view scanners using subsampled datasets; and (2) reconstructed datasets acquired in ultra-high-sensitivity mode versus high-sensitivity mode.

3 Study Design

This is a single institution, single-arm, paired-design, prospective diagnostic accuracy study of Flurpiridaz F-18 PET/CT as an imaging strategy to detect parathyroid adenomas in pre-surgical patients with primary hyperparathyroidism in comparison to standard of care imaging with dual time-point Tc-99m sestamibi SPECT/CT imaging.

Patients with primary hyperparathyroidism and are at least 18 years of age may be eligible. All participants will be receiving care at the clinical practices of the University of Pennsylvania. Patients will be approached about study participation regardless of race or ethnic background. We anticipate enrolling up to 20 evaluable participants with primary hyperparathyroidism who meet eligibility requirements for this study. Accrual is estimated to occur over approximately 1 year.

After reviewing patient medical records and verifying eligibility for study participation, subjects will be scheduled to undergo a Flurpiridaz F-18 PET/CT scan. For the study, subjects will be injected with Flurpiridaz F-18 and will undergo PET/CT imaging post injection.

Study imaging will be performed using a long-axis field of view PET/CT scanner. For each PET scan, dynamic images from the skull-base to thighs will be acquired over approximately 60 minutes. The protocol will be performed under the regulatory approval of the IRB (Institutional Review Board) and FDA. Each patient will receive 2.5 mCi (± 20%) of Flurpiridaz F-18 intravenously.

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4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Adult patients, at least 18 years of age
2. History of primary hyperparathyroidism as clinically confirmed by serum laboratory values of elevated calcium levels (>10.2 mg/dl) and abnormal or inappropriately normal parathyroid hormone concentrations (normal range: 15 to 65 pg/ml).
3. Participants must be informed of the investigational nature of this study and provide written informed consent in accordance with institutional and federal guidelines prior to study-specific procedures.
4. Participants must have had prior SPECT/CT sestamibi parathyroid imaging within 6 months of this investigational study or planned SPECT/CT sestamibi parathyroid imaging scheduled prior to this investigational study.
5. Planned surgery within 6 months following this investigational study.

4.2 Exclusion Criteria

1. Females who are pregnant or breast feeding at the time of the PET/CT scan will not be eligible for this study; a urine pregnancy test will be performed in women of child-bearing potential (as self-reported by menstrual history) before the injection of radiotracer.
2. Inability to tolerate imaging procedures, including but not limited to claustrophobia, inability to remain still during scanning, or any other condition that, in the judgment of the investigator or treating physician, would interfere with safe or adequate imaging.
3. Serious or unstable medical or psychological conditions that, in the opinion of the investigator would compromise the subject's safety or successful participation in the study.

Only individuals (aged 18 or over) who can understand and give informed consent will be eligible to participate in this study. All subjects must be able to give informed consent. We will not be using specific methods to assess decisional capacity. Economically disadvantaged persons will not be vulnerable to undue influence, as this study offers no compensation. All individuals will be told that their choice regarding study participation will in no way change their access to clinical care. This should negate any undue influence or coercion. Children, fetuses, neonates, or prisoners are not included in this research study.

4.3 Subject Recruitment and Screening

Patients will generally be offered enrollment at the time of their office visits to endocrinology or surgical oncology clinics at the Hospital of the University of Pennsylvania or will be contacted by phone, email or MyPennMedicine message by the investigator or study personnel to discuss the study.

Study personnel or an investigator will present the patient with information regarding the study and enrollment. Following confirmation of eligibility for participating in this study, a member of the study staff or investigator will provide potential subjects with a copy of the consent form. If a potential subject is not able to meet in person prior to the day of the planned imaging study then study staff or an investigator will call or email the potential subject to review the study, they will explain the study procedures, provide detailed information about potential risks and benefits of participating in the study and confirm the patient's understanding of the research protocol. Any questions the subject has will be answered fully. If the patient confirms they are interested in participating in the study, verbal agreement for the scheduling of the imaging study and ordering

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the investigational product will be obtained by the study personnel during the phone call or by email or MPM. This verbal/email agreement for scheduling will be documented. The study personnel or investigator will emphasize that participation in the study is voluntary and that the study participant may choose to withdraw from this study at any time without jeopardizing current or future treatment.

Written informed consent will be obtained in person prior to any study specific procedures being performed and an additional supplemental consent page, specific to the administration of the investigational radiopharmaceutical, will be reviewed and signed on the day of the F-18 Flurpiridaz administration. All patients being considered for the study and eligible for screening must sign an informed consent for the study prior to any study specific procedures. All patients must have clinical standard of care imaging- dual time-point parathyroid SPECT/CT with Tc-99m sestamibi within 6 months prior to this Flurpiridaz F-18 PET/CT study. Other imaging including parathyroid ultrasound, 4D parathyroid CT or MR of the neck may be ordered at the discretion of the treating physician. This Flurpiridaz F-18 PET/CT imaging study is not a substitute for clinical standard of care imaging. Following confirmation of eligibility for this imaging study, patients will undergo Flurpiridaz F-18 PET/CT scan.

Information related to demographics will be collected from the medical record, including date of birth, age, gender, race and ethnicity. General medical history, current medications and dates and information related to primary diagnosis of hyperparathyroidism, imaging and other lab results related to diagnosis.

4.4 Subject Withdrawal

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be discontinued from the study. A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, at any time, at either the investigator's discretion or the subject's request, an effort must be made to document the reason(s) why a subject fails to return to the study clinic for necessary visits or is discontinued from the study. The primary reason for discontinuing participation in the study may include, but is not limited to, one of the following:

- Withdrawal of consent for imaging protocol by patient.
- Noncompliance with protocol, e.g., the patient fails to appear at one or more imaging procedures.
- Development of an intercurrent illness, injury, or medical condition likely to interfere with subject safety, the overall assessment, or the required administration of study tracer.
- Development of any condition for which the investigator feels study withdrawal is justified.
- Termination of the study.

Follow-up information will be obtained for subjects who discontinue the study if possible.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit,

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every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The investigator may retain and continue to use any data collected before such withdrawal of consent.

5 Study Drug

5.1 Description (Flurpiridaz F-18)

FLYRCADO™ (Flurpiridaz F 18) injection is an FDA approved radioactive diagnostic drug indicated for positron emission tomography (PET) myocardial perfusion imaging (MPI) under rest or stress (pharmacologic or exercise) in adult patients with known or suspected coronary artery disease (CAD) to evaluate for myocardial ischemia and infarction. Flurpiridaz F-1, chemically Flurpiridaz F 18 is 2-tert-butyl-4-chloro-5-[[4-(2-(18F)fluoranylethoxymethyl)phenyl]methoxy]pyridazin-3-one, is a radiotracer with high affinity binding to mitochondrial complex 1. Given the similar mechanistic binding and action of both Tc-99m sestamibi and Flurpiridaz F-18 within mitochondrial rich cells, we postulate that the Flurpiridaz F-18 can be used to detect parathyroid adenomas.

The safety, tolerability, pharmacokinetic properties, and radiation dosimetry of Flurpiridaz F-18 have been investigated and reported in 12 adult patients. All dose levels were found to be safe; no drug-related adverse events were reported in any of the 12 subjects.

5.2 Receipt of Study Drug (Flurpiridaz F-18)

The dose will be delivered by an available commercially licensed radiopharmacy to the investigational site's hot lab in the Nuclear Medicine Department. Upon receipt, qualified personnel will ensure that the study drug is delivered in good condition, inventoried, stored properly, labeled and dispensed in compliance with standard hospital procedures, all regulatory agencies. Radioactive drug will only be handled by qualified nuclear medicine staff or physicians.

5.3 Study Drug Administration (Flurpiridaz F-18)

The dose will be measured by qualified personnel in a dose calibrator prior to dispensing. The injectable dose will be 2.5mCi (± 20%) of Flurpiridaz F-18; a lesser dose may be injected if, in the opinion of a Nuclear Medicine Authorized User complete imaging data could be generated. The dispensed dose will be intravenously injected under the supervision of a qualified nuclear medicine personnel as an IV injection. After the dose administration, the qualified personnel will return the syringe for residual measurement. Measured radioactivity values and times of measurement will be documented, as well as the total injected volume.

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6 Study Procedures

STUDY CALENDAR

Procedures	Screening (-180- 0 Days)	Enrollment (Day 0)	Study Imaging with PET/CT (Day 0- Day 90)	Surgery (Day 91 – Day 270)	Post-surgical Histopathology and biochemical values (Day 271- Day 360)
Recruitment (in-person or via phone, email or MPM)	X				
Pre-Screening Phone Questionnaire (if applicable)	X				
History of dual time-point SPECT/CT sestamibi parathyroid scan (extracted from medical record)	X	X			
Informed Consent		X			
Urine Pregnancy Test[1]		X	X		
Flurpiridaz F-18 PET/CT injection			X		
PET/CT scan			X		
Adverse Event Evaluation[2]			X		
Extraction of histopathologic results and clinical labs[3]				X	X

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[1] Urine pregnancy test will be required in women of childbearing potential prior to injection of the radiotracer.
[2]Follow-up may occur by telephone or in person, depending on the participant's schedule. Follow-up should take place the next available business day (i.e., not a weekend or a holiday). The AE monitoring period is 24 hours following the Flurpiridaz F18 injection. AE's only refer to those potentially attributed to the PET/CT scans, not those related to underlying disease or therapy.
[3]Pathology results (within 6 months of PET/CT scan) and clinical laboratory results (parathyroid hormone and calcium within 8-12 weeks post-surgery) will be collected from the medical record.

6.1 *Recruitment*

Eligible potential subjects will be identified through screening of medical charts or through direct referrals from treating physicians. Following confirmation of eligibility for participating in this study, a member of the study staff or investigator will provide potential subjects with a copy of the consent form. If a potential subject is not able to meet in person prior to the day of the planned imaging study then study staff or an investigator will call or email the potential subject to review the study, they will explain the study procedures, provide detailed information about potential risks and benefits of participating in the study and confirm the patient's understanding of the research protocol. Any questions the subject has will be answered fully. If the patient confirms they are interested in participating in the study, verbal agreement for the scheduling of the imaging study and ordering the investigational product will be obtained by the study personnel during the phone call or by email or MPM. This verbal/email agreement for scheduling will be documented. The study personnel or investigator will emphasize that participation in the study is voluntary and that the study participant may choose to withdraw from this study at any time without jeopardizing current or future treatment. Written informed consent will be obtained in person prior to any study specific procedures being performed and an additional supplemental consent page, specific to the administration of the investigational radiopharmaceutical, will be reviewed and signed on the day of the Flurpiridaz administration.

6.2 Pre-imaging Assessment

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the regulatory sponsor. The sponsor and IRB must review the informed consent form used during the informed consent process, and it must be available for inspection.

Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

Patients must have standard of care imaging prior to the study, as part of standard medical care by a treating physician. At a minimum, research subjects must have parathyroid SPECT/CT with Tc-99m sestamibi. Other imaging including neck ultrasound, 4D parathyroid CT or MR of the neck may be ordered at the discretion of the treating physician.

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The following additional patient data may be self-reported by the patient or obtained from medical chart review: demographics (including gender, date of birth and race), menopausal status, year of diagnosis, previous treatment history, radiology results, and other relevant medical history.

6.3 Flurpiridaz F-18 Administration and PET/CT Scan Visits

The following procedures will be done on the day of the Flurpiridaz F-18 PET/CT scan:

- Weight and height will be recorded.
- Urine pregnancy test performed for women of childbearing potential
- IV placed
- Injection of 2.5mCi (± 20%) of Flurpiridaz F-18
- One Flurpiridaz F-18 PET/CT exam will be performed

PET/CT imaging procedure:
After obtaining weight, height, and urine pregnancy test (for women of childbearing potential), one intravenous (IV) line will be placed per patient.

Prior to positioning on the PET/CT scanner, the patient will be allowed to use the restroom The patient will be positioned on the PET/CT scanner. A low-dose CT scan will be acquired according to standard PET/CT imaging procedures. This CT scan is used for attenuation correction and anatomical localization of findings in the PET scan.

A dose of 2.5 mCi (± 20%) of Flurpiridaz F-18 will be infused by bolus injection. A lesser activity may be injected if, in the opinion of a nuclear medicine authorized user, complete imaging data could be generated.
Patients will undergo dynamic PET imaging for approximately 60 minutes from the skull-base to thighs. All images will be reconstructed using standard reconstruction techniques.

Adverse events will be recorded for the period up to 24 hours post PET scan. Research personnel will conduct follow up by telephone or in person, depending on the subject's schedule. Follow-up should take place the next available business day (i.e. not a weekend or a holiday).

Clinical Follow-Up for correlative findings
Pathology results will be collected from the medical record if surgical intervention occurs within 6 months of the PET/CT scan. If the patient undergoes surgery, then clinical laboratory results for parathyroid hormone and/or calcium will be collected from the medical records if they are available approximately 8-12 weeks after surgery.

Measures to Minimize Bias
This study does not involve randomization. Flurpiridaz F-18 PET/CT scan and results will be available to the patients, pathologists and surgeons prior to surgery. Study team will be blinded to the results of prior standard of care imaging during interpretation of PET/CT.

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7 Image Interpretation

Flurpiridaz F-18 PET/CT scans will be interpreted both **qualitatively** and **quantitatively**.

Qualitative interpretation of uptake will be recorded as positive, negative, or mixed, as defined below:

- Qualitative Positive – All known lesions show uptake visible above background.
- Qualitative Negative – No known lesions show uptake visible above background.
- Qualitative Mixed – One or more lesions show uptake above background and one or more lesions do not show uptake above background.

Quantitative interpretation of lesional uptake will be recorded as a Standardized Uptake Value (SUV). Max, mean, and peak SUV values will be recorded for a region-of-interest encompassing a single primary lesion. This primary lesion will be the largest measured lesion or will be a lesion that has been sampled for tissue correlation. In addition, the SUV values (max, mean, peak) of several identified lesions will be evaluated.

8 Statistical Considerations

8.1 Design:

This is an exploratory study of Flurpiridaz F-18 PET/CT as an imaging biomarker for detecting parathyroid adenoma in patients with primary hyperparathyroidism. Up to 20 patients will be enrolled.

8.2 Objectives:

Primary Objective:
To estimate and compare sensitivity of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT

Secondary Objective:
To estimate and compare specificity, NPV, PPV of Flurpiridaz F-18 PET/CT imaging in detecting parathyroid adenoma in pre-surgical patients with hyperparathyroidism with that of standard of care imaging dual time-point sestamibi SPECT/CT.

Tertiary Objectives
• To measure the uptake of F-18 Flurpiridaz in parathyroid adenomas.
• To evaluate the safety of Flurpiridaz F-18 by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 during study reporting period.
• To compare imaging quality and lesion detectability across multiple PET/CT acquisition and reconstruction conditions, including: (1) imaging data from long-axis field-of-view PET/CT scanners versus simulated standard field-of-view scanners using subsampled datasets; and (2) reconstructed datasets acquired in ultra-high-sensitivity mode versus high-sensitivity mode.

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8.3 Endpoints:

Primary Endpoint:
Sensitivity

Secondary Endpoint:
Specificity, PPV, NPV.

Tertiary Endpoint:
Visual analysis and quantitative SUV max of parathyroid lesions detected on PET/CT

Reference Standard:

The reference standard is based on histopathology results from parathyroid surgery. Histopathology is the gold standard for diagnosing parathyroid adenoma. Pathologic analysis will examine each gland following multi-gland surgical exploration. Histopathology from multi-gland parathyroid exploration is justified as the reference standard because it is the most direct, objective confirmation of whether each resected gland is truly abnormal and thus provides a gland-level truth against which imaging can be compared. The primary endpoint is gland-level sensitivity, so a reference standard that operates at the same level (per-gland) is required; multi-gland exploration with histologic assessment of all removed glands provides that structure, allowing each imaged focus to be matched to a histologic outcome.

8.4 Plans for Data Analysis:

This is a single institution, single-arm, paired-design, prospective diagnostic accuracy study of Flurpiridaz F-18 PET/CT as an imaging strategy to detect parathyroid adenomas in pre-surgical adult patients with primary hyperparathyroidism in comparison to standard of care imaging with dual time-point Tc-99m sestamibi SPECT/CT imaging. The reference standard is histopathologic results following multi-gland parathyroid surgical exploration. The presence or absence of parathyroid adenoma/hyperplasia on PET/CT will be compared to the reference standard, in order to estimate gland-level sensitivity and specificity.

The primary outcome measure is **gland-level sensitivity**, defined as the proportion of parathyroid glands with histopathologically confirmed adenoma that are correctly identified as abnormal by each imaging modality (Flurpiridaz F-18 PET/CT and 99mTc sestamibi SPECT/CT).

Sensitivity will be estimated as: number of true-positive glands detected by the modality divided by the total number of diseased glands confirmed at pathology, at the gland level separately for each modality and presented with 95% confidence intervals estimated using methods for correlated data to reflect the multiple glands per patient. The sensitivities of the two tests will be compared using McNemar's test adjusted to account for the within-patient clustering.

Results will be summarized in tables showing the number of diseased glands, number correctly detected, sensitivity estimates, and corresponding uncertainty intervals by modality.

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Additionally, data will be collected from the cohort to evaluate image quality, and information on uptake of Flurpiridaz F-18 in parathyroid adenomas. Comparisons will be made to prior SOC imaging. PET/CT images will be evaluated for the presence of elevated radiotracer uptake in the neck and chest exceeding uptake of surrounding background, consistent with parathyroid adenomas. Using data analysis methods established in previous studies in the literature, the results of each PET/CT scan will be rated as negative, equivocal (low intensity uptake or uptake indistinguishable from uptake in the thyroid gland), or positive for hyperfunctioning parathyroid glands. Number and localization (left or right, located near superior or inferior pole of the thyroid, ectopic, or intrathyroidal) of focal lesions will be recorded. Second, peak and maximum standardized uptake values (SUVs) will be measured using a volume-of-interest technique. Additionally, left and right mean thyroid gland SUVs will be measured and then averaged. For calculation of the parathyroid gland uptake to thyroid uptake ratio (P/T ratio), parathyroid gland SUVmax will be divided by thyroid gland SUVmean. Data on patients who subsequently underwent surgical management will be analyzed to assess for correct localization rate of imaging, normalization of serum calcium and PTH levels after parathyroidectomy in the peri-operative setting, as well as serum calcium drawn weeks after surgery. Pathology results will also be used to assess for histologic subtypes of parathyroid adenomas identified at surgery.

8.5 Sample Size Justification:

Based on data in the literature from a metanalysis by Whitman et al (2021), we assume that the sensitivity of dual time point Tc-99m sestamibi SPECT/CT to detect parathyroid adenomas to be approximately 0.8. We hypothesize that the sensitivity of Flurpiridaz F-18 PET/CT will be higher than that of SPECT/CT sestamibi, at least 0.95.
To achieve 80% power using a one-sided 0.5 level Mcnemar's test, we need a sample size of 20 patients. This assumes each patient will contribute on average 4 glands, the correlation between multiple glands is low, about 0.1, that the two imaging tests (PET/CT vs SPECT/CT) are discordant 30% of the time, and that 90% of patients will have a gland with an adenoma .

8.6 Study Duration:

This study will enroll up to a target of 20 evaluable subjects over 1 year.

9 Safety and Adverse Events

9.1 Definitions

Adverse Events are classified as serious or non-serious.
Adverse Events that do not meet the established criteria for Serious Adverse Events (see below) should be regarded as **adverse events**.

Adverse Event
An ***adverse event*** (AE) is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure. It is any symptom, sign, illness or experience that develops or worsens in severity during the study

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procedure. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

A ***serious adverse event*** (SAE) is any Adverse Event that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the investigator's brochure
- An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator's brochure.

Adverse Event Grading

Grade denotes the severity of the AE.
1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

Adverse Event Attribution

Attribution is used to determine whether an AE is related to a study treatment or procedure. Attribution categories are:

Definite: The AE is **clearly related** to a treatment or procedure
Probable: The AE is **likely related** to a treatment or procedure
Possible: The AE **may be related** to a treatment or procedure
Unlikely: The AE is **likely unrelated** to a treatment or procedure
Unrelated: The AE is **clearly not related** to a treatment or procedure

Important Medical Events

Important Medical Events are those events that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject's health and may require medical intervention.

Preexisting Condition

A preexisting condition is a condition that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

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General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-Study Adverse Event
All unresolved adverse events should be followed by the investigator until the event is resolved, or the subject is lost to follow-up.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if the Principal Investigator believes the abnormality is related to participation in the study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be recorded as a serious adverse event. The event should be reported if the Principal Investigator believes the hospitalization is related to participation in the study.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. Since this is an imaging study with no treatment component, the study follow-up is defined as 4 days following the administration of the study radiotracer, Flurpiridaz F-18.

9.2 Recording of Adverse Events

All adverse events occurring during the adverse event reporting period following obtaining written consent at the screening visit through the completion of the post-scan follow up phone call, must be recorded if they are deemed related, unexpected and/or are grade 3 or higher. Adverse events will be recorded for the period up to 24 hours post injection of the radiotracer. Research personnel will conduct safety follow up by telephone or in person, depending on the subject's schedule. Follow up should take place the next available business day (i.e. not a weekend or a holiday). The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the adverse event reporting period must be followed up to determine the final outcome. Any serious adverse event that occurs after the adverse event reporting period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

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(see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study drug Flurpiridaz F-18

9.3.1 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

  Reporting Process

  Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

  Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

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9.4 Medical Monitoring

It is the responsibility of the Principal Investigator, Dr. Babatunde to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive).

All research personnel associated with this study have completed the University of Pennsylvania's Patient Oriented Research Training Program as well as HIPAA Compliance Training. Trained staff will assess eligibility, introduce the study rationale, procedures, study risks, and collect the combined informed consent/HIPAA authorization form. The study team will work to uphold the privacy of the participants in several ways. Communications made among study staff regarding participants will use ID numbers whenever possible and minimize the use of patient name or other identifying information except when necessary for conduct of the study. Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Whenever feasible, identifiers will be removed from study-related information. In data analysis sets, we will use ID numbers and/or patient initials only.

Precautions will be applied to protecting subject privacy and the protected health information detailed below:

1. Name
2. Address
3. Social Security Number
4. Electronic mail addresses
5. Telephone Number
6. Date of Birth
7. Medical Record Number
8. Health Plan ID numbers

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9. Any other unique identifying number, characteristic, or code
10. Current and past medications or therapies
11. Information from a physical examination that generally includes blood pressure reading, heart rate, and temperature
12. Information from the tests and procedures described earlier in this document
13. Previous procedure, diagnosis and treatment information from institutions other than Penn if it relates to study eligibility
14. Emergency contact number, name, and relationship

Data will be accessible to the study investigators, all study staff, Radiation Research Safety Committee members, UPenn IRB and Office of Clinical Research.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the study sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the

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EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject, and the investigator or investigator-designated research professional obtaining the consent.

12 Subject Stipends or Payments

We will pay for the cost of parking for patients parking in the patient garage, if not already covered through the hospital, on the day of the PET/CT scan. We will pay each patient a nominal stipend of $100 for their participation.

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