Amendment

Protocol Number: 03C0145-N **Reference Number:** 373118

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(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: Evaluation of the Natural History and Management of Pancreatic Lesions Associated with Von Hippel-Lindau

SIGNATURES

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Electron Kebebew, MD - applied signature on 10/04/2017 10:25 AM EDT

Accountable Investigator:

PI is the Accountable Investigator

Branch Chief/CC Department Head (**):

Electron Kebebew, MD - applied signature on 08/31/2017 3:14 PM EDT

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N/A

Lead Associate Investigator signature:

N/A

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Joy Zou - applied signature on 09/05/2017 7:34 AM EDT
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Shyni Simon - applied signature on 08/31/2017 1:43 PM EDT

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N/A

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N/A

APPROVALS

IRB Chair:

Michael Hamilton - applied signature on 10/07/2017 3:34 AM EDT

Clinical Director:

William Dahut - applied signature on 10/10/2017 8:41 AM EDT

CONCURRENCE

OPS Protocol Specialist:

Tonica Johnson	AM N	10/13/17
Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

Abbreviated Title: Pancreatic Lesions in VHL

CC Protocol#: 03-C-0145 N

Version Date: 08/23/2017

NCT Number: NCT00062166

Title: Evaluation of the Natural History and Management of Pancreatic Lesions Associated with Von Hippel-Lindau

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A. Obtain information by intervening or interacting with living individuals for research purposes

B. Obtaining identifiable private information about living individuals

C. Obtaining the voluntary informed consent of individuals to be subjects

D. Makes decisions about subject eligibility

E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes

F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes

G. Some/all research activities performed outside NIH

PRÉCIS

Background:

- Patients with the familial cancer syndrome von Hippel-Lindau (VHL) demonstrate manifestations in a variety of organs among them the pancreas. Pancreatic manifestations can range from benign cysts and micro cystic adenomas to neuroendocrine tumors of the pancreas which are capable of regional and distant spread. These neuroendocrine tumors can result in life-threatening complications.
- This protocol is designed to identify VHL patients with pancreatic manifestations and to follow these patients with serial imaging studies and germ line and tissue genetic analysis.

Objectives:

- To identify patients with VHL having pancreatic lesions defined by simple cysts, microcystic adenomas, neuroendocrine tumors and other solid lesions of the pancreas.
- To follow patients with VHL and pancreatic manifestations by serial examination with non-invasive imaging studies
- For patients with solid lesions of the pancreas, to determine the rate of growth and to correlate the growth rate with clinical measures of disease progression
- To validate non-invasive imaging methods for differentiating benign solid lesions from lesions with malignant potential
- To characterize the time from initial presentation with pancreatic tumors to the time that surgery is recommended.

Eligibility:

- Patients ≥ 12 years of age who have been diagnosed with VHL
- Patients/parent must be able to sign an informed consent and be willing to return to NIH for follow-up.

Design:

- Demographic data will be collected from the medical record and patient interview for each patient participant. Data will be securely stored in a computerized database.
- Patients will be evaluated by the Urologic Oncology Branch personnel as indicated to rule out or manage other manifestations of VHL. Imaging studies of regions other than the chest and abdomen will be dictated by best clinical practice for the workup and management of VHL manifestations as has been previously published.
- All patients enrolled on this study will be offered genetic counseling by a trained genetic counselor.

- After their initial on-study evaluation, patients who are not found to have solid lesions of the pancreas but rather have only cystic disease of the pancreas, will be re-screened every two years with non-invasive imaging studies
- Surgical resection of solid lesions of the pancreas will be recommended based on previously published criteria.
- Based on our analysis of likelihood of tumor growth or risk of metastasis, data will be analyzed every two years and appropriate revisions will be made to the surgical management guidelines, if indicated by data analysis.
- Projected accrual will be 25 patients per year for a total of 15 years. Thus, we anticipate accruing 600 patients on this protocol.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- To identify patients with VHL having pancreatic lesions defined by simple cysts, microcystic adenomas, neuroendocrine tumors and other solid lesions of the pancreas.
- To follow patients with VHL and pancreatic manifestations by serial examination with non-invasive imaging studies consisting of CT scan, MRI scan, PET-CT scan, and as clinically indicated, abdominal ultrasound.
- To determine if FDG and FDOPA PET scans can detect early tumor metastasis, and predict which patients will have tumor progression and require an operation based on uptake status. Note: this objective has been met for FDOPA PET imaging. See section **8** .
- For patients with solid lesions of the pancreas, to determine the rate of growth and to correlate the growth rate with clinical measures of disease progression such as symptoms.
- To validate non-invasive imaging methods for differentiating benign solid lesions, such as microcystic adenomas, from lesions with malignant potential, namely pancreatic neuroendocrine tumors.
- To characterize the time from initial presentation with pancreatic tumors to the time that surgery is recommended.

1.1.2 Secondary Objectives

- To obtain blood samples from patients to determine VHL mutation status and subtype the mutations for potential correlation with disease severity.
- When possible, to obtain tissue from pancreatic lesions for genetic analysis including CGH, tissue proteomics, and cDNA microarray analysis.

1.2 BACKGROUND AND RATIONALE

Patients with von Hippel-Lindau (VHL), a dominantly inherited familial cancer syndrome [1-6], are at risk for developing pancreatic cysts, microcystic adenomas, and pancreatic neuroendocrine tumors (PNETs) [7-9]. PNETs are detected in 12 to 17% of the patients with VHL and these tumors can behave in a malignant fashion, with up to 17% of patients developing metastatic disease [9, 10]. While these neuroendocrine tumors remain a relatively uncommon cause of death, there is a growing recognition of the potential consequences of these tumors if left untreated [6, 9, 10]. We have described previously our experience with the diagnosis and management of these lesions and have made recommendations regarding resection based on size and location of the primary tumor [9]. While this approach appears to have been successful thus far, it has become increasingly evident that some patients manifest a more aggressive phenotype with respect to their pancreatic lesions. Our recommendations for surgery were based on a retrospective review of VHL patients with PNETs who were managed at the NIH. The primary goal of the present protocol is to follow patients diagnosed with PNET in a prospective fashion and to

apply these management recommendations in order to offer surgery to patients at a time where it may impact on the course of their disease.

Additionally, it has become evident that some patients may manifest a more aggressive phenotype with respect to their pancreatic lesions [11]. Based on this observation, we have previously conducted a retrospective analysis of germ line mutations in patients with VHL and PNETs in order to determine whether or not particular mutations were associated with a more aggressive phenotype [10]. This preliminary study revealed a potential association between mutations in exon 3 and an increased risk of developing metastatic disease. However, given the small number of patients in the study, statistical significance was not reached. Therefore, one of the secondary end points of the present protocol is to conduct germ line mutation analysis in patients found to have PNETs and to correlate differences in germ line mutations with severity of disease.

Recent studies suggest that functional imaging with FDG and FDOPA-PET scans is helpful for localizing and for possibly distinguishing malignant from benign neuroendocrine pancreatic lesions [12, 13]. Therefore, we will include functional imaging of solid pancreatic lesions in the adult population to determine if an uptake threshold could be used to distinguish malignant from benign solid pancreatic lesions.

The FDG and FDOPA PET scans will be used in adult patients found to have a solid pancreatic lesion. In this cohort of patients, the use of FDG and FDOPA-PET scans may help detect early tumor metastasis, and predict which patients will have tumor progression and require an operation based on uptake status. Review of the imaging studies of this cohort of patients revealed that only 11 of the 98 lesions (11%) were positive on ^{18}F-DOPA as compared to CT scan. Based on this interim analysis, ^{18}F-DOPA did not seem likely to be useful for detecting pancreatic neuroendocrine tumors in patients with VHL and with amendment H was eliminated from this protocol.

PET-MRI imaging was recently approved for clinical use and may be more accurate for localizing pancreatic tumors, in general [14].Therefore, we will include PET-MRI imaging of solid pancreatic lesions in the adult population to determine if this modality could be used to detect pancreatic neuroendocrine tumors, predict growth, and distinguish between benign and malignant PNETs.

1.2.1 Surgical resection

Surgical resection of solid lesions of the pancreas will be recommended based on previously published criteria (10). These include:

High suspicion for a PNET with one of the following:

1. The solid lesion suspicious for a PNET is ≥ 2 cm when located in the head of the pancreas or ≥ 3 cm when located in the body or tail of the pancreas.
2. A solid lesion of the pancreas, which appears to be growing in size on serial imaging studies.
3. Systemic symptoms consistent with a functional neuroendocrine tumor.
4. Patients undergoing abdominal operations for other VHL manifestations, such as kidney tumors or adrenal tumors, where extirpation of the pancreatic lesion

would potentially save the patient an additional surgical procedure in the future.

For patients undergoing surgical procedures, tissue will be stored for analysis as outlined in Section **3.4**. Since this is a natural history study, our goal will be to enroll as many VHL patients with pancreatic manifestations as is possible.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients who have been diagnosed with VHL using the following criteria: either germ line analysis (12) or clinical criteria or a family history (8, 12) and who have at least 1 pancreatic manifestation of VHL as documented on any non-invasive imaging study. These manifestations may include:

- Pancreatic cyst(s)
- Solid lesions suspicious for microcystic adenoma(s)
- Solid enhancing lesions suspicious for PNET(s)
- Any other solid lesion(s) of the pancreas

2.1.1.2 Age ≥ 12 years of age.

2.1.1.3 Patients must be willing to return to NIH for follow-up.

2.1.1.4 Patients/parent must be willing and able to sign an informed consent.

2.1.2 Exclusion criteria

2.1.2.1 Patients unwilling to undergo serial non-invasive imaging.

2.1.3 Recruitment Strategies

The study will be posted on the CCR website and on clinicaltrials.gov.

2.2 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Note: All patients were taken off study between January and June of 2009 in anticipation of protocol termination. In July, 2009 it was decided not to terminate the protocol, but to amend it with Dr. Kebebew as the new PI. Patients who were taken off study during that time, but wished to continue to be followed at the NCI were re-consented and re-registered into their original slot.

3 STUDY IMPLEMENTATION

3.1 ON STUDY EVALUATION

3.1.1 Detailed demographic data will be collected from the medical record and patient interview for each patient participant. Data will be securely stored in a computerized database.

3.1.2 Patients will be evaluated by the Urologic Oncology Branch, Neurosurgical Branch or Neuro Oncology Branch personnel as indicated to rule out or manage other manifestations of VHL. Imaging studies of regions other than the chest and abdomen will be dictated by best clinical practice for the workup and management of VHL manifestations as has been previously published. Patients who have not been offered genetic counseling through the Urologic Oncology Branch may be referred for genetic counseling.

3.1.3 Non-invasive imaging

- CT scan with contrast of the chest, abdomen, and pelvis
- MRI of the abdomen with special attention to the pancreas as indicated
- Abdominal ultrasound exam as indicated by the CT and MRI scans to further evaluate cystic lesions.
- FDG PET scans for pancreatic lesions that are solid on CT scan or MRI.

NOTE: Due to the amount of radiation exposure, PET imaging will NOT be performed on children under the age of 18 or pregnant or nursing women.

Bi-dimensional tumor measurements will be performed on contrast CT scans to evaluate rate of tumor growth and tumor doubling, on scans obtained at baseline and at each follow up visit.

3.1.4 Laboratory evaluations

- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid
- Amylase
- Metanephrines and normetanephrines
- Genetic germ line mutational analysis, if not previously performed. (Ordered through the Urologic Oncology Branch and performed at Children's Hospital of Philadelphia - a CLIA certified laboratory)
- Chromogranin A
- Research blood may be collected for correlative studies (validation of biomarkers of disease identified from tumor tissue analysis).

3.1.5 NIH Advance Directives Form

As indicated in section **9.3**, all subjects ≥ 18 will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.2 FOLLOW-UP EXAMINATIONS

Scheduling of follow up evaluations will be coordinated with UOB and/or NOB as appropriate.

3.2.1 Patients who are found to have only cystic disease of the pancreas or who have had surgery and who no longer have PNETs may undergo the following evaluations yearly for 2 years and then every two years if no evidence of malignant disease:

- MRI, US and CT scan of the abdomen with contrast as indicated
- metanephrines and normetanephrines
- Chromogranin A
- Research blood may be collected during follow up (once a year for patients with solid lesions or every two years for patients with cystic lesion) for correlative studies (validation of biomarkers of disease identified from tumor tissue analysis).

Note: Patients may be evaluated on a more frequent basis if they develop symptoms consistent with their cystic disease or have evidence of malignant disease recurrence.

3.2.2 Patients with solid lesions of the pancreas that are suspicious for PNETs that have not yet reached size criteria where surgery will be recommended (see below) may undergo the following evaluations yearly:

- CT scans of the abdomen and pelvis with contrast, as well as an MRI scan of the abdomen.
- FDG PET and PET-MRI scans –patients with solid lesions will undergo PET imaging as follows: Patients who are enrolled on Amendment F will undergo PET imaging at baseline and at one year. Patients who were enrolled prior to Amendment F will undergo PET imaging at their next imaging time point and again in one year.
- Metanephrines and normetanephrines
- Chromogranin A
- Research blood may be collected during follow up (once a year for patients with solid lesions or every two years for patients with cystic lesion) for correlative studies (validation of biomarkers of disease identified from tumor tissue analysis).

Note: Due to the amount of radiation exposure, PET imaging will NOT be performed on children under the age of 18 or pregnant or nursing women.

3.3 SURGICAL MANAGEMENT

Surgery will be recommended to manage lesions within the pancreas under the following circumstances:

3.3.1 Patients with cystic disease who develop symptoms attributable to their cysts consisting of pain, early satiety or intestinal obstruction will undergo appropriate management of their cysts by best clinical practice (this may include cystectomy, cyst drainage, or internal bypass).

3.3.2 Patients with solid lesions of the pancreas that are thought to be PNETs by non-invasive imaging studies will be considered for surgery if:

- Their solid lesion is enlarging on serial imaging studies.
- Their solid lesion is associated with symptoms consistent with a pancreatic neuroendocrine tumor.
- A solid lesion in the head of the pancreas is ≥ 2 cm in size.
- A solid lesion in the body or tail of the pancreas is ≥ 3 cm in size.

3.3.3 Patients who present with evidence of a pheochromocytoma or other cardiac risk factors will undergo a cardiac evaluation prior to surgical intervention.

3.3.4 Patients will be offered surgical management if they meet one of these criteria and the type of operation will be dictated by best clinical management taking into account the desire to preserve as much normal pancreatic tissue as possible. Approaches to the management of solid lesions of the pancreas can range from simple enucleation to distal pancreatectomy and splenectomy or a pancreatico-duodenectomy. Whenever possible, lesions in the pancreas will be managed by a laparoscopic approach. In all cases, intraoperative ultrasound will be utilized during surgical procedures in order to identify and manage additional lesions, as well as to minimize the risk of injury to vessels or the pancreatic duct.

3.4 Tissue Collection and Analysis

No tissue will be stored for ongoing and future research on this protocol. Patients who are willing to have their samples used for ongoing and future use will be consented on protocol 09-C-0242 *Prospective Comprehensive Molecular Analysis of Endocrine Neoplasms*.

3.5 Off Study Criteria+

- Participant requests to be withdrawn from the study.
- Participant is consistently non-compliant with follow-up appointments.
- Participant is consistently non-compliant with imaging studies.
- Death.
- Loss to follow up.
- PI decision to close the study.

\+ Note: Subsequent to the approval of Amendment N, minors are to be retained on the study until they reach the age of majority if possible and can be consented for the future use of their data. If this consent is not obtained, samples and data may not be used in this or future research unless the reason for removal is loss to follow up (for which a waiver has been requested in section **9.6.2**) or death (as these samples would no longer fall under human subjects protections).

3.5.1 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Supportive care will be provided to the patients by the Endocrine Oncology Branch as is indicated by either their admission works-up needs or by their postoperative management after a surgical procedure to manage a pancreatic lesion.

Medical management of the symptoms related to the patient's disease may be provided by the patient's referring physician.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

At baseline and at the time of annual clinic visit, approximately 10ml of peripheral blood will be drawn in red/yellow top tubes (SST) and transported to the Endocrine Oncology Branch laboratory.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

- All samples sent to the Endocrine Oncology Branch will be barcoded with data entered and stored in the LabMatrix system utilized by the CCR, NCI. This is a secure system with access limited to defined personnel. All such personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.
- LabMatrix creates a unique barcode ID for every sample which cannot be traced back to patients without LabMatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, date/time drawn, as well as box and freezer location. Patient demographics associated with the Clinical Center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).
- Upon receipt in the lab, samples will be bar coded and logged in to the sample database. Samples will be stored in -20^{o}C or -80^{o}C freezers. All freezers are monitored and are on separate emergency generator lines.
- These freezers are located onsite, and access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the LabMatrix System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the NCI. It is the responsibility of the NCI

Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.2.1 Protocol Completion/Sample Destruction

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

The blood samples will have circulating nucleic acid extracted from them to test for 10 microRNAs and 20 gene transcripts found to be highly expressed in pancreatic neuroendocrine tumors from patients with VHL. This will be done in 50 consecutive patients until 50 different blood samples are obtained during their clinic visit.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

All data will be kept secure. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (LabMatrix) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Data prior to and during the course of the patient's participation will be collected in order to monitor patient eligibility, non-invasive imaging results, and blood work. If patients require surgery, data from preoperative and postoperative course and toxicities will be collected. Tumors visualized on imaging studies will be measured using bi-dimensional tumor measurements (or other appropriate units of measure) at baseline and at each follow up visit.

End of study procedures: Data will be stored according to HHS and FDA regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 DATA REPORTING

Patients will undergo monitoring of their disease, operative intervention when indicated, and follow up as per standard of care. Patients who meet the standard of care criteria for resection of their disease will undergo a major operative procedure and may receive

extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

6.2.1 Routine Data Reporting

All details of patient management and treatment will be documented in the patient medical record. Only the following information will be captured on the CRFs:

- Detailed demographic information including family history
- Laboratory markers
- Imaging results (CT, MRI and PET)
- Operative interventions as indicated

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. As this is a natural history study, no adverse events are expected. However, if an event does occur that is related to the research, the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the research in humans, whether or not the event is considered related to the research or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last research intervention.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

7.1.3 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.4 Serious Adverse Event

An adverse event is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.6 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.7 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.8 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
    a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
    b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;

- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.3 DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively enrolled on the trial to discuss each patient. All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB via iRIS. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

We will estimate the distribution of time from initial presentation with pancreatic tumors to the time that surgery is recommended with a Kaplan-Meier Curve. An age-adjusted comparison between this distribution by mutational status (missense vs non-missense mutation, for example) will be done with a proportional hazards model using the method of Wei, et al. (Wei, L.J., Lin, D.Y., and Weissfeld, L., Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. Journal of the American Statistical Association, 84, 1065-1073, 1989) to account for the lack of independence due to familial correlation.

We will estimate the growth rate in solid pancreatic tumors using linear and nonlinear mixed models (Davidian, M. and Giltinan, D.M., Nonlinear Models for Repeated Measurement Data, Chapman and Hall, New York, 1996). These models will allow for the various sources of correlation due to multiple members in the same family and multiple tumors on the same patient. We will compare the growth rate by mutational status as well as by clinical and imaging characteristics by including these factors as covariates in the mixed models. The choice of the form of the linear or non-linear model will depend on the observed data. We will use a linear mixed model on log-transformed volume data if the volume data appears approximately linear on the log-scale. Otherwise, we will investigate alternative models such as the Gompertz model for tumor growth.

The uptake levels of FDG on PET imaging will be compared between patients who require operative intervention and those who do not in order to determine the predictive value of PET imaging in this patient population. Power is based on comparing mean uptake between these two groups of patients. Based on the VHL patient characteristics collected at the Urologic Oncology Branch, NCI, assuming approximately 17% (52 patients) of the targeted 300 VHL patients screened in this study will have solid pancreatic lesion and 50% (26 patients) of them will require operation, we would have 94% power to detect 1 standard deviation difference in the mean uptake between the two groups. The comparison is based on the two-sample t-test at the 5% significance level.

Based on our analysis of likelihood of tumor growth or risk of metastasis, data will be analyzed every two years and appropriate revisions will be made to the surgical management guidelines, if indicated by data analysis.

As of February 1, 2011, 40 patients have been enrolled who have undergone all four imaging modalities (CT scan, MRI, 18F-DOPA, 18F-FDG). Only 11 of the 98 lesions (11%) were positive on 18F-DOPA as compared to CT scan. Based on this interim analysis, 18F-DOPA is not likely to be useful for detecting pancreatic neuroendocrine tumors in patients with VHL and as of amendment H this mode of imaging is no longer included in protocol evaluations.

As of April 15, 2014, 129 of 276 patients screened in the study had solid lesions. Of these 129 patients, 24 required operative intervention. ^{18}FDG-PET detected metastatic disease in 3 patients which were not detected by CT, and found non-neoplastic disease in 4 patients. Hence, ^{18}FDG-PET was able to find 29% of the surgical patients who either had metastasis not detected by CT or had non-neoplastic disease in which operation could be avoided. Using the method of Agresti-Coull (1998), the corresponding 90% confidence interval is (16.5%, 46%) with width 29.5%. Assume that the true proportion of diagnosis of metastatic as well as non-neoplastic disease by ^{18}FDG-PET which is not detected by CT is 30%. To reduce the width of the 90% expected confidence interval to 20%, a total of 52 surgical patients are required. Correspondingly, approximately a total of 600 VHL patients need to be screened.

Power calculation for the comparison of tumor growth rates between two groups is based on comparing linear growth on the log-scale. Assuming that approximately 9% (54 patients) of screened VHL patients will present or develop pancreatic tumors which require operation over follow-up, we would have 95% power to detect a 1 standard deviation change in the growth rate between two groups of equal numbers (27 in each group) with a two-sided test the 0.05 significance level. This calculation is based on comparing individually estimated slopes (using multiple follow-up measurements on each subject) with a two-sample t-test. This calculation is only an approximation since power may be slightly reduced due to correlation across multiple individuals in the same family and may be increased due to multiple tumors followed on each patient.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

Since this protocol is a natural history study of patients with VHL and pancreatic lesions, subjects will be selected for this protocol based on either a clinical diagnosis of VHL or a confirmed VHL germ line mutation and an associated pancreatic manifestation as previously described. Patient selection for this protocol will not be based on gender, race, ethnic background or other VHL manifestations.

9.2 PARTICIPATION OF CHILDREN

Patients over the age of 12 will be eligible for this study. Since it is unusual for patients under the age of 12 who have pancreatic manifestations, younger patients will not be enrolled. The investigators have experience working with young adolescents and their

parents in prior protocols. During adolescent participation, the services of the pediatric Clinical Nurse Specialist will be consulted to assist caregivers in addressing the adolescents' developmental needs.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **9.4**), all subjects ≥ 18 years old will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIHMEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 EVALUATION OF BENEFITS AND RISKS DISCOMFORTS

There is the potential for direct benefit for patients participating in this study by early detection of solid lesions of the pancreas associated with VHL and early management of these lesions, which may have an impact on the overall course of the disease. The risks associated with this study with respect to the serial imaging will be minimal. Risks associated with the surgical procedures to manage lesions in the pancreas will vary based on the type lesion and the planned surgical procedure. These risks will be discussed in depth on a patient-by-patient basis. The risks associated with germ line analysis and the potential impact of this genetic information will be discussed with patients through genetic counseling at their initial on-study visit as well as at any subsequent deemed appropriate.

9.5 RISKS/BENEFITS ANALYSIS

For patients who have solid tumors that are not currently amenable to surgical resection, the risk of blood drawing and non-invasive imaging is minor. This study also offers the benefit of surgery, when patients meet the criteria for resection, in an institution with vast experience with the patient with VHL. For pediatric patients, this protocol falls in pediatric risk category 2 because it has more than minimal risk but possible direct benefit.

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients and/or the patient's parent(s) or legal guardian (if he/she is <18 years of age) who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or one of his designees will perform the consenting process. Patients will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to.

Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed.

9.6.1 Consent of Children

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, documentation of custody status must be obtained.

9.6.1.1 Consent of Children when there is Joint Custody

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section**9.6.3.**

9.6.1.2 Verbal Consent of Children

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

9.6.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that may have transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who have completed their participation in the research study.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.

(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between a minor's enrollment and their age of majority, it is possible that more than a few subjects may be lost to follow up. A significant reduction in the number of samples analyzed could impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only plan to request a waiver of reconsent for those subjects who have been lost to follow-up or who, prior to the approval of Amendment N, have been taken off study prior to reaching the age of majority.

9.6.3 Telephone Re-Consent Procedure

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.4 Informed consent of non-English Speaking Subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

If there is an unexpected enrollment of a research participant for whom 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 Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will

be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

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INSTITUTE: National Cancer Institute

STUDY NUMBER: 03-C-0145 PRINCIPAL INVESTIGATOR: Electron Kebebew, M.D.

STUDY TITLE: Evaluation of the Natural History and Management of Pancreatic Lesions Associated With Von Hippel-Lindau

Continuing Review Approved by the IRB on 11/07/16
Amendment Approved by the IRB on 10/07/17 (N) Date posted to web: 10/14/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

The purpose of this research project is to study Von-Hippel Lindau in patients who have pancreatic lesions. We hope to improve our understanding of how these lesions affect people and how best to treat them. We also want to understand the genetic cause of these conditions. We want to learn about the changes, or alterations in the genes (the genetic material) that causes conditions involving pancreatic tumors.

Why are you being asked to take part in this study?

You have been referred to the National Institutes of Health because you, or a member of your family, is known or thought to have an inherited condition called Von Hippel-Lindau that may involve development of pancreatic tumors or lesions.

How many people will take part in this study?

Up to 600 people will take part in this study.

Description of Research Study

There are four main goals of this study:

1. Identify patients with Von Hippel-Lindau who have pancreatic lesions;
2. Study how fast lesions grow and their characteristics;
3. To study how well imaging studies can show us the characteristics of pancreatic lesions to help in diagnosis.
4. To study how blood levels of specific genetic markers correlate with tumor growth

What will happen if you take part in this research study?

As part of your being on this project, you may talk with an oncologist (cancer doctor), a surgeon (if you have lesions where surgery is recommended), and cancer nurses. These professionals will ask you questions about your condition and your family history. If the professionals in the Urologic Oncology Branch have already asked you these questions, we will get the information from your record, if you/ agree to participate in this study.

During the study

While you are on this study, you may have the following tests performed every 1-2 years; or more frequently if your condition changes.

- CT scan of the abdomen / chest / pelvis using contrast (a type of dye)
- MRI of the abdomen
- Ultrasound of the abdomen
- FDG-PET scan
- Blood chemistry studies including tests specific to the pancreas
- 24 hour urine studies
- Blood sample for genetic markers (if not already performed)
- Research blood to compare with tumor growth

These studies are those done routinely to diagnose or manage a person with a lesion in the pancreas. Rarely, light anesthesia may be recommended for children undergoing some of the studies. This would only be done in situations in which a child would benefit directly from the information gained from the study. A description of the most common tests is listed below:

Blood tests: Blood will generally be drawn from an arm vein. This will be used for standard or common blood tests that determine whether you meet the requirements for participating in a specific protocol. This may include taking blood to see what your HLA type is or if you have had any history of hepatitis. There will also be about 2 teaspoons of blood drawn for research.

MRI: also known as Magnetic Resonance Imaging, is a scan that allows the doctor to view parts of the body in small section views, so they can look closely at each part of the body. It does not use any radiation and it can be done with or without contrast, which is a dye-like material that helps make the picture clearer. Since the MRI uses large magnets to put the cells in a position so they can be seen more clearly, you must remove anything that is metal before having this test. This test takes between 35-50 minutes to complete and is entirely painless.

CT: is also called Computerized tomography or computerized axial tomography (CAT), also allows the doctor to view the organs inside your body in small sections. It can be done from different angles and allows a three-dimensional picture of the part of the body being studied. It may be done with or without contrast and may take between 30-90 minutes.

FDG PET: also called Positron emission tomography, lets the doctor see the cell's activity in specific tissues of the body. It requires that you be given an intravenous (IV) fluid, such as a sugar fluid, on which we have attached a radioactive particle that allows the sugar to be seen with a special camera. The radioactive sugar goes to cells that are most active, like cancer cells, and allows the doctors to see if you have a tumor.

During the PET scan you will lie down on your back on the padded scanner table with a foam cushion supporting your knees. The scanner table then slides, moving only your head into the PET scanner, which resembles a large donut. Through the entire procedure you will be monitored by a healthcare provider. Immediately after the PET scan you will be asked to empty your bladder. You will be asked to continue to do this every two hours for the remainder of the day. This is to reduce the length of time that your body is exposed to the radioactive agents.

An ultrasound of the abdomen is done with a scanner and a probe or "transducer" which is placed on the abdomen. Very high frequency sound waves are emitted from the probe while it is moved over the abdomen to "look at" (likened to a light shined from a torch) any particular part of the abdomen. Moving the ultrasound beams back and forth allows information obtained from different directions to be recomposed into a picture which is shown on the monitor screen (a sonogram, or ultrasonogram). This procedure is entirely painless.

You will be evaluated in the outpatient clinic of the Clinical Center at NIH. Tests will be done in either one day or may be done over 2-3 days. After your tests are done, you will meet with one of the doctors who will discuss the findings of these tests. If you have a lesion in the pancreas that meets certain criteria, the doctor will discuss with you the option of having surgery to remove as much tumor as possible. The specific type of surgery would depend on the size and location of the lesion or lesions. Your doctor or surgeon will discuss with you the specific procedure and the risks of that procedure, if that is an option. You will be asked to sign a separate consent for the surgery. You may meet with the genetic counselor who will spend time with you to discuss the effects of the information you receive and will explain anything you do not understand.

The specific criteria that would make you/ eligible for surgery include:

- Scans and x-rays show the tumor(s) in the pancreas is getting bigger;
- In addition to having a tumor in the pancreas, you have symptoms that show the tumor is a certain kind of tumor, known as a neuroendocrine tumor;
- If you have a tumor in the tip of the pancreas that is larger than 2 cm (approximately the size of a penny);
- If you have a tumor in the main body or end (known as the tail) of the pancreas that is larger than 3 cm (approximately the size of a 50 cent piece.

If you have not previously had blood drawn for genetic markers, a sample of your blood will be sent to a clinical laboratory to look for the alteration in the DNA that is responsible for your condition. There is a possibility that the genetic alteration will not be found. If you wish to have the information, your DNA results will be given to you. If you desire, a written summary will be provided to you by a professional involved in your clinic visits. If you choose, documentation will also be provided to your local health care provider(s) along with recommendations for additional evaluations or management options.

You will be asked to return to NIH for scans and x-rays every year if you have a lesion in your pancreas which does not require surgery at this time. We will watch for growth of your lesion, and if, at a later time, surgery may benefit you/, we will discuss it as an option then. If you have cystic disease in your pancreas you will be asked to return to NIH every two years for scans, to watch the progression of this condition. Your local doctors should continue to manage your care. Any of your test results that may affect the management of your condition and any recommendations we have will be shared with your doctor with your knowledge and permission. Specific details regarding any return visits will be reviewed with you.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

All of the tests and procedures included in this protocol are routine and standard for patients who have Von Hipple-Lindau. Like most medical tests, there are some associated risks and discomforts. The following brief summary describes the most common risks of these tests and procedures, but the doctor or nurse will discuss with you in detail any risks or discomforts of the test(s) you will be scheduled to undergo.

Blood tests: The blood drawing may cause a sharp pricking pain for just a moment when the needle goes into the vein in your arm. Rarely, a bruise may form at the needle puncture site. This will generally go away on its own without any treatment.

Scans: MRI, CT, and FDG-PET Scans are common standard imaging tests used in the diagnosis of cancer and related diseases. The most common discomfort is the length of time a patient must lay still during a scan. Occasionally, a patient may become uncomfortable with the closed space of the machines, particularly the MRI. If this occurs, your doctor can order a medicine to help you relax during this scan. If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. In that small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely do these symptoms require any treatment. In very rare cases, people have had severe reactions that affect their breathing and heart rhythm. If you have had a reaction in the past, be sure to tell you doctor or nurse about it. The radiation dose you receive if your scan includes the use of radioisotopes is well within the NIH Radiation Safety Guidelines, and is considered essential for your medical care.

If you are considered for surgery, your surgeon will discuss the surgical procedure and associated risks. Regardless of the specific nature of the surgery, all general surgery carries potential risks and complications. There are risks of infection, the risk of anesthesia, healing difficulties and death. In rare circumstances major surgery can cause damage to the various organs of the body, including but not limited to, changes in consciousness, damage to the nervous system, heart failure, lung failure, kidney failure, or liver failure.

Other risks that are associated with the surgical procedure include bleeding which might require transfusions or a second operation to correct, and blood clots that have the risk of moving to the lungs causing difficulty breathing. As a result of the surgery, an infection can develop in the abdomen, where the incision was made, or in the lungs (pneumonia). An infection in the abdomen may need to be drained. All types of infections would be treated with antibiotics. During surgery, handling the organs in the abdomen may cause irritation to the bottom-lining underneath the lung. In rare instances, patients have developed fluid under the lung, known as a

pleural effusion, as a result of this. This may cause you to be short of breath. In most cases the fluid goes away on its own. Occasionally, it must be removed with a needle and syringe. Because we will be doing surgery on or near the pancreas, rarely (less than 5% of patients) an inflammation of the pancreas may occur, known as pancreatitis. This may cause pain and increase the pancreas enzymes in the blood. It is treated by fasting to allow the pancreas to rest.

Emotional and Social Risks: Genetic information about you and your family may be discovered during this research project. There are many aspects of life which can be affected by knowing this kind of information. Some things to consider in thinking about whether or not to participate in genetic studies include the possible effect it might have on your emotional well-being. In other words, how might you feel about yourself and your life if information is provided about risks that could affect your own health or that of your children?

Relationships with other family members may be affected by learning about these risks if they did not want to know this information. An example would be if your children, brothers or sisters find out they have risks for health problems because of information found out about you. Some individuals may feel anxious, depressed or additionally stressed by learning genetic or medical information about themselves which in some cases may not have treatment options available. You may experience similar feelings or may have other reactions. If you are feeling anxious, we recommend you discuss this with the genetic counselor. We can arrange this for you, if you wish.

Information about the parents may be discovered in the course of this research project. In other words, issues of adoption and paternity (fatherhood) may be discovered. It is our policy to not discuss such information unless it has direct medical or reproductive implications for you or your family.

Risk very unlikely, but serious: We will not release any information about you or your family to any insurance company or employer unless you request us to do so. However, instances are known in which genetic information has been obtained or requested when a person applies for health insurance and/or a job. Any information we collect or discover about you or your family is confidential. However, courts may have the ability to subpoena medical records. If you file a claim for genetic counseling with your private insurance company, the company may obtain some information about you that may affect your insurability.

Any information collected or discovered about you or your family is considered confidential, however, our commitment to confidentiality does not override the court's ability to subpoena medical records. Release of any information contained in these files is controlled by you and access by others, including other family members, is possible only through your expressed written approval. Research results containing information about your genetic make-up are locked in secured research offices within the Clinical Center. Medical records containing this information will be housed within the Clinical Center at the National Institutes of Health. This

potentially may allow other researchers at NIH access to your information without your expressed written approval.

Protections against misuse of genetic information: Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Potential benefits may include early detection and management of abnormalities in your pancreas which may lead to a better outcome of your disease. You will be offered follow up evaluation of lesions you may have in your pancreas, and if appropriate, we may offer you surgery to remove your pancreatic lesions.

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

Stopping Study Participation

We will follow you at NIH until this study closes, or until you decide you no longer wish to participate in this natural history study.

Your doctor may also decide to take you off of the study if he/she believes that it is in your best interest. In this case, you will be informed of the reason why your study participation is ending.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Certificate of Confidentiality

This study has received a Certificate of Confidentiality which helps to protect your research information. The researchers involved in this study cannot be forced to disclose the identity or any information collected in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you request the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review your records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Use Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your data will be used for research purposes only and will not benefit you. It is also possible that the stored data may never be used. Results of research done on your data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored data used for future research, please contact us in writing and let us know that you do not want us to use your data. Then your data will not be used for future research. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Electron Kebebew, M.D., Building 10, Room 3C428, Telephone: 240-760-6153. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:	
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. Signature of Adult Patient/ Legal Representative _____ Date _____ Print Name _____	**B. Parent's Permission for Minor Patient.** I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) Signature of Parent(s)/ Guardian _____ Date _____ Print Name _____

C. Child's Verbal Assent (If Applicable)
The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 07, 2016 THROUGH NOVEMBER 06, 2017.

Signature of Investigator _____ Date _____	Signature of Witness _____ Date _____
Print Name _____	Print Name _____

INSTITUTE: Instituto Nacional del Cáncer [National Cancer Institute]

STUDY NUMBER: 03-C-0145 PRINCIPAL INVESTIGATOR: Electron Kebebew, M.D.

STUDY TITLE: Evaluación de la evolución natural y el tratamiento de las lesiones pancreáticas que se asocian con la enfermedad de Von Hippel-Lindau [Evaluation of the Natural History and Management of Pancreatic Lesions Associated With Von Hippel-Lindau]

Continuing Review Approved by the IRB on 11/07/16
Amendment Approved by the IRB on 10/07/17 (N) Date posted to web: 10/14/17

Standard (Spanish)

INTRODUCCIÓN

Deseamos invitarlo a participar en un estudio de investigación en los Institutos Nacionales de Salud (National Institutes of Health, NIH).

En primer lugar, queremos que usted sepa que:

La participación en una investigación de los NIH es totalmente voluntaria.

Usted puede decidir no participar o retirarse del estudio en cualquier momento. En cualquier caso, no perderá ninguna prestación a la que pueda tener derecho. No obstante, para recibir atención médica en los NIH, usted debe participar en un estudio o estar en evaluación para participar en uno.

Es posible que no reciba ningún beneficio por su participación. Con la investigación podemos adquirir conocimientos que ayuden a otras personas en el futuro.

En segundo lugar, algunas personas pueden tener creencias personales, religiosas o éticas que limiten los tipos de tratamiento médico o de investigación que deseen recibir (por ejemplo, transfusiones de sangre). Si usted es una de esas personas, hable al respecto con sus médicos o con el equipo de investigación de los NIH antes de acceder a participar en el estudio.

El estudio se describe en las siguientes páginas. Antes de decidir participar, tómese todo el tiempo que necesite para formular preguntas y hablar del estudio con cualquier persona de los NIH, o con su familia, sus amigos, su médico personal u otro profesional de la salud.

Si usted va a firmar este formulario en nombre de un menor de edad, cada vez que en el documento de consentimiento se hable de "usted" nos estamos refiriendo a "su hijo".

¿Por qué se está realizando este estudio?

El propósito de este proyecto de investigación es estudiar la enfermedad de Von Hippel-Lindau en pacientes que tienen lesiones pancreáticas. Esperamos ampliar nuestros conocimientos sobre la forma en que estas lesiones afectan a las personas y sobre la mejor manera de tratarlas. También

queremos averiguar la causa genética de estas afecciones. Queremos descubrir los cambios o alteraciones de los genes (material genético) que causan las afecciones que se manifiestan con tumores pancreáticos.

¿Por qué le hemos pedido que participe en este estudio?

Le han remitido a los Institutos Nacionales de Salud porque usted o un pariente suyo tiene o podría tener una enfermedad hereditaria llamada enfermedad de Von Hippel-Lindau, en la que pueden presentarse tumores o lesiones del páncreas.

¿Cuántas personas participarán en este estudio?

Un máximo de 600 personas participarán en este estudio.

Descripción del estudio de investigación

Este estudio tiene cuatro objetivos principales:

1. Identificar a los pacientes con enfermedad de Von Hippel-Lindau que tienen lesiones pancreáticas
2. Determinar qué tan rápidamente crecen las lesiones y cuáles son sus características
3. Investigar qué tan bien pueden las pruebas de diagnóstico por imagen mostrar las características de las lesiones pancreáticas para contribuir al diagnóstico
4. Investigar qué relación hay entre las concentraciones sanguíneas de ciertos marcadores genéticos y el crecimiento tumoral

¿Qué pasará si usted participa en este estudio?

Como parte de su participación en este proyecto, usted puede hablar con un oncólogo (médico especialista en cáncer), un cirujano (si tiene lesiones para las que se recomiende una operación) y enfermeras de oncología. Estos profesionales le harán preguntas sobre su enfermedad y sus antecedentes familiares. Si los profesionales de la Sección de Oncología Urológica ya le han hecho estas preguntas, obtendremos la información de su expediente médico si usted accede a participar en el estudio.

Durante el estudio

Mientras esté en este estudio se puede someter a las siguientes pruebas cada 1 o 2 años, o más frecuentemente, si se presentan cambios en la enfermedad.

- Tomografía computarizada del abdomen, el tórax o la pelvis con medio de contraste
- Resonancia magnética del abdomen
- Ecografía del abdomen
- Tomografía por emisión de positrones con desoxiglucosa marcada con flúor (FDG-PET, por sus siglas en inglés)
- Análisis de bioquímica sanguínea, entre ellos, los análisis específicos para el páncreas

- Análisis en orina de 24 horas
- Muestra de sangre para determinación de marcadores genéticos (si no se ha realizado)
- Muestra de sangre para investigación a fin de comparar el crecimiento tumoral

Estas pruebas son las que se hacen habitualmente durante el diagnóstico o el tratamiento de una persona que tiene una lesión en el páncreas. En raras ocasiones se puede recomendar anestesia ligera en niños que se sometan a algunos de los estudios. Esto solo se haría en situaciones en las que un niño se beneficie directamente de la información que se obtenga en el estudio. A continuación se encuentra la descripción de las pruebas más comunes:

Pruebas de sangre: La sangre se extrae por lo general de una vena del brazo. Esta sangre se usa para pruebas corrientes de sangre que determinan si usted cumple los requisitos para participar en un protocolo específico. Estas pruebas pueden consistir en tomar muestras de sangre para determinar el tipo de HLA o si ha estado expuesto a la hepatitis. También se le extraerán cerca de dos cucharaditas de sangre para la investigación.

Resonancia magnética: La resonancia magnética es una prueba que le permite al médico observar partes del cuerpo en secciones pequeñas, con lo cual puede ver de cerca cada una de ellas. No utiliza ningún tipo de radiación y se puede hacer con o sin medio de contraste, el cual es un material parecido a un colorante que ayuda a que la imagen sea más clara. Ya que en la resonancia magnética se usan imanes grandes para poner las células en una posición en que se puedan ver más claramente, usted deberá quitarse todos los objetos metálicos antes de la prueba. La prueba dura entre 35 y 50 minutos y es completamente indolora.

Tomografia computarizada: La tomografía computarizada (TC), que se conoce también como tomografía axial computarizada (TAC), le permite al médico ver los órganos internos del cuerpo en secciones pequeñas. Se puede realizar desde ángulos diferentes y permite obtener una imagen tridimensional de la parte del cuerpo que se está estudiando. Se puede realizar con o sin medio de contraste y la técnica dura entre 30 y 90 minutos.

Tomografía por emisión de positrones con desoxiglucosa marcada con flúor (FDG-TEP) La tomografía por emisión de positrones (PET, por sus siglas en inglés) le permite al médico ver la actividad celular de tejidos específicos del cuerpo. Para realizarla hay que darle al paciente un líquido intravenoso, por ejemplo, un líquido que contenga un azúcar al cual se le ha fijado una partícula radioactiva que hace que el azúcar se pueda ver con una cámara especial. El azúcar

radioactivo va a las células más activas, como las células cancerosas, y así los médicos pueden ver si el paciente tiene un tumor.

Durante la PET, usted estará acostado boca arriba en una camilla acolchonada, con un cojín de espuma sosteniéndole las rodillas. La camilla se desliza dentro del aparato, que tiene forma de túnel, de modo que solo la cabeza queda dentro de él. Durante toda la técnica, un profesional de la salud le vigilará. Inmediatamente antes de la primera prueba le pediremos que vacíe la vejiga. Tendrá que seguir haciendo esto cada dos horas durante el resto del día. Esto se hace para reducir la cantidad de tiempo que su cuerpo está expuesto a las sustancias radioactivas.

Ecografía del abdomen: Esta prueba se realiza con un ecógrafo y con un transductor que se le pasa sobre el abdomen. El transductor emite ondas sonoras de muy alta frecuencia a medida que se mueve sobre el abdomen para "examinar" una zona específica (como si fuera la luz de una antorcha). Al mover los haces de ultrasonido de un lado a otro, la información que se obtiene desde diferentes direcciones sirve para componer una imagen que aparece en la pantalla. Esta imagen es la ecografía. La técnica es completamente indolora.

Lo evaluaremos en la clínica para pacientes ambulatorios del Centro Clínico de los NIH. Las pruebas se realizarán en un solo día o en el transcurso de 2 o 3 días. Después de que se realicen las pruebas, se reunirá con uno de los médicos, quien le explicará los resultados. Si tiene una lesión del páncreas que reúna ciertos criterios, el médico le hablará de la alternativa de someterse a una operación para retirar la mayor cantidad posible de tumor. El tipo específico de operación depende del tamaño y la ubicación de la lesión o de las lesiones. El médico o el cirujano le hablarán de la intervención específica y de los riesgos que implica, si operarse es una alternativa. Se le pedirá que firme un documento aparte de consentimiento para la operación. Usted puede reunirse con el asesor genético, quien dedicará tiempo para hablarle de las repercusiones de la información que reciba y le explicará lo que no entienda.

Los criterios específicos que determinan si usted puede someterse a la operación son:

- Las radiografías y otras pruebas de diagnóstico por imagen muestran que el tumor o los tumores del páncreas están aumentando de tamaño.
- Además del tumor en el páncreas, usted tiene síntomas que muestran que el tumor pertenece a un tipo específico de tumores que se conocen como tumores neuroendocrinos.
- Usted tiene un tumor de más de 2 cm (el tamaño de una moneda de un centavo) en la punta del páncreas.

- Usted tiene un tumor de más de 3 cm (el tamaño de una moneda de 50 centavos) en el cuerpo o en la cola del páncreas.

Si no le han extraído sangre antes para análisis de marcadores genéticos, una muestra de su sangre se enviará a un laboratorio clínico para investigar la alteración del ADN responsable de su enfermedad. Existe la posibilidad de que no se encuentre la alteración genética. Si desea que le demos los resultados del análisis del ADN, se los entregaremos. Si lo desea, uno de los profesionales con quienes tenga consultas clínicas le entregará un resumen escrito. Si usted lo solicita, también les entregaremos esta documentación a los profesionales médicos que le atienden en donde vive, junto con recomendaciones sobre evaluaciones adicionales o alternativas de tratamiento.

Se le pedirá que regrese a los NIH a hacerse radiografías y otras pruebas de diagnóstico por imagen todos los años si tiene una lesión en el páncreas que no requiera operación en este momento. Observaremos si la lesión crece y si más adelante consideramos que la operación podría beneficiarle, le hablaremos de esa opción cuando llegue el momento. Si tiene fibrosis quística del páncreas, le pediremos que regrese a los NIH cada dos años a hacerse pruebas de diagnóstico por imagen para vigilar la evolución de esta enfermedad. Los médicos que le atienden en donde vive deben seguir encargándose de su atención. Le comunicaremos a su médico —con el conocimiento y permiso de usted— todo resultado que pueda afectar el tratamiento de su enfermedad y toda recomendación que tengamos. Le explicaremos los detalles específicos de cada consulta para la cual tenga que regresar.

Riesgos o molestias relacionados con la participación

¿Qué efectos secundarios o riesgos puedo esperar por el hecho de participar en este estudio?

Todas las pruebas y las técnicas que se incluyen en este protocolo se realizan de manera habitual y corriente en pacientes que tienen la enfermedad de Von Hipple-Lindau Como sucede con la mayoría de las pruebas médicas, estas implican algunos riesgos y molestias. El siguiente resumen describe los riesgos más frecuentes, pero el médico o la enfermera le explicará en detalle los riesgos o molestias de las pruebas a las que deba someterse.

Pruebas de sangre: La extracción de sangre puede causar un dolor punzante y agudo por un momento, cuando la aguja entra en la vena del brazo. En raras ocasiones se puede formar un moretón en el sitio de punción, que desaparece generalmente sin necesidad de tratamiento.

Pruebas de diagnóstico por imagen: La resonancia magnética, la tomografía computarizada y la FDG-PET son pruebas corrientes de diagnóstico por imagen que se emplean en el diagnóstico del cáncer y de las enfermedades relacionadas con este. La molestia más frecuente es la cantidad de tiempo que el paciente debe permanecer acostado e inmóvil durante la prueba. A veces el paciente se puede sentir incómodo debido al espacio cerrado de las máquinas, especialmente en la resonancia magnética. Si esto ocurre, el médico puede formularle un medicamento para que pueda relajarse durante la prueba. Si durante la prueba se administra un medio de contraste (un colorante especial) existe un riesgo pequeño de que se produzca una reacción al mismo. En el pequeño grupo de pacientes que presentan una reacción, los síntomas más frecuentes son náuseas, dolor en la vena en la cual se aplicó el medio de contraste, sabor metálico o amargo y una sensación de calor o de rubor que dura entre 1 y 3 minutos. Muy pocas veces estos síntomas requieren tratamiento. En casos muy poco frecuentes, algunas personas han presentado reacciones graves que afectan la respiración y el ritmo cardíaco. Si usted ha tenido una reacción en el pasado, asegúrese de contarle al médico o a la enfermera al respecto. Si en la prueba se usan isótopos radioactivos, la dosis de radiación que recibirá se encuentra dentro de las normas de seguridad de radiación de los NIH y se considera esencial para su atención médica.

Si se está contemplando la posibilidad de hacerle una operación, el cirujano le hablará de la intervención y de los riesgos que implica. Independientemente de la naturaleza específica de la operación, todas las intervenciones de cirugía general implican posibles riesgos y complicaciones. Hay riesgo de infección, riesgos asociados con la anestesia, dificultades de cicatrización y riesgo de muerte. En circunstancias poco comunes, las intervenciones de cirugía mayor pueden causar lesiones en distintos órganos del cuerpo, entre ellas, alteraciones de la consciencia, lesiones del sistema nervioso e insuficiencia cardíaca, pulmonar, renal o hepática.

Otros riesgos que se relacionan con la intervención quirúrgica consisten en sangrado, que puede requerir transfusiones, en la necesidad de una segunda operación para corregir el problema y en coágulos de sangre que pueden pasar a los pulmones y causar dificultad para respirar. Como resultado de la operación puede presentarse una infección en el abdomen, en el lugar de la incisión o en los pulmones (neumonía). Si hay infección en el abdomen, puede ser necesario drenarla. Todas las infecciones se tratarán con antibióticos. Durante la intervención, la manipulación de los órganos del abdomen puede irritar la membrana que recubre la parte posterior de los pulmones. En raras ocasiones, algunos pacientes han presentado acumulación de líquido debajo de los pulmones (derrame pleural) como resultado de esta situación. El derrame pleural puede causar dificultad para respirar. En la mayoría de los casos, el líquido desaparece por sí solo. Ocasionalmente es necesario retirarlo con aguja y jeringa. Como la operación se realizará en el páncreas o cerca de él, en raras ocasiones (menos del 5% de los pacientes) puede presentarse inflamación del páncreas, que se conoce como pancreatitis. Esto puede causar dolor y aumentar la

concentración de las enzimas pancreáticas en la sangre. Se trata haciendo ayunar al paciente, para darle al páncreas tiempo para descansar.

Riesgos emocionales y sociales: Durante esta investigación se puede descubrir información genética sobre usted y su familia. Muchos aspectos de su vida se pueden ver afectados por enterarse de este tipo de información. Algunos factores que hay que considerar para tomar la decisión de participar o no participar en estos estudios genéticos abarcan las posibles repercusiones sobre su bienestar emocional. En otras palabras, ¿se imagina cómo se sentiría acerca de sí mismo y de su vida si se enterara de riesgos que podrían afectar su salud o la de sus hijos?

Su relación con otros miembros de su familia puede verse afectada si estos averiguan que están corriendo riesgos de los que no hubieran querido enterarse. Por ejemplo, imagínese si, a través de la información que se obtenga sobre usted, sus hijos o sus hermanos averiguan que corren el riesgo de sufrir determinados problemas de salud. Algunas personas pueden sentir ansiedad, depresión o estrés al recibir información genética o médica que les afecte y para la que, en algunos casos quizá no haya opciones de tratamiento. Usted puede tener sentimientos parecidos u otras reacciones. Si se siente angustiado, le recomendamos que hable de esto con el asesor genético. Podemos hacer los arreglos para que se realice esta conversación, si lo desea.

Durante este proyecto de investigación puede descubrirse información sobre los padres de una persona. En otras palabras, se pueden descubrir asuntos relacionados con adopción y paternidad. Nuestra norma consiste en no hablar de este tipo de información a menos que tenga implicaciones médicas o reproductivas directas para usted o su familia.

Riesgos que son muy poco probables pero importantes: No le daremos ningún tipo de información sobre usted o su familia a compañías de seguros ni a empleadores, a menos que usted nos pida que lo hagamos. Sin embargo, se sabe de casos en los que un tercero obtiene o solicita información genética sobre una persona cuando dicha persona se presenta a un empleo o solicita un seguro médico. Toda la información que se obtenga o se descubra sobre usted o su familia será confidencial. Sin embargo, los tribunales pueden ordenar la entrega de la copia de un expediente médico. Si usted presenta una reclamación en concepto de asesoría genética ante su aseguradora particular, la aseguradora podría obtener información suya que pueda afectar su asegurabilidad.

Toda información que se obtenga o se descubra de usted o de su familia se considera confidencial. Sin embargo, nuestro compromiso con la confidencialidad no invalida la capacidad de un tribunal de obtener su expediente médico mediante un citatorio. Usted controla la entrega de toda información contenida en estos archivos; el acceso a ella por parte de otras personas, incluso de

miembros de su familia, solo es posible con su aprobación por escrito. Los resultados de investigación que contengan información sobre su composición genética se conservan con llave en oficinas seguras de investigación del Centro Clínico. Los expedientes médicos que contienen esta información se conservarán en el Centro Clínico de los Institutos Nacionales de Salud. En teoría, esto podría permitirles a otros investigadores de los NIH tener acceso a su información sin su aprobación expresa por escrito.

Medidas de protección contra el uso inadecuado de la información genética: Dado que algunas variaciones genéticas pueden ayudar a pronosticar problemas médicos en el futuro para usted y sus parientes, esta información puede ser de interés para los proveedores de atención médica, compañías de seguros médicos y otras personas. Sin embargo, las leyes federales y estatales disponen algunas medidas de protección contra la discriminación con base en información genética. Por ejemplo, la Ley Antidiscriminatoria por Información Genética [Genetic Information Nondiscrimination Act (GINA)] dispone que es ilegal que las compañías de seguros, grupos colectivos de salud y la mayoría de empleadores lo discriminen con base en su información genética. Sin embargo, GINA no impide que las compañías que venden seguros de vida, de incapacidad o de atención a largo plazo usen su información genética como justificación para negar cubrimiento o determinar primas. GINA tampoco aplica para los miembros de las Fuerzas Armadas de los Estados Unidos, para las personas cubiertas por el Seguro de Salud para Indígenas Estadounidenses ni para los veteranos que obtengan seguro médico por medio del Departamento de Asuntos de los Veteranos. Finalmente, GINA no prohíbe la evaluación de riesgo de seguros médicos con base en su estado de salud actual, aunque la Ley de Cuidado de Salud a Bajo Precio [Affordable Care Act] limita la consideración de enfermedades preexistentes por parte de las aseguradoras.

Posibles beneficios derivados de la participación

¿Hay beneficios asociados con la participación en este estudio?

Los beneficios probables incluyen la detección y el tratamiento temprano de las lesiones que tenga en el páncreas, lo que pudiera conducir a mejores resultados con respecto a su condición. Le ofreceremos la evaluación de seguimiento de las lesiones que tenga en el páncreas y, si corresponde, podemos ofrecerle una operación para extirparlas.

Estrategias o tratamientos alternativos

¿Qué otras alternativas tengo si no participo en este estudio?

En vez de participar en este estudio, usted tiene estas alternativas:

- Recibir tratamiento o atención para el cáncer sin participar en un estudio.
- Participar en otro estudio.

- Recibir atención médica que le proporcione alivio, lo cual se conoce como cuidados paliativos. Este tipo de atención ayuda a disminuir el dolor, el cansancio, los problemas de apetito y otros problemas causados por el cáncer. No trata el cáncer directamente, sino que trata de mejorar la forma en que usted se siente. Los cuidados paliativos tratarán de mantenerlo lo más activo y cómodo posible.

Hable con su médico sobre estas y otras alternativas.

Derechos de los participantes en la investigación

¿Cuál es el costo de participar en este estudio?

Si decide participar en el estudio, se aplicará lo siguiente, según las normas de los NIH:

- Usted recibirá el tratamiento del estudio completamente gratis. El tratamiento puede comprender una operación, medicamentos, pruebas de laboratorio, radiografías y otras pruebas de diagnóstico por imagen que se realicen en el Centro Clínico de los Institutos Nacionales de Salud o fuera de él, si en los NIH no se cuenta con ese tratamiento relacionado con el estudio y el equipo de investigación ha hecho arreglos para que se realice en otro centro.
- Hay fondos limitados para pagar el costo de algunas pruebas e intervenciones que se realicen fuera del Centro Clínico de los NIH. Es posible que tenga que pagar el costo de estas pruebas e intervenciones si su compañía de seguros no lo cubre.
- El Centro Clínico de los NIH no proporcionará los medicamentos que no formen parte del tratamiento del estudio ni pagará por ellos.
- Cuando usted haya finalizado su participación en el estudio, ya no se le prestará atención médica en el Centro Clínico de los NIH.

¿Se mantendrá en confidencialidad su información médica?

Haremos todo lo posible por asegurarnos de mantener la confidencialidad de la información personal contenida en su expediente médico. Sin embargo, no podemos garantizarle privacidad completa. Las organizaciones que pueden ver o copiar su expediente médico para efectos de investigación, garantía de calidad y análisis de datos comprenden:

- El Instituto Nacional del Cáncer (NCI) y otros organismos gubernamentales —como la Administración de Alimentos y Medicamentos (FDA)— que se encargan de que las investigaciones no constituyan un peligro para las personas
- El comité de ética en investigación (IRB) del Instituto Nacional del Cáncer

Suspensión de la participación en el estudio

Le haremos seguimiento en los NIH hasta que el estudio concluya o hasta que usted decida que ya no desea participar en él.

El médico también puede decidir retirarle del estudio si cree que esto es lo que más le conviene a usted. En ese caso, se le informará la razón por la que su participación en el estudio se da por terminada.

Usted puede dejar de participar en el estudio en cualquier momento. Sin embargo, si decide dejar de participar, nos gustaría que hablara primero con el médico del estudio y con su médico personal.

Si decide en algún momento retirar su consentimiento para participar en el estudio, no obtendremos ninguna información médica adicional acerca de usted. Si retira su consentimiento y se va del estudio, todas las muestras que se hayan obtenido de usted para el estudio y que se conserven en el NCI se pueden destruir cuando usted lo solicite. Sin embargo, las muestras y los datos obtenidos a partir de ellas que ya se hayan entregado a otros investigadores o que ya se hayan incluido en las bases de datos de investigación **no se podrán** recuperar ni destruir.

Certificado de confidencialidad

Este estudio ha recibido un Certificado de Confidencialidad que contribuye a la protección de sus datos de investigación. Los investigadores que realizan este estudio no pueden verse obligados a revelar la identidad de los participantes ni ninguna información que se recolecte en este estudio a causa de ningún procedimiento legal a nivel federal, estatal o local, sin importar que se trate de un procedimiento penal, administrativo o legislativo. Sin embargo, usted o el investigador pueden decidir revelar voluntariamente la información protegida en ciertas circunstancias. Por ejemplo, si usted solicita por escrito la entrega de la información, el Certificado no protege contra esa revelación voluntaria. Además, ciertos organismos federales pueden examinar sus expedientes en circunstancias limitadas; por ejemplo, el Departamento de Salud y Servicios Sociales (DHHS) podría solicitar información para efectos de auditoría o de evaluación de un programa, o la FDA puede hacer una solicitud de conformidad con la ley sobre alimentos, medicamentos y cosméticos [Food, Drug and Cosmetics Act]. El Certificado de Confidencialidad no protegerá contra la denuncia obligatoria que debe hacer el personal de un hospital si sospecha abuso de menores, si tiene conocimiento acerca de enfermedades contagiosas de notificación obligatoria o si alguien expresa una posible amenaza de hacerse daño o hacerles daño a otras personas.

Uso e información para futuras investigaciones

A fin de realizar avances científicos, es útil para los investigadores compartir la información que obtienen al estudiar de seres humanos. Esto se hace al registrar esta información en una o más bases de datos científicas, donde se almacena junto con datos de otros estudios. Un investigador

que desee estudiar la información debe solicitar acceso a la base de datos y recibir autorización. Los investigadores usan la información almacenadas en bases de datos científicas para realizar avances en la ciencia y aprender sobre la salud y las enfermedades.

Anticipamos mantener algunas de sus datos que obtengamos, usarlos en futuras investigaciones y compartirlos con otros investigadores. No lo contactaremos para que autorice cada uno de los usos futuros. A estas datos se les retirarán los identificadores, como nombre, dirección o número de cuenta, para que puedan usarse en futuras investigaciones sobre cualquier tema y se puedan compartir ampliamente con fines investigativos. Sus datos se usarán solo con fines investigativos y no lo beneficiarán. También es posible que nunca se usen ni los datos almacenados. Los resultados de la investigación que se realice con sus datos no estarán disponibles para usted ni para su médico, pero pueden ayudar a personas con cáncer y otras enfermedades en el futuro.

Si no desea que sus datos se usen en futuras investigaciones, por favor, escríbanos para avisarnos que no desea que lo hagamos. Entonces, y no se usará su información para futuras investigaciones. Sin embargo, es posible que no se puedan retirar o borrar o los datos una vez se hayan compartido con otros investigadores.

INFORMACIÓN PERTINENTE ADICIONAL

1. Confidencialidad. Cuando los resultados de un estudio de investigación de los NIH se dan a conocer en revistas médicas o reuniones científicas, no se menciona la identidad de los participantes. En la mayoría de los casos, los NIH no divulgará ninguna información sobre su participación en una investigación a menos que usted otorgue su permiso por escrito. No obstante, si usted firma una autorización de divulgación de información, por ejemplo, a una empresa aseguradora, los NIH le proporcionarán a esta información de su expediente médico. Esta información podría influir (en forma favorable o desfavorable para usted) en la disposición de la aseguradora de venderle el seguro.

La Ley Federal de Protección de la Vida Privada [Federal Privacy Act] protege el carácter confidencial de sus expedientes médicos en los NIH. Sin embargo, es importante que sepa que esta ley permite la divulgación de cierta información de su expediente médico sin su autorización, por ejemplo, si lo solicitan la Administración de Alimentos y Medicamentos (FDA), los miembros del Congreso, los agentes encargados del cumplimiento de la ley o las organizaciones autorizadas para efectos de acreditación hospitalaria.

2. Normas sobre lesiones relacionadas con la investigación. El Centro Clínico le dará atención médica a corto plazo para cualquier lesión que se deba a su participación en una investigación que se realice allí. En general, ni los Institutos Nacionales de Salud, ni el Centro Clínico, ni el gobierno federal le darán atención médica a largo plazo ni indemnización económica por lesiones relacionadas con la investigación. Sin embargo, usted tiene derecho a buscar una compensación legal si cree que la lesión justifica dicha medida.

3. Pagos. El monto del pago que se ofrece a los voluntarios de investigación se rige por las normas de los Institutos Nacionales de Salud. En general, a los pacientes no se les paga por participar en estudios de investigación en los Institutos Nacionales de Salud. Se ofrecerá reembolso de gastos de viaje y de viáticos según las normas de los NIH.

4. Problemas o preguntas. Si tiene algún problema o una pregunta respecto a este estudio, a sus derechos de participante en un estudio de investigación clínica o a alguna lesión relacionada con la investigación, debe comunicarse con el investigador principal, el doctor Electron Kebebew, Building (edificio) 10, Room (sala) 3C428, teléfono: 240-760-6153. También puede llamar al representante de los pacientes del Centro Clínico, al teléfono (301) 496-2626. También puede comunicarse con la Oficina del Director Clínico al teléfono 240-760-6070 si tiene alguna pregunta sobre el uso de sus datos en futuros estudios de investigación.

5. Documento de consentimiento. Le sugerimos que conserve una copia de este documento para consultarla posteriormente.

COMPLETE LAS CASILLAS CORRESPONDIENTES A CONTINUACIÓN:

A. Consentimiento de un paciente adulto.

He leído la explicación relacionada con este estudio y he tenido la oportunidad de comentarla y hacer preguntas. Por este medio otorgo mi consentimiento para participar en este estudio.

Firma del paciente adulto o de su representante legal _____ Fecha _____

Nombre en letra de imprenta _____

B. Permiso otorgado por el (los) padre(s) de un paciente menor de edad.

He leído la explicación relacionada con este estudio y he tenido la oportunidad de comentarla y hacer preguntas. Por este medio otorgo permiso para que mi hijo participe en este estudio.
(Anéxese el formulario de asentimiento para menores de edad, NIH 2514-2, Asentimiento de un menor de edad, si corresponde.)

Firma del (los) padre(s) o del tutor legal _____ Fecha _____

Nombre en letra de imprenta _____

C. Asentimiento verbal de un niño (si corresponde)

Se le explicó a mi hijo la información contenida en el formulario de consentimiento anterior y mi hijo accede a participar en el estudio.

Firma del (los) padre(s) o del tutor legal _____ Fecha _____ Nombre en letra de imprenta _____

EL USO DE ESTE DOCUMENTO DE CONSENTIMIENTO ESTÁ APROBADO DESDE EL 07 DE NOVIEMBRE DE 2016 HASTA EL 06 DE NOVIEMBRE DE 2017.

Firma del investigador _____ Fecha _____ Firma del testigo _____ Fecha _____

Nombre en letra de imprenta _____ Nombre en letra de imprenta _____