Study Identification

Unique Protocol ID: HEM-3331-20-20-1

Brief Title: Germline Mutations Associated With Hereditary Pancreatic Cancer in Unselected Patients With Pancreatic Cancer in Mexico.

Official Title: Prevalence Estimation of BRCA1, BRCA2 and Other Germline Mutations Associated With Hereditary Pancreatic Cancer Using a Comprehensive Gene Panel in an Unselected Cohort of Patients With Pancreatic Adenocarcinoma in a Mexican Population.

Document date: Version 1.1 (20 July 2020).

Study Protocol:
Prevalence estimation of *BRCA1*, *BRCA2* and other germline mutations associated with hereditary pancreatic cancer using a comprehensive gene panel in an unselected cohort of patients with pancreatic adenocarcinoma in a Mexican population.

Principal investigator:
[redacted], Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Vasco de Quiroga 15, Col. Belisario Domínguez Sección XVI, CP 14080, Mexico city, Mexico.

Version:
1.1 of July 20, 2020.

Background:
According to GLOBOCAN 2018, pancreatic cancer accounts for 458,918 new cases and 432,242 deaths worldwide (Bray F, et al). It is a highly lethal disease. In Mexico, it represents the 12th most common cancer with 4,849 new cases in both sexes. Pancreatic cancer represents the 7th cause of cancer death with 4,475 deaths in both sexes (https://gco.iarc.fr).
The incidence and mortality of pancreatic cancer varies across regions and populations. Both are expected to increase from 2018 to 2040. Africa, Latin America and the Caribbean will be most affected (Rawla P, et al.).
The cause of pancreatic cancer is multifactorial. However, around 10% of cases are associated with hereditary predisposition. Germline mutations in *BRCA1* and *BRCA2*, *CDKN*2*A*, *STK*11, DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* or *PMS2*), *PALB2, FANCC, FANCG,* and *ATM* have been associated with an increased risk for pancreatic cancer (Hruban RH, et al). Most of which are involved in mechanisms of DNA repair.
BRCA1 and *BRCA2* are tumor suppressor genes. *BRCA1* is located in chromosome 17 and *BRCA2* in chromosome 13. Their proteins play a key role in the maintenance of genomic integrity through the DNA repair by homologous recombination (Venkitaraman AR). Germline mutations in these genes have been linked to increased risk for breast, ovarian, prostate cancer, and gastrointestinal cancer, including pancreatic cancer. About 70-80% of the mutations in *BRCA* genes result in protein dysfunction or absence of protein product (Gorodetska I et al).
In pancreatic cancer, the prevalence of *BRCA* germline mutations varies across populations. For instance, the prevalence of *BRCA1/2* germline mutations in high-risk populations, including the Ashkenazi Jewish population, can be up to 20% (Murphy KM, et al and Stadler ZK, et al). On the other hand, in unselected patient population, the prevalence of *BRCA1/2* germline mutations is 5-7% (Golan T, et al). The relative risk of pancreatic cancer in *BRCA1/2* mutation carriers varies between 2.3 and 7-fold (Risch HA, et al).
In Mexico, prevalence of *BRCA* mutations in none cancer patients has been explored. Recently, Fernández-López JC, et al. identified a population frequency of deleterious mutations of 0.10% (1:996) for *BRCA1* and 0.27% (1:362) for *BRCA2*, and combined of 0.37% (1:265). They included 3985 Mexican samples, none of the subjects had diagnosis of cancer. However, data on the

prevalence of *BRCA1/2* inherited mutations in patients with pancreatic cancer in Mexican population are lacking.

Identification of *BRCA* germline mutations in patients with pancreatic cancer has implications for treatment. Recently, the POLO trial, a phase 3 trial, evaluated the efficacy of olaparib as maintenance therapy in patients who had a germline *BRCA1* o *BRCA2* mutation and metastatic pancreatic cancer without progression during first line platinum-based chemotherapy. Patients were randomized to receive maintenance olaparib or placebo. Olaparib showed longer progression-free survival than placebo (7.4 months vs. 3.8 months; hazard ratio for disease progression or death, 0.53; 95% CI, 0.35 to 0.82; P=0.004) (Golan T, et al.). On October 2018, the US Food and Drug Administration (FDA) granted orphan drug designation to olaparib for the treatment of patients with metastatic pancreatic cancer, according to the POLO trial results.

Moreover, the National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2019 Pancreatic Adenocarcinoma recommends germline testing for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes.

The identification of *BRCA* inherited mutations also allows family members to have genetic testing, counselling and possible screening in those high-risk individuals.

Problem:

Olaparib has recently been approved as a maintenance therapy for patients with germline *BRCA* mutation and metastatic pancreatic cancer that had not progressed during first line platinum-based chemotherapy. In the POLO trial, the reported prevalence of germline *BRCA* mutations was 7.5%. Patients from North America, Europe and the Asia-Pacific region were included. Mexico did not participate in the POLO trial. The prevalence of germline *BRCA* mutation in patients with pancreatic cancer in Mexico is unknown. Given possible therapeutic implications for patients with pancreatic cancer and opportunities for genetic counselling and screening for family members, it is mandatory to determine the prevalence of germline *BRCA* mutations in Mexican patients with pancreatic cancer.

Justification:

These data will highlight the importance of universal screening for germline mutations in pancreatic cancer. This will allow to identify germline mutations most frequently associated with pancreatic cancer. In addition, this knowledge will contribute to develop surveillance strategies in family members affected.

Hypothesis:

The prevalence of germline mutations in BRCA1/2 genes in an unselected sample (by family history) of patients with pancreatic cancer is similar to that reported in other unselected populations.

Objectives:

Primary:

To determine the prevalence of *BRCA1* and *BRCA2* germline mutations in a cohort of patients with pancreatic adenocarcinoma.

Secondary:
To determine the prevalence of other germline mutations in patients with pancreatic adenocarcinoma associated with hereditary pancreatic cancer (*ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*).
To describe the clinical and pathological characteristics of patients with pancreatic adenocarcinoma and *BRCA1*, *BRCA2* and other germline mutations.
To provide oncologic and genetic counselling for patients with pancreatic adenocarcinoma and germline mutations.
To establish a registry of family members of mutated patients eligible for genetic testing and provide appropriate cancer screening strategies for previvors or asymptomatic carriers.

Study design:
This is an observational, cross-sectional study. Prevalence will be determined by testing all consecutive patients with histologic diagnosis of pancreatic adenocarcinoma (PAC) regardless of family history, clinical stage and treatment. In other words, the prevalence will be determined in an unselected patient population. To decrease potential survivorship bias, we will include only patients with PAC within 6 months of diagnosis. Participants will provide inform consent and they will allow access to medical records. Patients´ demographics and cancer treatment information will be obtained from questionnaires completed by the participants and/or abstracted from medical records. A clinical geneticist will evaluate all patients, with emphasis on the cancer family history. They will provide a blood sample from peripheral access for DNA analysis; 10 mL of whole blood mixed with EDTA will be collected from each patient. We will use a commercial panel (Invitae Multi-Cancer Panel®) for DNA analyses.
Invitae Multi-Cancer Panel® analyzes 84 genes associated with hereditary cancers, including all genes specifically associated with hereditary pancreatic cancer. Invitae is a College of American Pathologist (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified clinical diagnostic laboratory performing full-gene sequencing and deletion/duplication analysis using next-generation sequencing technology (NGS). The Invitae Multi-Cancer Panel includes 84 genes: *AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, CTNNA1, DICER1, DIS3L2, EGFR, EPCAM, FH, FLCN, GATA2, GPC3, GREM1, HOXB13, HRAS, KIT, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RECQL4, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1.* Genes are tested for punctual variations in the sequence and for deletion/duplication using Next Generation Sequencing, and Multiplex Ligation Probe Amplification, respectively.

All results will be shared with patients according to the instructions approved by themselves in the informed consent. A clinical geneticist will discuss results with patients and provide counselling accordingly and will recruit the relatives at risk of inheriting the pathogenic variant with clinical significance. A medical oncologist will explain treatment options if it is appropriate.

Furthermore, genetic counselling will be provided to relatives of patients with germline mutations; we will recommend cancer screening as appropriate.
The study will be conducted at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) in Mexico City. Our site is a reference hospital for pancreatic diseases nationwide.

Inclusion Criteria:
- Female and male participants ≥ 18 years of age.
- Diagnosed within the previous 6 months with histologically confirmed pancreatic adenocarcinoma stage I to IV.
- Participant provides written informed consent for the study.
- Participant must agree to sample collection and genetic testing using the Invitae Multi-Cancer Panel ®.

Exclusion Criteria:
- Diagnosed with pancreatic adenocarcinoma more than 6 months before presenting to the clinical site.
- Diagnosed with intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, pancreatic neuroendocrine tumors.

Statistical methods:
This is an observational, cross-sectional study. To estimate the prevalence of *BRCA1* and *BRCA2* germline mutations in unselected pancreatic cancer patients, a sample size of 107 patients is required assuming a prevalence of 7.5%, precision of 5% and 95% Confidence Interval. We use a formula for a prevalence survey, with finite population correction.
BRCA1 and *BRCA2* prevalence will be defined as the proportion of patients with pathogenic germline mutations in *BRCA1*/*BRCA2*. Prevalence will be presented as percentage.
Prevalence of other germline mutations will be defined as the proportion of patients with pathogenic germline mutations in genes previously identified as increasing pancreatic cancer susceptibility. Prevalence will be presented as percentage.
Clinical and family history descriptive statistics will be calculated for study variables stratified by BRCA mutation status (positive or negative). The Fisher´s exact test will be use to compare the distribution of selected categorical variables between BRCA- positive or negative patients. All statistical test are two-sided with a statistical significance level of $P \leq 0.05$. All statistical analyses will be performed using IBM SPSS Statistics Version 21.

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Document date: Version 1.1 (20 July 2020).

INSTITUTO NACIONAL DE CIENCIAS MEDICAS Y NUTRICION SALVADOR ZUBIRAN

LETTER OF INFORMED CONSENT TO PARTICIPATE IN THE PROJECT:

Prevalence estimation of BRCA1, BRCA2 and other germline mutations associated with hereditary pancreatic cancer using a comprehensive gene panel in an unselected cohort of patients with pancreatic adenocarcinoma in a Mexican population.
Version 1.1 of July 20, 2020.

Principal investigator: [redacted].
Investigator's address: Avenida Vasco de Quiroga 15, Colonia Belisario Domínguez Sección XVI, C.P. 14080, Tlalpan, Mexico City, Mexico.
Investigator's contact telephone number (including one for 24-hour emergencies): 55 54 87 09 00, extension 2254, cell phone (24-hour emergency telephone number) 044 55 18 07 48 15.
Participating investigators: [redacted].
Name of study sponsor: This is an original research project under the responsibility of the principal investigator. AstraZeneca S. A. de C. V. will provide financial support for the payment of the required molecular tests.
Sponsor's address: Does not apply.
Informed consent version and date of its preparation: Version 1.1 dated July 20, 2020.

INTRODUCTION

This document is an invitation to participate in a research study from the institute. Please, take the necessary time to read this document; ask to the investigator or investigators any doubt you have.

Procedure for giving consent. You have the right to decide if you want to participate or not as a research subject in this project. The investigator must explain the benefits and risks of the project, without any pressure; you will have all the time necessary to think and consult with who you decide, before accepting to participate. Your decision will have no effect on your medical care at the institute.

To make a truly informed decision on whether you agree to participate in this study, you should have sufficient knowledge of the potential risks and benefits to your health when participating. This document will give you detailed information about the research study, which you can discuss with whoever you want, for example, a relative, your treating doctor, the principal investigator of this study, or a member of the research team. Your decision has no effect on your medical care at the institute. At the end once you read and understand this information. You will be invited to be part of the project and if you accept, without any pressure or intimidation, you will be invited to sign this informed consent. You may withdraw consent at any time.

At the end of the explanation, you must understand the following points:

I. The justification and objectives of the investigation.
II. The procedures to be used and their purpose, including identifying what are experimental procedure.
III. The anticipated risks or annoyances.

IV. The benefits that can be observed.
V. The alternative procedures that might be advantageous for you.
VI. Guarantee to receive answers to question and to clarify any doubts about procedures, risks, benefits, and other matters related to research and treatment.
VII. The freedom you have to withdraw your consent at any time and stop taking part in the study, without affecting your medical care and treatment at the institute.
VIII. The safety that you will not be identified in a particular way and that the confidentiality of your privacy information will be maintained.
IX. The investigator's commitment to provide you with the updated information that may be obtained during the study, although this may affect your willingness to continue your participation.
X. The availability of medical treatment and compensation to which you are legally entitled, in the event of damage caused directly by the investigator.

You can ask for more time or to take this document home before taking a final decision in the future.

INVITATION TO PARTICIPATE AS A RESEARCH SUBJECT AND DESCRIPTION OF THE PROJECT

About 10% of the patients diagnosed with pancreatic cancer have a family or hereditary component. Genes changes (mutations) associated with a high risk of developing pancreatic cancer have been identified. Genetics tests allow estimation of the risk of developing pancreatic cancer, allow early diagnosis of mutation carriers, and personalized treatment in patients with pancreatic cancer with specific mutations.

Dear Mr./Mrs. _____

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), through the gastrointestinal oncology research group, invites you to participate as a research subject in this study aims at: to know the frequency of gene alterations or changes (mutations) that are inherited and may be present in patient with pancreatic cancer using a genetic test, a blood sample will be taken for this purpose on only one occasion.

Total duration of the study: 15 months.
Your participation in the study: 3 months.
The approximate number of participants: 107.
You were invited to the study because you have the following characteristics: you are a man or a woman 18 years old or older diagnosed with pancreatic cancer in the last 6 months and your disease is being treated in the INCMNSZ.

PROCEDURES OF THE STUDY

Your participation in the study consists of an initial interview in which we will ask questions about your personal and family history of cancer, taking a blood sample to study possible changes or alterations (mutations) in genes in patients with pancreatic cancer, and a final interview to report the results of the previously performed blood study.

Study procedures include:

1) Initial interview: you will be asked for detailed information on your personal and family history of cancer. The interview will last approximately and will be conducted by a genetic doctor. There are not experimental interventions.

2) Blood sample is obtained of the arm's vein, in the same way it is taken for routine blood tests in a clinical laboratory, it is not necessary to fast. 10 mL (2 teaspoons) of blood should be obtained. Your blood sample will be sent and processed at the Invitae Laboratory in San Francisco, California, United States. The blood sample will be used to obtain DNA (deoxyribonucleic acid or genetic material) and to search for mutations. The remaining blood samples after carrying out the current investigation may be stored for up to 15 years for use in future research studies which will allow us to answer other questions related to pancreatic cancer. Biological samples shall not be used for the establishment of cell lines or immortals. There are not experimental interventions.

3) Genetic consultation: the results of the genetic study will be given to you or to the persona assigned as the recipient of the information of the results (specified in this same consent). You will be extensively explained the test results of your genetic material, to tell you whether you have or not genetic variants that confers risk of developing any other type of cancer. If you do not have genetic variant related with hereditary cancer; it does not merit further genetic follow-up and you will receive advice for a multifactorial disease. If you have in your genetic material a genetic variant that gives you an increased risk for developing other related neoplasms, you will be told what additional screening studies should be performed, as well as the importance of transmitting information to your family members who are at risk of having inherited the mutation that may lead to the appearance of pancreatic cancer in you. All these procedures result from everyday practice in the external consultation of genetics and are part of their evaluation and treatment in the institute, thus generating the usual cost of consultation according to their socio-economic level. There are not experimental interventions.

Mark the indicated statement that best describes your wishes:

_____ I authorize to share the results of the genetic study to my family members that can benefit from my result.

_____ I do not authorize to share the results of the genetic study to my family members that can benefit from my result.

Please write the name(s) of the person or people that are authorized to receive the result in case that you decide it this way:

_____

RISKS AND INCOVENIENTS

The regulation of the general health law on research for health states that the obtaining of biological samples represents a minimum risk within the research. The risks of obtaining the blood sample are minimum: local pain at the time of puncture, possibility of light bleeding or hematoma at the puncture site, dizziness or fainting sensation, and arterial puncture may occur rarely. The personnel who will take the blood sample are trained to do this, which will minimize the risks of complications.

The data about your identity and medical information will not be disclosed at any time as stipulated by law, therefore, in the collection of clinical data you do not face greater risks than those related to the protection of confidentiality which will be protected through the coding of the samples and their information.

There is the possibility that participating in this study will cause you concern or anguish about the possibility of having an alteration or change in genes (mutations) that increases the risk of developing cancer or transmitting (inheriting) this risk to your children. Also, talking about a family history of cancer may bring up painful memories and feelings. If you feel this way during the study, you can contact one of the researchers who can advise you and help you identify possible solutions.

On the other hand, there is the possibility of discrimination at work or for the granting of health insurance due to the results of genetic studies. To reduce this risk, we will not provide your results to anyone without your written permission.

POTENTIAL BENEFITS

Molecular test (blood sample) to look for genetic alterations or changes in blood (germline mutations or mutations inherited from your parents) associated with hereditary pancreatic cancer at no cost to you. Identify patients eligible for treatment with olaparib according to international recommendations: patients with metastatic pancreatic cancer without progression during first-line platinum-based chemotherapy and germline BRCA1 / 2 gene mutations. Receive specific recommendations to reduce the risk of suffering from another type of cancer. If you have a genetic alteration or change in the blood (mutation), a genetic study may be carried out in your asymptomatic relatives.

Advantages of the genetic study in asymptomatic relatives
Carrying out genetic tests on the relatives of people who have been identified as having an alteration in their hereditary material allows:

1) Detect individuals who are at risk of disease before the appearance of symptoms, the molecular tests that are required for their first-degree relatives (parents, children, siblings) will be free for their family.
2) Receive genetic counseling to discuss how the disease is inherited, complications of the disease, and reproductive options.
3) Detect neoplasms associated with the gene in question in earlier stages and minimize their severity.
4) Include the family member who inherited the mutation in a surveillance program for neoplasms related to the identified mutation, in accordance with international guidelines.

In addition, thanks to your altruistic participation, other patients with pancreatic cancer can benefit significantly from finding new ways to treat this disease.

ECONOMIC CONSIDERATIONS
No fee will be charged to participate in the study and no payment will be made to you. The investigator will cover the costs of the genetic test.

COMPENSATION
This study does not create a risk to your health. In the event of identifying alterations or genetic changes in the blood (germline mutations or mutations inherited by your parents) that have an impact on you or

any of your family members, we will provide you with specific recommendations and guidance to comply with these standard recommendations. However, the costs generated by compliance with these recommendations must be covered by you or your family members.

ALTERNATIVES TO YOUR PARTICIPATION:
Your participation is voluntary. So, you can choose not to participate in the study. If you decide not to participate, you will continue to receive the usual (standard) treatment or management for your condition.

POSSIBLE COMMERCIAL PRODUCTS DERIVED FROM THE STUDY:
The results or materials obtained in the study will be property of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). If a commercial product is developed because of the study, such input will be the property of the Institute or those they designate. In such case, you will not receive a financial benefit for it.

ACTIONS TO FOLLOW AFTER THE END OF THE STUDY:
You can request the results of your clinical examinations and the conclusions of the study from [redacted] of the INCMNSZ (tel. 5554870900 extension 2254). Research is a long and complex process. Obtaining the results of the study can take several months.

PARTICIPATION AND WITHDRAWAL FROM THE STUDY:

Remember that your participation is VOLUNTARY. If you decide not to participate, both your regular relationship with INCMNSZ and your right to receive medical care or any services to which you are entitled will not be affected. If you decide to participate, you are free to withdraw your consent and discontinue your participation at any time without impairing your attention at INCMNSZ. In that case, we will ask you to fill out the consent revocation form. If you withdraw your consent, you may request the destruction of your stored samples; however, information that has already been generated will not be destroyed. You will be informed in time if new information becomes available that may affect your decision to continue in the study. The study investigator may exclude you from the study if you do not provide the information or samples required for the study. You will not need to perform any procedures if the investigator withdraws you from the study.

CONFIDENTIALITY AND HANDLING OF YOUR INFORMATION

Your name will not be used in any of the study's public reports. The biological samples obtained will not contain any personal information and will be encoded with a consecutive number to avoid any possibility of identification. By legal provision, biological samples, including blood, are classified as hazardous biological-infectious waste and for this reason, during the investigation, your sample cannot be returned to you. It is possible that your biological samples, as well as your medical and/or genetic information, may be used for other analogous research projects related to the disease under study. They cannot be used for research studies that are related to conditions other than those studied in this project, and these studies must be submitted for approval by an Ethics Committee.

Leftover samples can be stored by researchers for up to 15 years.

The codes that identify your sample will only be available to the titular investigators, who are obliged by law not to disclose their identity. These codes will be kept in a locked file cabinet. Only researchers will have access to them.

Although there is the possibility that your privacy will be affected because of your participation in the study, your confidentiality will be protected as required by law, assigning codes to your information. The code is an identification number that does not include personal data. No information about you will be shared with others without your authorization, except:

- If it is necessary to protect your rights and well-being (for example, if you have suffered an injury and require emergency treatment); or
- It is required by law.

The INCMNSZ Research Ethics Committee approved the conduct of this study. This committee is the one who reviews, approves, and supervises the research studies in humans at the Institute. In the future, if we identify information that we consider important to your health, we will consult with the Research Ethics Committee to decide the best way to provide this information to you and your doctor. In addition, we ask that you authorize us to contact you, if necessary, to request information that could be relevant for the development of this project.

Scientific data obtained as part of this study could be used in medical publications or presentations. Your name and other personal information will be deleted before using the data.

If you request it, your medical doctor will be informed about your participation in the study.

Because of your participation in the study, it may be necessary to contact your family members. Your family members will not be contacted without your permission.

Your genetic material will not be used for purposes other than those mentioned in this document. If cells are obtained, they will not be used to create immortal cell lines. If the investigator wishes to use them for different purposes, he must notify you and request your signature on a document like the one you are reading, in addition to having the approval of the Research Ethics Committee.

The results of genetic studies could be a cause of discrimination for people who have an abnormality that predisposes them to a disease. We will take the necessary precautions and actions to prevent your information from being known to third parties that could take discriminatory actions against you. The results of genetic studies will not be included in your file at the Institute unless they have implications for your treatment.

IDENTIFICATION OF THE INVESTIGATORS:

In case you suffer damage related to the study, please contact [redacted] at INCMNSZ (tel. 5554870900 extension 2254). If you have questions about the study, you can contact [redacted] at INCMNSZ (tel. 5554870900 extension 2254).

If you have questions about your rights as a participant in the study, you can speak with the President of the Research Ethics Committee of INCMNSZ ([redacted], tel. 5554870900 ext. 6101).

STATEMENT OF INFORMED CONSENT

I have read this informed consent carefully; I have asked all the questions I have had, and they have all been answered to my satisfaction. To participate in the study, I agree to all the following:
I agree to participate in the study described above. The general and particular objectives of the recruitment and the possible damages and inconveniences have been explained to me to my complete satisfaction.
I agree to voluntarily donate my biological samples (blood) to be used in this study. Likewise, my medical and biological information may be used for the same purposes.
I agree, if necessary, to be contacted in the future if the project requires the collection of additional information or if they find information relevant to my health.
My signature also indicates that I have received a duplicate of this informed consent.

Please answer the following questions:

		YES (Mark please)	**NO (Mark please)**
a.	Have you read and understood the informed consent form, in your native language?	☐	☐
b.	Have you had a chance to ask questions and discuss this study?	☐	☐
c.	Have you received satisfactory answers to all your questions?	☐	☐
d.	Have you received enough information about the study, and have you had enough time to make the decision?	☐	☐
e.	Do you understand that your participation is voluntary and that you are free to suspend your participation in this study at any time without having to justify your decision and without affecting your medical care or without the loss of benefits that you would otherwise have right?	☐	☐
f.	Do you understand the possible risks, some of which are still unknown, of participating in this study?	☐	☐
g.	Do you understand that you may not receive any direct benefit from participating in this study?	☐	☐
h.	Do you understand that you are not giving up any of your legal rights to which you are otherwise entitled as a subject in a research study?	☐	☐
i.	Do you understand that the study physician may withdraw you from the study without your consent, either because you did not follow the study requirements or if the study physician considers that your withdrawal is medically in your best interest?	☐	☐

		YES (Mark please)	NO (Mark please)
j.	Do you understand that you will receive a signed and dated original of this Consent Form for your personal records?	☐	☐

Patient statement:

I, _____ declare that it is my decision to participate as a clinical research subject in the study. My participation is voluntary.

I have been informed that I may refuse to participate or terminate my participation at any time in the study without incurring any penalty or loss of benefits. If I suspend my participation, I will receive the usual medical treatment to which I am entitled at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) and I will not suffer damage in my medical care or in future research studies. I may request additional information about the potential benefits or risks of my participation in this study. I can also get the results of my clinical exams if I request them.
If I have questions about the study, I can contact [redacted] tel. 5554870900 extension 2254.

I have read and understand all the information given to me regarding my participation in this study. I have had the opportunity to discuss it and ask questions. All questions have been answered to my satisfaction. I understand that I will receive a signed copy of this informed consent.

I am clear that in case I have questions about my rights as a clinical research subject in this study, problems, concerns, or doubts, and I wish to obtain additional information, or to comment on the development of the study, I am free to speak with him. President of the Research Ethics Committee of the INCMNSZ ([redacted], tel: 5554870900. ext. 6101).

_____ _____

Name of the participant Signature of the participant

_____

Date

_____

Place the participant's fingerprint on this line if he/she can´t write

_____ _____

Name of legal representative (if apply) Signature of legal representative

_____

Date

_____ _____

Name of the investigator that explained this document Signature of the investigator

_____

Date

_____ _____

Name of witness 1 Signature of witness 1

_____ _____

Date Relationship with the participant

Address:

_____

_____

_____ _____

Name of witness 2 Signature of witness 2

_____ _____

Date Relationship with the participant

Address:

_____

_____

Place and date: _____

(This document is original and consists of 9 pages)