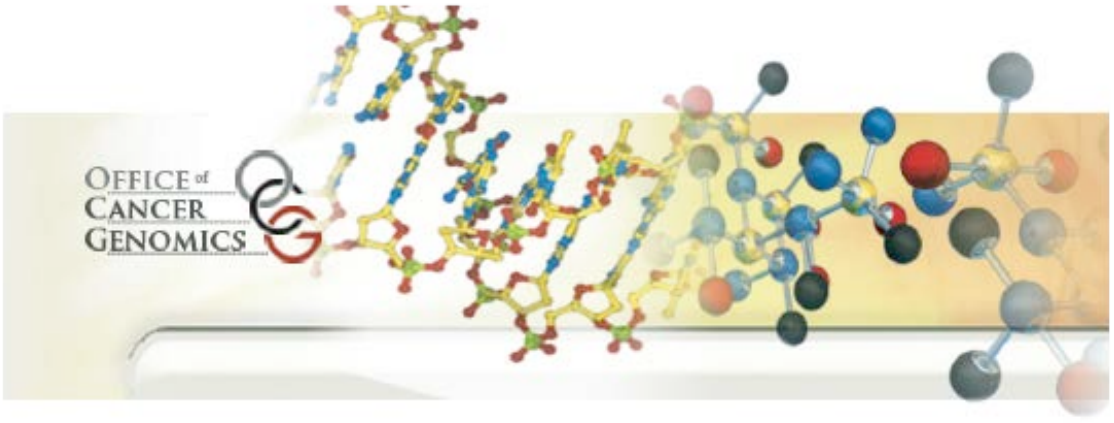
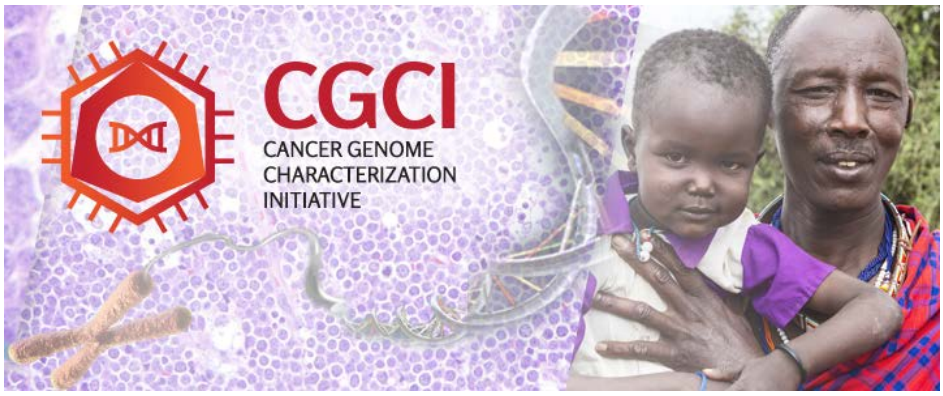
National Cancer Institute



Office of Cancer Genomics (OCG) Cancer Genome Characterization Initiative (CGCI) General Templates

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health



Dear Colleague,

You are about to review the latest version of the National Cancer Institute Office of Cancer Genomics book of Standard Operating Protocols (SOPs) that should be followed when you contribute samples and data to our large-scale genomic characterization project(s).

The sample and data acquisition process is explained in comprehensive detail to ensure that all materials contributed will be of sufficient quality to be utilized in the projects. However, the actual process is simple and requires only six basic steps:

1. Creation of an IRB approved protocol and informed consent forms.
2. Institutional Certification of patient consent.
3. Acquisition and freezing of tumor samples.
4. Acquisition and freezing of patient-matched normal samples (*e.g.* blood).
5. Acquisition of unstained formalin-fixed paraffin-embedded sections for pathology review.
6. Shipment of tissues and data.

The book is divided into general protocols and templates that apply to all projects, as well as tissue/disease-specific ones. Although many protocols are included in this book, only a handful of them may apply to yourself, depending on your role in the acquisition process:

- Clinical Practitioners
    - IRB approved protocol and informed consent templates (OCG Templates #101-103).
    - General guidelines on the process and clinical data requirements (HTMCP SOP #201, BLGSP SOP #301).
- Institutional Officials
    - Material Transfer Agreement (MTA; OCG Template #104).
    - Institutional Certification letter (OCG Template #105).
- Laboratory or research personnel
    - General guidelines on the process and clinical data requirements (HTMCP SOP #201, BLGSP SOP #301).
    - Processing tissue for molecular characterization (HTMCP SOP #205, BLGSP SOP #305).
    - Processing normal tissue samples (HTMCP SOP #206, BLGSP SOP #306).
    - Shipping guidelines and procedures (HTMCP SOP #207 & 208, BLGSP SOP #307 & 308).

Should you require any clarification on the protocols and/or process, please do not hesitate to contact the appropriate OCG personnel listed in your SOPs.

OCG Template #102: Office of Cancer Genomics Suggested Language for Prospective Tissue Collections in Genomic-Scale Projects

NOTE: Highlighted text of this document has to be used as provided in your Institution's informed consent forms for the samples to be acceptable to the project

Purpose of the Project

We would like to invite you to participate in a research project called **[Project Name]**. The purpose of the **[Project Name]** project is to discover genetic changes associated with cancer, thus potentially leading to better prevention, detection and treatment of cancer, and perhaps other diseases as well.

This project is being sponsored by the National Cancer Institute (NCI), part of the government agency known as the National Institutes of Health (NIH).

Bodily tissues are made up of cells containing DNA, which is part of the unique genetic material carrying the instructions for your body's development and function. Cancer can result from changes in this genetic material, thereby causing cells to divide in an uncontrolled way and possibly to travel to other organs. Some of the genetic changes leading to cancer are currently known, however many remain to be discovered.

The **[Project Name]** project is designed to identify genetic changes that can cause cancer in humans. As such, we would like to study the genetic material obtained from your tumor tissue as part of the **[Project Name]**. We will compare the genetic material from your cancerous tissue with the genetic material from your normal tissue to find any differences that may exist. By combining information about genetic differences between normal and disease tissues along with information contained in your medical records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. This same process will be performed with normal and cancerous tissues obtained from a number of other people who have agreed to participate in this research project. In this way, we expect to identify most of the genetic changes associated with many different kinds of cancer. By comparing treatment responses of patients with various cancers (through recorded medical information), this project could also lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatment options could potentially become customized to a patient's unique genetic make-up.

Description of the Research

Collection of Samples and Medical Information

- Your scheduled surgery is part of the medical treatment that you agreed upon with your doctor. During surgery, cancerous tissue will be removed. Usually, when cancerous tissue is removed, very small amounts of nearby normal tissue are removed as well. Your surgery is <u>not</u> part of the

[Project Name] research project. We will receive some of these cancerous and normal tissues following your surgery.

- We will collect a sample of blood (approximately 4 tablespoons), drawn from a vein in your arm, as a second type of normal tissue.
- Should you object to having blood drawn, we will instead swab cells from inside of your mouth through gentle sweeping of the inner cheeks to obtain a secondary source of normal tissue.
- We will also collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information

- Your tissues, blood or buccal (cheek swab) sample, and medical information will be labeled with a confidential project-assigned ID.
- Only Dr. **[Physician Name]** at **[Institution Name]** will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number, or social security number. Dr. **[Physician Name]** will keep the information that matches the confidential code to this identifying information in a safeguarded database. Only authorized personnel, who have specifically agreed to protect your identity, will have access to this database. All materials conveyed to the **[Project Name]** will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information

- Your coded tissue samples will be sent to an NCI-sponsored storage facility. The facility will process the samples and then send portions of your samples to different types of laboratories for analysis as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other laboratories will study your samples by different methods. The remaining tissue from your samples might be stored for an unlimited period of time for use in future research related to cancer, or perhaps in other research projects.
- Information obtained from analyses performed on your coded samples and medical information will be entered into Internet-accessible databases along with information acquired from the other research participants in this project.
    - Anonymous information from the analyses, which cannot be traced to any individual patient, will be available to anyone in a completely public Internet database.
    - Information obtained from more detailed analyses, along with your confidential coded medical information, will be put into a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access Committee. In gaining access to such information, researchers have to agree to use the data only for research projects and not to ever try to use it in order to identify the donor of the material. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Please note that traditionally-used identifying information about you, such as your name, address,

telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Recontact

- In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Should this be needed, a person from **[Institution Name]** will contact you with an explanation of the reasons for any follow-up and to ask whether you would be interested in participating in this additional research.

Financial Compensation/Costs

You will not be paid to participate in this project. Your tissue samples and your medical information will be used for research purposes only and will not be sold. It is possible that some of the research conducted using your tissue samples or medical information will eventually lead to the development of new diagnostic tests, drugs or other commercial products. Should this occur, you will not receive any part of the profits generated from such products.

You will not incur any expenses from participating in this project. The chance that you will be physically injured as a result of participating in this project is highly unlikely. However, if you are physically injured as a result of participating in this project, emergency medical treatment for your research-related injury will be provided to you at no cost.

Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research, aside from the knowledge that your participation will help researchers and health professionals around the world to better understand the causes of cancer and other diseases. Research projects such as this lead to better ways to prevent, detect, treat, and cure such illnesses.

Potential Risks of Participating in the Project

Physical Risks

- There are very few physical risks associated with this project. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually lasts only a few minutes. Every precaution will be taken to minimize these effects.

Psychological or Social Risks Associated with Loss of Privacy

- Your privacy is very important to us, and we use many safety measures to protect your privacy. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you (your name, address, telephone number, or social security number), technology may be developed in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information back to you. Because some genetic variations can help to predict the current or future health problems of you and your relatives, this information may be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could potentially be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative).
- There also may be other privacy risks that we have not foreseen.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is currently no federal law that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these potential risks.

Confidentiality

We will make every attempt to protect your confidentiality and to ensure that your personal identity remains anonymous. This signed consent form will be stored in a locked file that will be accessible only to authorized people involved with this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section on pages 1 and 2 of this document.

Project Results

Your individual results from this research project will not be given back to you or put into your medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as your name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **[Project Name]** website.

Alternatives to Participating in the Project

The alternative option is not to participate in this project.

Voluntary Participation

The choice to participate in this research by donating your tissues and medical information is

completely up to you. **No matter what you decide, your decision will not affect your medical care**.

Withdrawal from the Project

Once your coded samples have been distributed to the participating research laboratories and centers, and your information transferred to the appropriate databases, you will **not** be able to withdraw your information from this research project. However, you may be able to request the return or destruction of the tissue samples if you so desire.

Contact Information

If you have any questions about the project or your participation, [*please use specific institutional language here, but do not automatically promise ability to withdraw*].

Agreeing to Participate in the Project
To participate in this research, you must agree to ALL of the following statements:

- I voluntarily agree to donate cancerous tissue and normal tissue to be used for this and for other research projects.
- I agree to release information from my medical records for this and for other research projects.
- I agree to have my coded genetic information and coded medical information placed into Internet-accessible databases as described in the *Storage and Release of Samples and Medical Information* section on page 2 of this document.
- I understand that my coded genetic information and coded medical information contained in the Internet-accessible databases will be used in this and in other research projects.
- I understand that there is a risk that someone in the future may be able to use information in these databases to identify me or possibly my relative(s).
- I agree to be contacted in the future about my willingness to provide additional samples or follow-up information about my health or medical care if it is required.

Please sign your name here if you agree to the six statements listed above.

Your signature: _____

Date: _____

Signature of Doctor/Nurse/Other Witness_____

Date: _____

OCG Template #103: Office of Cancer Genomics Suggested Language for Retrospective Tissue Collections in Genomic-Scale Projects

NOTE: Highlighted text of this document has to be used as provided in your Institution's informed consent forms for the samples to be acceptable to the project.

Purpose of the Project

We would like to invite you to participate in a research project called **[Project Name]**. The purpose of the **[Project Name]** project is to discover genetic changes associated with cancer. This should lead to better ways to prevent, detect, and treat cancer and, perhaps, other diseases as well.

This project is being sponsored by the National Cancer Institute (NCI), part of the government agency known as the National Institutes of Health (NIH).

Body tissues are made up of cells. Cells contain DNA, which is part of your unique genetic material that carries the instructions for your body's development and function. Cancer can result from changes in a person's genetic material that cause cells to divide in an uncontrolled way and, sometimes, to travel to other organs. Currently, researchers and doctors know some of the genetic changes that can cause cancer, but they do not know all of the genetic changes that can cause cancer.

The **[Project Name]** project is designed to identify most of the genetic changes that can cause cancer in people. Therefore, we would like to study the genetic material from your cancer tissue as part of the **[Project Name]**. We will compare the genetic material from your cancer tissue to the genetic material from your normal tissue to find the differences that exist. By combining this information with information from your medical records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. We will perform this same process with many (hundreds of) other people who have agreed to participate in this research project. By studying many different kinds of cancer in this way, we expect to identify most of the genetic changes associated with different kinds of cancer. Since we also will combine genetic information with information from medical records, such as the responses of different kinds cancers to different treatments, this project could lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatments potentially could become customized to a patient's unique genetic make-up.

Description of the Research

Collection of Samples and Medical Information

- You already have had surgery as a part of the medical treatment that you agreed upon with your doctor. During your surgery, cancerous/tumor tissue was removed. As usually happens, when your cancerous tissue was removed, very small amounts of nearby normal tissue were

removed along with it. Your surgery was not part of the **[Project Name]** project. For this research project, we seek permission to receive some of these cancerous and normal tissues.

- If a second type of normal tissue (e.g., blood) was collected from you before or after your surgery, we request permission to obtain some of this tissue and genetic material that already may have already been extracted from this tissue.
- If an adequate blood sample is not available for this project, we will collect a sample from you by drawing approximately 4 tablespoons of blood from a vein in your arm. If you object to having blood drawn, we will collect normal tissue from you by swabbing cells from the inside of your cheeks.
- We will also collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information

- Your tissues, blood or buccal (cheek swab) sample, and medical information will be labeled with a project-assigned ID.
- Only Dr. **[Physician Name]** at **[Institution Name]** will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number, or social security number. Dr. **[Physician Name]** will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only authorized people, who have specifically agreed to protect your identity, will have access to this database. All materials conveyed to the **[Project Name]** will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information

- Your coded tissue samples will be sent to an NCI-sponsored storage facility that will process the samples and then send portions of your samples to different types of laboratories as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other laboratories will study your samples by different methods. The remaining portions of your samples will be stored for an unlimited period of time for future use in research related to cancer, or perhaps in other research projects.
- Information obtained from analyses performed on your coded samples and your coded medical information will be put into databases along with information from the other research participants. These databases will be accessible by the Internet.
    - Anonymous information from the analyses will be put into a completely public database, available to anyone on the Internet.
    - Your coded medical information and information from more detailed analyses of your coded samples will be put into a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access Committee. In gaining access to such information, researchers have to agree to use the data only for research projects and not to ever try to use it in order to

identify the donor of the material. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Please note that traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Recontact

- In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Should this be needed, a person from **[Institution Name]** will contact you to ask whether you would be interested in participating in this additional research.

Financial Compensation/Costs

You will not be paid to participate in this project. Your tissue samples and your medical information will be used only for research purposes and will not be sold. It is possible that some of the research conducted using your samples or information will eventually lead to the development of new diagnostic tests, new drugs or other commercial products. Should this occur, you will not receive any part of the profits generated from such products.

You will not incur any expenses from participating in this project. It is unlikely that you will be physically injured as a result of participating in this project. However, if you are physically injured as a result of participating in this project, emergency medical treatment for your research-related injury will be provided to you at no cost.

Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research. The main reason you may want to participate is to help researchers and health professionals around the world to better understand the causes of cancer, and other diseases, and potentially to find better ways to prevent, detect, treat, and cure such illnesses. We hope that you will feel good knowing that you may be helping future cancer patients, as well as patients with other diseases.

Potential Risks of Participating in the Project

Physical Risks

- If no blood sample is taken from you, there are no physical risks associated with this project.
- There are very few physical risks if a blood sample is taken from you. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

Psychological or Social Risks Associated with Loss of Privacy

- Your privacy is very important to us, and we use many safety measures to protect your privacy. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do

share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you (your name, address, telephone number, or social security number), technology may be developed in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information back to you. Because some genetic variations can help to predict the current or future health problems of you and your relatives, this information may be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could potentially be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative).
- There also may be other privacy risks that we have not foreseen.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is currently no federal law that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these potential risks.

Confidentiality

We will make every attempt to protect your confidentiality and to make sure that your personal identity remains anonymous. This signed consent form will be stored in a locked file that will be accessible only to a very small number of authorized personnel involved in this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section on pages 1-3 of this document.

Project Results

Your individual results from this research project will not be given back to you or put into your medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as your name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **[Project Name]** website.

Alternatives to Participating in the Project

The alternative option is not to participate in this project.

Voluntary Participation

The choice to participate in this research by donating your tissues and medical information is completely up to you. **No matter what you decide to do, your decision will not affect your medical care**.

Withdrawal from the Project

Once your coded samples have been distributed to the participating research laboratories and centers, and your information transferred to the appropriate databases, you will **not** be able to withdraw your information from this research project. However, you may be able to request the return or destruction of the tissue samples if you so desire.

Contact Information

If you have any questions about the project or your participation, [*please use specific institutional language here, but do not automatically promise ability to withdraw*].

Agreeing to Participate in the Project

To participate in this research, you must agree to <u>ALL</u> of the following statements:

- I voluntarily agree to donate cancerous tissue and normal tissue to be used for this <u>and</u> for other research projects.
- I agree to release information from my medical records for this <u>and</u> for other research projects.
- I agree to have my coded genetic information and coded medical information placed into databases accessible by the Internet, as described in the *Storage and Release of Samples and Medical Information* section on page 2 of this document.
- I understand that my coded genetic information and coded medical information in the Internet-accessible databases will be used in this <u>and</u> in other research projects.
- I understand that there is a risk that someone in the future might be able to use information in these databases to identify me or possibly my relative(s).
- I agree to be contacted in the future to see if I am willing to provide additional samples or follow-up information about my health or medical care if they are needed.

Please sign your name here if you agree to the six statements listed above.

Your signature: _____
Date: _____

Signature of Doctor/Nurse/Other Witness_____
Date: _____

OCG Template #104:
Institutional Material Transfer and Data Use Agreement

This Material Transfer and Data Use Agreement (the "Agreement") is entered into by and between _____ ("Provider") and _____ ("Recipient"), regarding the transfer of human specimens and associated data to the Recipient as part of tumor characterization projects and associated research coordinated by the National Cancer Institute's Office of Cancer Genomics ("the Projects"), including **[Project Name]**. Throughout this Agreement, Provider and Recipient are collectively referred to as the "Parties" and individually as "Party." This Agreement will become effective upon the date of the last signature affixed below (the "Effective Date").

WHEREAS, in order to improve the ability to diagnose, treat, and prevent cancer, the National Cancer Institute ("NCI"), a member institute of the National Institutes of Health, an agency of the federal government, has undertaken the Projects as a comprehensive and coordinated research effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing;

WHEREAS, the Projects are managed by the NCI Office of Cancer Genomics;

WHEREAS, under the Projects, clinically annotated tissue samples will originate from several clinical Tissue Source Sites, and the tissue samples and associated data will be processed by centralized core facility(ies);

WHEREAS, Recipient has been selected to act as a centralized core facility, pursuant to a subcontract with NCI's Operations and Technical Support ("OTS") contractor, Leidos Biomedical Research, Inc. or directly with the NCI (either, the "OTS Contractor"), and the tasks with which it is charged include receiving and processing human biospecimens, derivative materials and associated data and distributing all of the foregoing to NCI approved characterization centers ("the Centers") and distributing only the associated data to a data coordinating center that is operated by NCI ("DCC");

WHEREAS, Recipient, as a subcontractor of NCI's OTS Contractor, desires to receive and, in conjunction with subcontractors of Recipient and the NCI and/or Leidos Biomedical Research, Inc. (collectively, "the Project Subcontractors"), process biospecimens, derivative materials and associated data from the Provider and distribute the same to the Centers and a DCC, as appropriate;

WHEREAS, Provider, acting as a Tissue Source Site under the Projects, desires to transfer certain human biospecimens, derivative materials, and associated data to Recipient for further distribution to the Centers and a DCC, as appropriate;

WHEREAS, the Centers and the DCC, pursuant to policies and practices established as part of the Projects, may not make a claim for intellectual property rights in the MATERIAL (as defined below), nor may they make a claim for intellectual property rights in DATA (as defined below) prior to its public availability;

WHEREAS, Provider and Recipient desire to protect the privacy and provide for the security of certain information disclosed to Recipient in compliance with applicable laws and regulations; and

WHEREAS, Provider, if an entity of the United States of America ("U.S."), may be a covered entity subject to the Health Insurance Portability and Accountability Act of 1996, as amended ("HIPAA"), and, if not a U.S. entity, desires to protect the privacy of certain information disclosed to the Recipient in a manner consistent with HIPAA and the applicable laws of its jurisdiction that are similar in nature.

NOW, THEREFORE, in consideration of the mutual promises in this Agreement and for other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties hereby agree as follows:

1. DEFINITIONS. Within this Agreement, the following terms will have the same meaning and effect as those used in the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 CFR Parts 160 and 164 ("HIPAA Privacy Rule"). These terms are repeated here for convenience.

(a) Under 45 CFR 160.103 ("Definitions"), a "covered entity" is an organization, individual, institution, or other entity that is subject to the standards, requirements, and implementation specifications of the HIPAA Privacy Rule with respect to protected health information.

(b) Under 45 CFR 164.514 ("Other requirements relating to uses and disclosures of protected health information"), "De-identified" information is information that formerly contained individually identifiable health information but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information. Identifying information includes, but is not limited to, the 18 categories of identifiers described in 45 CFR 164.514(b)(2).

(c) Under 45 CFR 164.103 ("Definitions"), "Protected Health Information" or "PHI" means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

(d) Under 45 CFR 164.514(e)(2) ("Implementation Specification: Limited data set"), a "limited data set" (herein "LDS") is protected health information that excludes the 16 direct identifiers listed in that

section. Any such information that identifies the individual who is the subject of the PHI, his or her relatives, employers, or household members must be removed for the PHI to constitute an LDS.

2. DESCRIPTION OF MATERIAL AND DATA.

(a) The material to be transferred ("ORIGINAL MATERIAL") is a set of human biospecimens described specifically as: Human Tumors, Matching Normal Specimens or Blood, and Formalin Fixed Paraffin Embedded Tissues.

(b) The data to be transferred to Recipient are clinical, biological, technical and/or other information describing the ORIGINAL MATERIAL ("DATA"). Some of the DATA may be Protected Health Information and will be transferred in the form of an LDS.

3. COLLECTION OF MATERIAL AND DATA. The Provider represents and warrants to Recipient that: (a) as necessary, all ORIGINAL MATERIAL and DATA provided to Recipient by Provider were collected pursuant to and in accordance with a protocol approved by an Institutional Review Board ("IRB"); (b) the IRB's oversight of the collection of any ORIGINAL MATERIAL and DATA included a review of all necessary informed consents and authorizations, which consents do not prohibit redistribution of the ORIGINAL MATERIAL or materials derived from the ORIGINAL MATERIAL, e.g., DNA and RNA products ("DERIVATIVE MATERIAL," together with the ORIGINAL MATERIAL, the "MATERIAL") or DATA in the manner described in Section 4 of this Agreement; (c) the transfer, processing and analysis of the ORIGINAL MATERIAL and DATA, as part of the Projects and for the Purpose (as defined below), is authorized by or consistent with the general principles of the informed consent of the patient supplying such ORIGINAL MATERIAL and DATA, as determined by an IRB; and (d) the collection of the ORIGINAL MATERIAL and DATA was conducted in compliance with all applicable laws, regulations and policies for the protection of human subjects, including, in the case where Provider is a covered entity, 45 CFR Part 46, "Protection of Human Subjects" (the "Common Rule") and the HIPAA Privacy Rule, and any necessary approvals, authorizations, human subjects assurances, informed consent documents, and IRB approvals were obtained.

4. TRANSFER OF ORIGINAL MATERIAL AND DATA; PURPOSE. (a) Provider agrees to provide to Recipient the ORIGINAL MATERIAL and DATA, in the form of an LDS pursuant to Case Report Forms provided by the Recipient to the Provider, in accordance with applicable laws, regulations and policies, including but not limited to the Common Rule, the HIPAA Privacy Rule, and any necessary authorizations, human subjects assurances, informed consent documents, and IRB approvals. The sole and limited purpose of the Provider's transfer to Recipient of the ORIGINAL MATERIAL and the DATA is to enable Recipient to receive, process and distribute the MATERIAL and the DATA, in the appropriate form as indicated below, to the Centers, a DCC, and the Project subcontractors in fulfillment of its contractual obligations to NCI's OTS Contractor (the "Purpose"). If Provider is a HIPAA Covered Entity, the Parties expressly intend for this Agreement to constitute a Data Use Agreement, authorizing use and disclosure only in furtherance of the Purpose, in accordance with 45 CFR 164.514(e)(4). Provider is responsible for removing all of the prohibited direct identifiers from the DATA, such that the DATA will be in the form of an LDS, before transfer to Recipient.

(b) Provider has the authority and hereby grants Recipient explicit permission to further distribute the MATERIAL and De-identified DATA to the Centers and the Project Subcontractors.

(c) Provider has the authority and hereby also grants Recipient explicit permission to further distribute the DATA, in the form of an LDS, to a DCC upon execution by both Recipient and NCI of a Data Use Agreement that is consistent with the requirements of the HIPAA Privacy Rule. Furthermore, Provider acknowledges and agrees that Recipient may allow the DCC to provide all or part of the LDS to third parties pursuant to separate Data Use Agreements that are no less restrictive than this Agreement and that prohibit such third parties from further distributing the LDS.

(d) The Agreement does not restrict the Provider's right to distribute the MATERIAL and DATA to third parties.

5. RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT

(a) Recipient's IRB has approved the Recipient's participation in the Projects (IRB approval number: IRB 12-00222). Recipient agrees to handle and distribute the MATERIAL in accordance with all applicable laws, regulations and policies, including, as applicable, the Common Rule, the HIPAA Privacy Rule, and any necessary human subject's assurances, informed consents and IRB approvals.

(b) Recipient further agrees that it will only use and/or disclose the DATA for the Purpose described herein and shall not use or disclose the DATA in a manner inconsistent with the HIPAA Privacy Rule.

(c) Recipient is not authorized and shall not further disclose the DATA other than as permitted by this Agreement or as otherwise required by law. Recipient shall not distribute the DATA to other third parties without written consent from Provider and the NCI Program Director or designee for the particular Project in question.

(d) Recipient shall use appropriate administrative, technical, and physical safeguards to prevent use or disclosure of the DATA other than as provided for in this Agreement.

(e) Recipient shall notify Provider in writing within five (5) working days of its discovery of any use or disclosure of the DATA not permitted by this Agreement of which Recipient, its officers, employees, or agents become aware. Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure required by applicable federal law.

(f) Recipient shall ensure that any of its agents or subcontractors agree with Recipient in writing that such agent or subcontractor will hold any DATA transmitted from the Recipient to such agent or subcontractor confidential and will use or disclose the information only for the purpose for which it was used or disclosed to the agent or subcontractor, or as required by law. Additionally, the agent or subcontractor shall notify Recipient of any instances, of which it is aware, in which the DATA has been used or disclosed inconsistent with this Agreement.

(g) Recipient agrees to not identify or contact any donor, or living relative of a donor, who provided the MATERIAL or any DATA received by Recipient under this Agreement from Provider. Furthermore, Recipient will not attempt to obtain or otherwise acquire any PHI associated with the MATERIAL beyond that which is provided in the DATA by the Provider.

(h) Recipient will retain and abide by this Agreement for as long as it retains the DATA or other PHI received from the Provider, plus six (6) years after the date it returns or destroys all such information.

6. BREACH OR VIOLATION. Provider is not responsible for Recipient's violations of this Agreement, unless Provider knows of a pattern of activity or practice that constitutes a material breach or violation of this Agreement, in which case it must take reasonable steps to cure the breach, end the violation or withhold the LDS or other PHI delivered to Recipient. If this is not possible, the breach will be reported to the Secretary of the Department of Health and Human Services ("DHHS").

7. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

8. DISCLAIMER. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. SUBJECT TO THE REPRESENTATIONS IN SECTION 3 ABOVE WITH RESPECT TO THE MATERIAL OR DATA, PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL OR DATA WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

9. DISPOSAL OF MATERIAL AND DATA. At the end of its subcontract with the NCI's OTS Contractor or upon the termination of this Agreement by either Party, Recipient will dispose of the MATERIAL and DATA in its possession in the manner decided at the sole discretion of the NCI Office of Cancer Genomics or designee for the particular Project in question and consistent with law and the informed consent of the individual providing the ORIGINAL MATERIAL. Such disposition may include, but is not limited to, continued storage on behalf of Provider for future research, transfer to the Provider, use in an expansion of the Projects, transfer to another organization acting on NCI's behalf, or destruction. NCI shall be responsible for ensuring that any directive given to the Recipient regarding the disposition of the MATERIAL and DATA is consistent with the informed consent of the patient who provided the ORIGINAL MATERIAL. Provider acknowledges that any ORIGINAL MATERIAL transferred by Recipient to the Centers may be destroyed as a consequence of the analyses conducted in accordance with the Projects.

10. INTELLECTUAL PROPERTY. Provider explicitly retains ownership of ORIGINAL MATERIAL and DATA. Provider acknowledges and agrees that it does not by virtue of this Agreement acquire any intellectual property rights in the future inventions or discoveries made by third parties using the MATERIAL or DATA distributed by Recipient. Recipient acknowledges that it serves only as the custodian of the MATERIAL and DATA, and therefore agrees that it does not by virtue of this

Agreement acquire any intellectual property rights in the MATERIAL or DATA, nor any future intellectual property rights in any research conducted by third-parties using the MATERIAL or DATA.

11. ASSIGNMENT; SUCCESSORS AND ASSIGNS; NO THIRD-PARTY RIGHTS. Recipient may not assign its rights or cause to be assumed its obligations hereunder without the prior written consent of Provider, which consent shall not be unreasonably withheld or delayed. Subject to the foregoing, this Agreement shall apply to, be binding in all respects upon and inure to the benefit of the Parties hereto and their respective successors and assigns. Nothing expressed or referred to in this Agreement shall be construed to give any person or entity other than the Parties hereto any legal or equitable right, remedy or claim under or with respect to this Agreement or any provision of this Agreement.

12. COST. The MATERIAL and DATA are provided at no cost to Recipient.

13. SHIPPING. Provider will notify Recipient when the ORIGINAL MATERIAL and DATA are ready for shipment. Recipient will be responsible for the pick-up and shipment, including shipping costs, of the ORIGINAL MATERIAL and DATA.

14. ENTIRE AGREEMENT. This Agreement constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes and replaces all prior agreements, understandings, commitments, communications and representations made between the Parties, whether written or oral, with respect to the subject matter hereof. This Agreement may not be amended, supplemented, or otherwise modified except by a written agreement executed by each of the Parties.

15. TERMINATION. Either Party has the right to terminate this Agreement at any time upon sixty (60) days prior written notice to the other Party.

16. INDEMNIFICATION. Each party shall indemnify, defend and hold the other party and its parent and affiliates and their officers, directors, employees, and agents, harmless from and against any claims, charges, judgments, costs, liabilities, damages, losses, or expenses (including reasonable attorneys' fees and expenses of litigation) resulting from any third party claims, allegations, suits, actions, or demands (collectively "Claims") that arise out of or result from the indemnifying party's acts or omissions relating to this Agreement or the indemnifying party's failure to perform any obligation undertaken or covenant made in this Agreement. The indemnified party shall promptly notify and provide reasonable cooperation to the indemnifying party in the defense of any Claim for which indemnification is sought at the indemnifying party's expense. The indemnifying party shall have the right to settle Claims; provided, however, that the indemnifying party shall make no admission of fault or wrongdoing or other statement reflecting negatively on the indemnified party, without the indemnified party's prior express written consent.

17. INSURANCE. Each party shall maintain liability coverage of the types and at the levels that are usual and customary to insure its obligations and activities under this Agreement.

18. NOTICE. All notices, requests, demands, and other documentation required or permitted to be given under this Agreement shall be provided in writing and will be deemed to have been fully given and received (i) when delivered in writing personally; (ii) when sent by confirmed electronic message or facsimile; (iii) five (5) days after having been sent by registered or certified mail, return receipt requested, postage prepaid; or (iv) one (1) day after deposit with a commercial overnight carrier, with written verification of such receipt, to the addresses provided below.

19. WAIVER. No waiver by either Party of any term or condition of this Agreement, no matter how long continuing or how often repeated, shall be deemed a waiver of any subsequent act or omission, nor shall any delay or omission on the part of either Party to exercise any right, power, or privilege or to insist upon compliance with any term or condition of this Agreement be deemed a waiver of such right, power or privilege or excuse a similar subsequent failure to perform any such term or condition. All waivers must be in writing and signed by the Party granting such waiver.

20. EXECUTION OF AGREEMENT. This Agreement may be executed in two or more counterparts, each of which will be deemed to be an original copy and all of which, when taken together, will be deemed to constitute one and the same agreement. The exchange of copies of the Agreement and of signature pages by facsimile or electronic transmission will constitute effective execution and delivery of this Agreement as to the Parties hereto and may be used in lieu of the original Agreement for all purposes. Signatures of the Parties transmitted by facsimile or electronic transmission will be deemed to be their original signatures for all purposes.

[The rest of this page was left blank intentionally. Signature page follows.]

IN WITNESS WHEREOF, the Parties have executed this Agreement through their duly authorized representatives as of the Effective Date.

Signature for Provider

Provider Scientist:
Provider Organization:
Address:

Name of Authorized Official:
Title of Authorized Official:

_____
Signature of Authorized Official Date

Certification of Provider Authorized Official: This Agreement __has / __has not been modified from the original template.

Signature for Recipient

Recipient Scientist
Recipient Organization:
Address:

Name of Authorized Official:
Title of Authorized Official:

_____
Signature of Authorized Official Date

OCG Template #105: Institutional Certification for Participation in Office of Cancer Genomics Projects

Notes: This Institutional Certification must be submitted on the Principal Investigator's Institutional letterhead. Please complete the highlighted portions of the document with the relevant information.

Date: Month Day, Year

To: Dr. Elizabeth Gillanders
GWAS Program Administrator
National Cancer Institute, NIH, DHHS
EPN, Room 5116
6130 Executive Blvd
Rockville, MD 20892

Re: Institutional Certification of [name of PI's institution] to Accompany Submission of the Dataset for the [name of project] to the NIH Database of Genotypes and Phenotypes (dbGaP).

Dear Dr. Gillanders:

[Name of PI's institution] hereby certifies that submission of data from the study entitled [name of project] to dbGaP meets the following expectations, as defined in the *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),* Notice Number: NOT-OD-07-088:

- The data submission is consistent with all applicable laws and regulations, as well as institutional policies.
- The appropriate research uses of the data and the uses that are specifically excluded by the informed consent documents are delineated.

Data Use Limitation:
Use of the data is limited to scientific research relevant to the etiology, prevention, treatment, and late complications of treatment of cancer and for the development of applications proposing analytical methods, software, or other research tools.

Are the aggregate level data appropriate for general research use[1]? ☐ Yes ☐ No

- The identities of research participants will not be disclosed to dbGaP.
- An Institutional Review Board and/or Privacy Board, as applicable, reviewed and verified that:

- The submission of data to dbGaP and subsequent sharing for research purposes are consistent with the informed consent of the study participants from whom the data were obtained;
- The investigator's plan for de-identifying datasets is consistent with the standards outlined in the policy;
- It has considered the risks to the individuals, their families, and groups or populations associated with data submitted to NIH GWAS data repository; and
- The genotype and phenotype data to be submitted were collected in a manner consistent with 45 CFR Part 46.

Sincerely,

Authorized Institutional Official:

Name: _____ Title: _____

Signature: _____ Date: _____

Principal Investigator:

Name: _____ Title: _____

Signature: _____ Date: _____

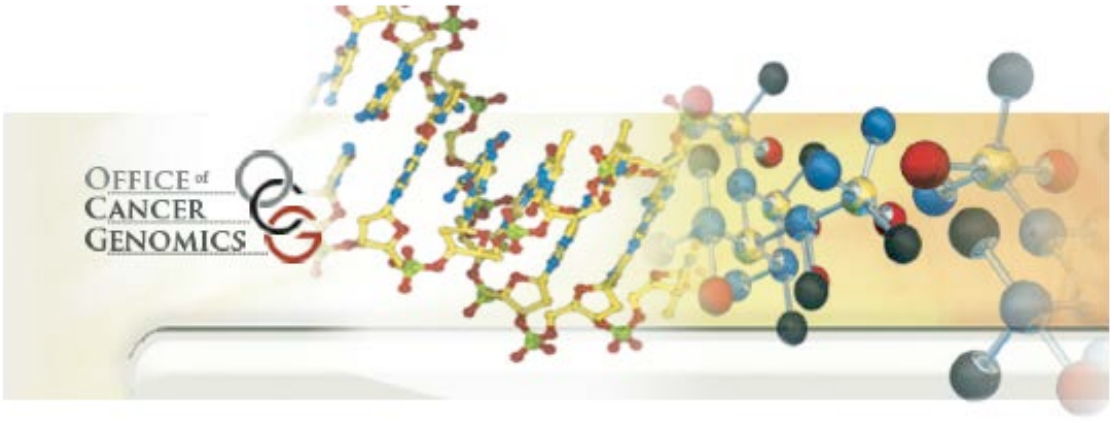
[1] To be included in the Compilation of Aggregate Genomic Data, a collection of analyses across many dbGaP studies that can be accessed with a single Data Access Request.

Acknowledgement Statement

The suggested Publication Statement to accompany the data set is:

This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. [Funding mechanism].

National Cancer Institute



HIV+ Tumor Molecular Characterization Project (HTMCP) General Protocols

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

OCG Template #101: Template for HIV+ Tumor Molecular Characterization Project (HTMCP) Biology Protocol

Principal Investigator:

Co-Investigators:

HTMCP Project Contact:

Statistician:

Table of Contents

1.0 Schema

Tumors to be accrued

- HIV-Associated Diffuse Large B Cell Lymphoma
- HIV-Associated Non-Small Cell Lung Cancer
- HIV-Associated Cervical Cancer

Procedures

- Samples (tissues) to be obtained prior to oncologic treatment (e.g. neo-adjuvant therapy)
    - Tumor tissue biopsy, tissues from surgical resection and/or tumor bone marrow aspirate (for lymphomas)
    - Case matched normal peripheral blood mononuclear cells; buccal cells or adjacent normal tissues. Blood mononuclear cells are purified and frozen
- In lieu of frozen tissue, FFPEs may be used if it meets the following requirements:
    - At least 10-20 mg of tissue
    - Fixative buffer pH should be noted
    - No age requirement, but age of FFPEs should be noted
- All tissues must be snap frozen
- Tissue block or unstained slides from formalin fixed, paraffin-embedded (FFPE) tissue (tumor and/or adjacent normal) and/or bone marrow biopsy must be available

Sample Distribution

- Frozen tissues, bone marrow, and/or peripheral blood mononuclear cells will be shipped to British Columbia Genome Science Center, Vancouver, Canada
- Unstained slides of formalin fixed tissue and/or bone marrow biopsy will be shipped to the appropriate designated central pathology lab

Data Submission

- Clinical report forms are submitted to the NCI Data Coordinating Center

2.0 Background and Rationale

2.1 HIV-Associated Malignancies

HIV infection is associated with a variety of malignancies, including “AIDS-defining cancers” and “non-AIDS-defining cancers” [1]. The AIDS-defining cancers are non-Hodgkin’s lymphomas, Kaposi’s sarcomas, and cervical cancer. AIDS-defining non-Hodgkin’s lymphomas are predominantly diffuse large B-cell lymphomas, Burkitt lymphomas, and less commonly primary effusion lymphomas and plasmoblastic lymphomas. Non-AIDS defining cancers that are increased in prevalence among HIV-1 infected individuals include anal carcinomas, Hodgkin’s lymphomas, non-small cell lung cancers, and hepatocellular carcinomas.

The cause for increased prevalence of malignancies in HIV-1 infected individuals is poorly understood, and no systematic molecular characterization of these neoplasias has been reported to

date. Many HIV-associated malignancies are also associated with other oncogenic virus infections. These include members of the human papilloma viruses and gamma herpes viruses, including Epstein-Barr virus and Kaposi's sarcoma herpes virus (KSHV), however not all AIDS associated malignancies have been linked to such co-infections. Viruses are associated with a variety of malignant and pre-malignant conditions [2]. Human papilloma viruses are the cause of almost all anogenital carcinomas, and approximately 50% of oral malignancies [3, 4]. Epstein-Barr virus is associated with Burkitt lymphoma, nasopharyngeal and gastric carcinomas, NK/T cell lymphomas, AIDS lymphomas, Hodgkin's lymphomas, post-transplant lymphoma, and pediatric AIDS-associated leiomyosarcomas [5]. KSHV (human herpes virus 8, HHV8) is associated with Kaposi's sarcoma, primary effusion lymphomas, and multicentric Castleman's disease [6]. Human T-cell leukemia virus (HTLV) type 1 causes adult T-cell leukemia and HTLV-associated myelopathy, as well as pneumopathy, uveitis, and immunosuppressive conditions [7]. A recently discovered polyoma virus, Merkel's carcinoma virus, is associated with the majority of cases of Merkel's neuroendocrine skin malignancies. Hepatitis viruses type B (HBV) and C (HCV) are associated with hepatocellular carcinoma, and HCV is also associated with splenic marginal zone lymphomas. Another recently identified virus, xenotropic murine leukemia-related virus (XMRV) may be associated with human prostate malignancy and chronic fatigue syndrome, although this remains controversial [8]. Other viruses have been implicated in collagen vascular, hepatobiliary, and other malignancies, but definitive information is currently lacking [9, 10]. These infections may be pathogenic in immunosuppressed individuals as a result of an impaired cell-mediated immune response resulting in chronic and incompletely suppressed infection. Malignancies may also arise from cytokine release from activated T cells induced by HIV infection or other opportunistic infectious agents complicating HIV infection.

HIV-1 and -2 are associated with immunodeficiency, which predisposes individuals to infections by opportunistic infectious agents, including oncogenic viruses. HIV-associated immunodeficiency also inhibits anti-tumor mechanisms that result in an increased frequency of a variety of tumors [11, 12]. Thus, HIV-1 infection is associated with markedly increased prevalence in AIDS-defining malignancies, such as Kaposi's sarcoma, non-Hodgkin-s lymphoma, and cervical malignancies, as well as increased prevalence of non-AIDS defining malignancies, including Hodgkin's lymphoma, anal carcinomas, as well as plasma cell neoplasms, hepatocellular malignancies, lung and testicular malignancies. The effects of HIV and other viruses on mechanisms of tumorigenesis remain to be defined, and this information may provide a solid foundation for new therapeutic approaches.

Comprehensive sequencing of genomes and transcriptomes in cancers that arise in HIV-infected individuals through the HIV+ Tumor Molecular Characterization Project (HTMCP, http://cgap.nci.nih.gov/Cancer_Types) may provide a starting point for a systems biology approach towards understanding differences in pathway activation among identical histological subtypes of cancers in immunocompetent and immunodeficient patients. The results obtained should provide important clues to the pathways that either allow tumors to counteract immune surveillance mechanisms or are redundant in the presence of an extrinsic oncogenic influence such as oncogenic viruses.

2.2 Rationale

Rapidly evolving sequencing and informatics tools are substantially diminishing costs of comprehensive characterization of tumor transcriptomes and tumor genomes. These advances have resulted in detailed information on the repertoire of alterations in cancers. Novel approaches of

genomic sequencing analyses have provided new tools of pathogens discovery and new information on cellular genetic alterations associated with viral pathogenesis.

The availability of high quality, clinically annotated patient samples is crucial for the study of biologic factors that influence the progression and treatment response of HIV-1 malignancies. Comprehensive genomic sequence of HIV-associated cancers may identify diagnostic or prognostic disease signatures, and recurrent "driver" alterations that may be targets for new therapies. It is also possible that the comparison of transcriptomes and genomes between lymphomas from HIV^+ and HIV^- individuals might identify novel non-human sequences that could potentially suggest the presence of transcripts from hitherto undiscovered oncogenic viral agents.

3.0 Objectives

The primary objective of this HTMCP biological protocol is to support investigation of the hypothesis above by accrual of high quality, clinically annotated tissue from patients with HIV-1 malignancies. This material will be used to study clinical, genetic, and immunologic parameters that might have prognostic significance and/or are involved in the initiation and progression of HIV-1 malignancies in the context of the HTMCP initiative. The project include complete genomic and transcriptomic sequencing of HIV-associated diffuse large B cell lymphomas, lung and cervical cancer and matched normal tissue from the same individuals.

4.0 Eligibility Criteria

1. **Diagnosis**. Patients must have a diagnosis of one of the HIV-associated malignancies aforementioned or clinical findings suggestive of a possible HIV-associated malignancy. Patients that had undergone neo-adjuvant therapy are not eligible for the HTMCP.
2. **Age**. Patients must be ≥ 18 years old.
3. **Informed Consent.** Patients must have signed an IRB-approved informed consent document that permits the use of the samples for genomic-based molecular characterization projects.

5.0 Sample and Data Acquisition and Processing

Samples will be obtained and processed using protocols developed for HTMCP.

5.1 Tumor Sample Acquisition

Samples will be obtained from HIV positive patients who had diagnosis of any of the cancers listed in page 3 and will undergo either surgery or biopsy from which sufficient quantity of tissue will available along with case matched blood, buccal cells and/or normal adjacent tissue. Not all samples accrued yield RNA and DNA in sufficient quantities or meet the technical quality criteria (DNA: 80% of molecular weight 10,000 or higher; RNA: RNA Integrity Number (RIN) of seven or higher).

Specifically, this protocol requests:

- Permission to obtain solid tumor tissues donated by the patient at the time of the surgery; OR
- Biopsy tissue from a lymph node or other organ involved with malignancy that remains after the necessary samples are used for optimal medical care of the patient. The sample may be obtained by either surgical biopsy(ies) or needle core biopsies (concurrent

additional biopsies taken at the same time as biopsy for pathological diagnosis are acceptable).

- The minimum requirement of tumor tissue amount varies with the cancer type, however, as a general rule, 100 mg of tissue is necessary for the HTMCP. All tissues must be snap-frozen in liquid nitrogen within 20 minutes of removal following the established protocol provided in HTMCP SOPs.
- About 4 tablespoons of blood drawn from a vein. If the patient objects to having blood drawn, an alternative is to collect normal tissue by swabbing cells from the inside of their cheeks.
- A tissue block (or in its absence, unstained slides) from FFPE tumor must be submitted for centralized pathology.
- Permission to collect information from the patient medical records, including age, ethnic background, diagnosis, disease history, medical treatments, surgical pathology, and response to treatments.

5.2 Case-matched Normal Tissue Acquisition

All participants in this study will have a 10 mL sample of peripheral blood drawn by venipuncture or cannulation of an indwelling venous access device. Samples will be placed in sterile EDTA, or sodium citrate or heparin anticoagulant vacutainer tubes, and cryopreserved following the established protocol. This blood draw may occur at the same time as a blood draw for routine medical care.

In cases when blood draw is not possible, buccal cells will be collected. Adjacent normal tissue from surgery samples could be collected as well.

5.3 Sample and Data Storage

5.3.1 Sample Identification and Assurance of Anonymity

All biological materials and medical information will be coded in HTMCP. Only the designated gatekeeper at each Institution will keep the code key that matches the project identifying number to the personally identifiable information, as indicated in the NIH Guide for Identifying Sensitive Information: http://datacenter.cit.nih.gov/interface/interface241/PIIguide.html (Note: this is applicable in the US, other countries may have different regulatory frames that must be complied with) using procedures in place and approved by the local institution. Researchers, including those who will be working with the patient samples and medical information, will not have access to any of the traditionally used identifying information about the patient. All materials submitted to the HTMCP will be labeled with a project-assigned ID.

5.3.2 Storage and Release of Samples and Medical Information

The coded tissue samples will be sent to the Genome Science Center of the British Columbia Cancer Agency (BC-GSC), which is the characterization center for the HTMCP. The samples will be processed there and the molecular analytes extracted from samples will be used for sequencing. Any remaining samples will be stored at the BC-GSC until the end of the project. At the end of the project, any remaining samples will be handled in accordance with the protocol of contributing institution as designated in the disposition form.

Data stripped of identifiers, in compliance with the definition specified in the HIPAA Limited Data

Set definition: http://hipaa.wisc.edu/ResearchGuide/limiteddatasets.html, will be submitted by the contributing institution to the Data Coordinating Center (DCC). The DCC serves as a central HTMCP project database. The DCC also stores the molecular profiling data generated with the DNA and RNA.

5.4. Sample Shipment

The complete sample sets (tumor and case-matched normal DNA source) will be shipped to the BC-GSC following the procedures.

5.5. Research Plan Outline

Samples will be processed and analyzed at the GSC by high-coverage genomic and transcriptomic sequencing. The results will be analyzed will be made between tumor and normal DNA to identify the somatic changes present in the cancer tissues. These alterations include detection of chromosomal changes, such as, but not limited to, amplification (and levels), deletions, loss of heterozygosity, translocations, etc., expression profiling as well as detection of transcripts resulting from translocations and mutations, including single nucleotide variants, insertions, deletions etc. . The results from the tumors of one type will be examined for patterns of common changes, including mutations as a first step to identify the molecular changes that drive the cancer etiology. The alterations will also be analyzed within the context of biological pathways and systems biology.

5.6. Clinical Data Collection

For patients whose samples will become part of HTMCP, clinical information will be collected as described in the clinical report form (for lymphoma lung and cervical malignancies, HTMCP SOP #101A, B and C respectively). These patients will be followed prospectively in order to record the types of treatment given and treatment outcome and toxicity. Follow-up information will include the results of subsequent laboratory and imaging tests, pathology, cytogenetic and molecular diagnostic reports, and records describing the patient's course in the inpatient and outpatient setting. (Note: this enumeration of data points is specific for HTMCP project but might not be necessary in the protocol depending on your IRB practices).

5.7. Data Dissemination

- Information (data) from analyses of the coded samples and the coded medical information will be deposited into publicly available databases. These databases will be accessible by the Internet. Medical information and molecular characterization results on the coded samples will be stored in a controlled-access database. The information in this database will be available only to researchers have received approval from the NCI Data Access Committee after their institutions have certified their adherence to patient data protection policies for the project (http://epi.grants.cancer.gov/dac/charter.html).
- Anonymous information from the analyses will be put in a public database, available to anyone on the Internet.

6.0. Financial Compensation/Costs

Patients will not be paid to participate in this project. Tissue samples and the medical information will be used only for research purposes and will not be sold. It is possible that some of the research

conducted using the samples or information eventually will lead to the development of new diagnostic tests, new drugs or other commercial products. Should this occur, the patient will not receive any part of the profits generated from such products.

The patient will not incur any expenses from participating in this project.

The chance that the patient will be physically injured as a result of participating in this project is very small. However, if the patient is physically injured as a result of participating in this project, emergency medical treatment for the patient's research-related injury will be provided to the patient at no cost. (**Note**: this paragraph might not be applicable to your institution, if so, please remove)

7.0. Potential Patient Risks/Benefits

7.1. Potential Benefits of Participating in the Project

The patient should not expect to personally benefit from this research. The main reason the patient may want to participate is to help researchers and health professionals around the world to better understand the causes of cancer and so that they can find better ways to prevent, detect, treat, and cure the disease in the future.

7.2. Potential Risks of Participating in the Project

This project is considered a *minimal risk* protocol.

7.2.1 Physical Risks

- If a blood sample is NOT taken, there are no physical risks associated with this project.
- If a blood sample is taken, the physical risks are minimal. Possible risks from blood draw include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Short faint or light-headedness can sometimes occur.

7.2.2. Psychological or Social Risks Associated with Loss of Privacy

Breach of confidentiality is likely the greatest risk of participating in this study. Every effort will be exerted to minimize this risk. There also may be other privacy risks that we have not foreseen. While we believe that the risks to the patient and his/her family are very low, we are unable to tell exactly what all of the risks are.

Despite the extensive security measures employed to protect the identities of patients and their donated tissue specimens, there is a possibility that the identities of patients enrolled in this study could be discovered or linked to genetic sequence data obtained from their tissue specimens. Consequently, it is possible to use this information to link them to the identities of their children, parents, siblings, and other relatives. It may be possible to identify patients as carriers of genetic mutations. It is also possible that there could be violations of the security used to store the codes linking patient's genetic information. In the case of such breach, there could be risks of denial of employment, insurance, etc.

8.0. Project Results

Individual results from this research project will not be given back to the patient or put into the patient's medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as the patient's name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the HTMCP website: http:/ocg.cancer.gov.

9.0. Alternatives to Participating in the Project

The alternative option is not to participate.

9.1 Voluntary Participation

The choice to participate in this research by consenting the use the patient's donated tissues and medical information for the HTMCP project is completely up to the patient. No matter what the patient decides to do, his/her decision will not affect their medical care.

9.2 Withdrawal from the Project

Once the molecular analysis and patient information have been transferred to the DCC, it will not be possible to destroy those data. At the end of the project, unused tissue samples will be destroyed or returned to the contributing institution as is specified in protocol (HTMCP SOP #108).

Literature Cited

1. Boshoff C, Weiss R: **AIDS-related malignancies.** *Nature Reviews in Cancer* 2002, **2:**373-382.
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HTMCP SOP #201: Document Requirements for Sample Submission to the HIV+ Tumor Molecular Characterization Project

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. It is possible that the comparison of transcriptomes and genomes between tumors from HIV^+ and HIV^- individuals may or may not identify novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

It is imperative that all personnel involved in the project read all the protocols and adhere to them at all times. It is your responsibility as a contributor to the HTMCP to familiarize yourself with all aspects of the procedures and assure their compliance.

Scope and Purpose

1. To list all the documents needed in order to start collection of samples for the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200A-D) with the details.

Requirements

1. Every TSS must have an Institutional Review Board (IRB)-approved protocol in place that allows collection of tumor tissue, matched normal tissue (blood, whenever possible) and clinical data that can be used in a characterization project. The protocol must have explicit language permitting the molecular characterization of the samples by genomic-scale methodologies, and subsequent deposition of the data into a public, but protected database. HTMCP SOP #202 provides advice for writing a study protocol to submit to an IRB. A sample protocol with the suggested language is provided as OCG Template #101.

2. Every patient accrued to the project must be enrolled in the protocol and agree to participate by signing an informed consent. A sample informed consent document which contains the required language is provided as OCG Template #102.
3. If you require additional assistance drafting such a protocol or informed consent form, please contact the PT representative (see HTMCP SOP #200A-D).
4. TSSs must have in place a materials transfer agreement (MTA) with the Genome Science Center at British Columbia (GSC-BC; see HTMCP SOP #200A-D), Nationwide Children's Hospital (NCH; see HTMCP SOP #200A-D), and the Pathology Coordinator (see HTMCP SOP #200A-D) to allow transfer of tissues and pathology reports. A sample MTA is provided as OCG Template #104. Contact the PT manager if you need assistance.
5. OCG will store a copy of the IRB-approved protocol and a blank informed consent form. Additionally, certification that such a protocol exists, and that patients have been consented, must be provided to the NCH and OCG by the TSS institution before the samples can be accepted and costs can be reimbursed. A template of such a certification document is provided as OCG Template #105.
6. The completed Institutional Certification must be sent to the PT and the NCH before any sample can be shipped.

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HTMCP SOP #202: How to Complete a Study Protocol Request to an Institutional Review Board (IRB) for the HIV+ Tumor Molecular Characterization Project

Introduction

The HIV+ Tumor Molecular Characterization Project's (HTMCP) goal is to develop a comprehensive database of the molecular changes in Human Immunodeficiency Virus (HIV)-associated cancers (from HIV-infected patients) that will be available to the research community world-wide. It will allow the comparison between the cancer related alterations in HIV+ patients and HIV- patients. The project aims to generate large scale, high quality data on the cancers' genomes and transcriptomes using 2nd generation sequencing technology which means that the changes identified range from large genomic rearrangements, expression profile changes and detection of mutations.

In order for cases to be included in the project, the patients must provide consent of participation in an approved IRB protocol specifying that the samples can be used for genomic characterization and that the data deposited in a publicly available, yet patient privacy designed database. The Office of Cancer Genomics of the National Cancer Institute has created a generic template that contains the appropriate language to help the Tissue Source Site (TSS) in producing the IRB document. This template lacks details that are Institution-specific and should not be considered complete.

Scope and Purpose

1. To establish a set of guidelines for TSSs to create their own study protocol to submit to their IRB in order to contribute samples to the HTMCP.
2. This SOP is meant to be useful to TSSs contributing samples to the HTMCP, but if an Institution has their own process, as long the study protocol includes the specifics provided below, that is also acceptable.

Instructions

1. Obtain the IRB-approved study protocol template (OCG Template #101) from either the OCG SOP package sent when you agreed to participate in the HTMCP or the OCG SharePoint site: https://ocg-sps.nci.nih.gov/HIV_Tumors/default.aspx. You may also request a copy from the Project Team representative (see contact sheet).

2. Fill in your organization name, PI's name and other pertinent information in the form. The Project name is "HIV+ Tumor Molecular Characterization Project" and its acronym is HTMCP.
3. The project rationale can be found in the introduction section of SOP#201.
4. The total number of samples that will be analyzed for each tumor type is 100.
5. Details on amount of tissue requested are given in HTMCP SOP#203 under the sample requirement section.
6. Details on the blood collection for germline DNA extraction can be found in HTMCP SOP#206.
7. Cheek swabs will not be used as a source of normal DNA in this project; please delete that language in the template.
8. All the operational details of the project are clearly specified in the SOPs sent to the TSSs. It is expected that all participating personnel will read the SOPs, be familiar with the project procedures and requirements and follow them in all instances.

Questions regarding this protocol should be directed to the Project Team representative (see HTMCP SOP #200).

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HTMCP SOP #204: Sample Identifier Standards for the HIV+ Tumor Molecular Characterization Project

Introduction

To assure the privacy of all human subjects that have consented to donate their tissues and clinical data to the HIV+ Tumor Molecular Characterization Project (HTMCP), all the materials given to the project must be de-identified prior to shipment and study. This project-assigned ID must have a rational structure that permits tracking of which subproject, tissue source site (TSS), and case is labeled.

Scope and Purpose

1. To establish a sample identifying standard to be applied to all samples and data contributed to the HTMCP.
2. This procedure applies to all laboratory personnel.

Adopted Standards

Samples contributed to the HTMCP must be labeled with a project-assigned ID obtained from the Data Coordinating Center (DCC, see HTMCP SOP #200A-D) by the TSS previous to shipment.

These codes must have the following form:

HTMCP - ## - ## - ##### - ##X - ##Y

Where:

1. HTMCP stands for HIV+ Tumor Molecular Characterization Project
2. The next 2 digits identify the tumor type (01=DLBCL, 02=Lung, 03= Cervical, 04= Anal)
3. The next two digits identify the Tissue Source Site
4. The next five digits are the case identifier
5. The next three characters
    a. The two digits specify the tissue code (see table on next page)
    b. The letter identifies the aliquot/section of the sample
6. The final three characters denote the nucleic acid code if applicable (see list on next page)

Tissue Codes

Sample Code	Description	Code
Primary Tumor	Primary Solid Tumor	01
Recurrent Tumor	Recurrent Solid Tumor	02
Primary Blood Cancer	Primary Blood Derived Cancer – Peripheral blood	03
Recurrent Blood Cancer	Recurrent Blood Derived Cancer - Bone Marrow	04
Addtl - New Primary	Additional - New Primary	05
Metastatic	Metastatic	06
Addtl Metastatic	Additional Metastatic	07
Post neo-adjuvant therapy	Tissue disease-specific post-adjuvant therapy	08
Primary Blood Cancer BM	Primary Blood Derived Cancer – Bone Marrow	09
Blood Derived Normal	Blood Derived Normal	10
Solid Tissue Normal	Solid Tissue Normal	11
Buccal Cell Normal	Buccal Cell Normal	12
EBV Normal	EBV Immortalized Normal	13
BM Normal	Bone Marrow Normal	14
Fibroblast Normal	Fibroblasts from Bone Marrow Normal	15
Cell Line Control	Cell Line Control (Control Analyte)	20
Recurrent Blood Cancer	Recurrent Blood Derived Cancer – Peripheral blood	40
Post treatment Blood Cancer Bone Marrow	Blood Derived Cancer- Bone Marrow, Post-treatment	41
Post treatment Blood Cancer Blood	Blood Derived Cancer- Peripheral Blood, Post-treatment	42
Cancer cell line	Cell line from patient tumor	50
Xenograft, primary	Xenograft from patient not grown as intermediate on plastic tissue culture dish	60
Xenograft, cell-line derived	Xenograft grown in mice from established cell lines	61
Granulocytes	Granulocytes after a Ficoll separation	99

Nucleic acid codes

- 01D = DNA, unamplified, from the first isolation of a tissue
- 01W = DNA, WGA'ed by Qiagen (1 of the 2 done)
- 01X = DNA, WGA'ed by Qiagen (2 of the 2 done)
- 01R = RNA

Note: If additional isolations are needed, the # would change to 02D, etc.

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HTMCP SOP #205: Processing Tissue for Molecular Characterization of HIV+ Tumors

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. It is possible that the comparison of transcriptomes and genomes between tumors from HIV+ and HIV- individuals may or may not identify novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

Scope and Purpose

1. To establish a procedure for tissue processing and storage at Tissue Source Sites (TSSs).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200A-D) with the details.

Safety Precautions

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are made to withstand liquid nitrogen, eye protection (preferably face shield) and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; use in a well-ventilated area.
3. Acute overexposure to formaldehyde solutions and/or vapors causes severe eye, skin, and respiratory tract irritation.

Equipment and Materials

Note: The vendors/part numbers listed below for each item are only suggestions and primarily intended to provide examples of the needed items. It is permissible to order another product with equivalent specifications. Contact the Project Team manager if you have questions.

1. Personal protective equipment (PPE) to include nitrile gloves, heavy duty gloves, eye protection (preferably face shield), lab coat, and closed-toe shoes
2. Plastic cassette mold(s) for formalin fixation

3. Cryovials (*e.g.* 2 mL vials from ChartBiomed, Part Number 10778828)
4. Freezer resistant labels with project-assigned ID (obtained from Project Team manager, see HTMCP SOP #203A-D and #204)
5. Dewar thermo-flask, 1 L (*e.g.* Fisher Scientific Catalog Number 03-692-155)
6. Isopentane (2-methylbutane, certified) (*e.g.* Fisher Chemical Catalog Number O3551-4)
7. Liquid Nitrogen
8. Formalin (10% solution)
9. 15 ml conical tube (*e.g.* polypropylene tubes from BD Biosciences, Part Number 352097)
10. Fine point Cryomarker (*e.g.* Nalge Nunc Cryomarker Black #6313-0020)
11. Ice bucket
12. Dry ice
13. Three-prong beaker tongs, (*e.g.* Fisher Scientific Catalog Number 15-212)
14. Sterile forceps (*e.g.* Fisherbrand fine point forceps, Catalog Number 22-327-379)
15. Long forceps, 8-12" (*e.g.* Fisher Scientific Catalog Number 10-316B)
16. Metal beaker, 100 mL (*e.g.* Fisher Scientific Catalog Number 02-583A)
17. Sterile scalpel
18. Sterile dissection tray
19. Scale
20. Timer

Mark all containers with the freezer-resistant labels carrying the patient's project-assigned ID obtained from the Project Team manager prior to surgery.

Procedure

A. A lymph node or tissue diagnosed as tumor should be processed as follows:
   1. Wearing sterile gloves, using a sterile scalpel, on a sterile dissection tray, cut the tissue into multiple 2 mm thin sections.
   2. Place tissue into various containers as follows:
      i. **24-hour formalin fixation**: Fix at least two representative tissue pieces (including lymph node capsule for DLBCL) in a labeled 15 mL conical tube containing 10% formalin solution. Tissue in formalin should be no more than 2 mm in thickness for proper fixation. Prepare a formalin-fixed paraffin embedded (FFPE) tissue block from each fixed tissue piece. Submit 1 block to your Histology Lab for diagnosis. Submit the other block, or unstained 4 µm sections on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides, to the Pathology Coordinator (see HTMCP SOP #200A-D) using the labels provided by the OCG.
      ii. **Freezing tissue**: Select one to six representative pieces of tissue each measuring about 10 x 10 x 2 mm in dimension (approximately 100 mg). Do not freeze tissue pieces larger than this size or mass. Use a scale to ensure mass is 100 mg or less. If you have a larger tissue piece, cut it into smaller pieces and freeze them separately. Freeze as many pieces as possible. At least one piece is required. Do not freeze the tissue with Freon. **Note: Perform snap freezing of fresh tissue ASAP**
         - It is generally accepted that for the best tissue preservation snap freezing should

take place within 20 minutes after tissue is excised from the patient.

- Do not perform snap freezing with bare hands. Wear gloves at all times and heavy duty gloves when working with liquid nitrogen, dry ice, or cooled isopentane.

a. **Set Up Freezing Station**
   1) Fill a small 100 mL metal beaker with about 40 mL isopentane.
   2) Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
      Use extreme caution when dispensing liquid nitrogen.

b. **Label Cryovials** (as many as needed for the tissue quantity obtained from tumor)
   1) Use a cryovial for tissue snap freezing.
   2) Label cryovials with freezer-resistant labels obtained from the PT manager prior to surgery (see HTMCP SOP #203A-D).

c. **Freezing Tissue in Cryovials**
   1) Put **one** piece of tissue (no more than 100 mg) into **one** labeled cryovial, using a pair of forceps washed in 70% ethanol.
   2) Screw on the cap tightly or else isopentane will seep into the vial.
   3) Store the tissue-containing cryovials awaiting freezing by placing them on dry ice in an ice bucket.
   4) Repeat steps 1 through 3 for additional tissue pieces.
   5) Use beaker tongs to very carefully lower the 100 mL metal beaker containing isopentane halfway into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered, when the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.
   6) Use beaker tongs to lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes).
   7) Use long forceps to hold one to three cryovials down into the cooled isopentane. Hold for at least 1 minute.
   8) Use the long forceps to take out the cryovials containing frozen tissue.
   9) Store frozen cryovial(s) in liquid Nitrogen storage tanks.
   10) If there are more than three cryovials to be frozen, repeat steps 5-9.

B. Make a gross report of the sample using the dictation template on the next page of this SOP. **Patient information must be de-identified.**

C. Any questions regarding this protocol should be directed to the HTMCP Project Team manager (see HTMCP SOP #200A-D).

The frozen specimens should be kept frozen on dry ice at all times during transport to and from storage tanks.

History:

The patient is a…

Source/Gross:

The specimen is received (**fresh vs. fixed**) in (**# containers**), each labeled with the project-assigned ID "#" and designated "#." The specimen consists of (**gross to include number of fragments, size, appearance, etc.**)

Specimens submitted are:

Fixed in formalin for 24 hours – (**size, # of pieces in each block, and cassette designation**)
Snap Frozen – (**size and # of blocks**)

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HTMCP SOP #206: Processing Non-Tumor Samples for the HIV+ Tumor Molecular Characterization Project: Blood and Buccal Cells

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer-related alterations in HIV+ patients and HIV- patients. The HIV+ Tumor Molecular Characterization Project (HTMCP) aims to generate large scale, high-quality data on the cancers' genomes and transcriptomes using 2nd and 3rd generation sequencing technology. Case-matched normal control tissue is required to exclude DNA alterations that are not tumor-specific. For HTMCP, the normal control tissue requested is white blood cells isolated from whole blood.

Scope and Purpose

1. To establish a common procedure for processing case-matched non-tumor samples, such as blood or buccal cells, prior to shipment to the Genome Science Center at British Columbia (GSC-BC) by tissue source sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200A-D) with the details.

Safety Precautions

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection (preferably Face Shield), and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.

Equipment and Materials

Note: The vendors/part numbers listed below for each item are only suggestions and primarily intended to provide examples of the needed items. It is permissible to order from another vendor

as long as the product specifications are equivalent. Contact the Project Team manager if you have questions.

1. Common Equipment and Materials
    a. Personal protective equipment (PPE) to include latex or nitrile gloves, heavy duty gloves, eye protection (preferably Face Shield), lab coat, and closed-toe shoes
    b. Clinical Centrifuge with swinging bucket rotor
    c. 250 mL flask containing 50 mL bleach for waste disposal
    d. Cryovials (*e.g.* 2 mL screw-cap vials, ChartBiomed Part Number 10778828)
    e. Freezer-resistant labels with project-assigned ID (from PT manager, see HTMCP SOP #203A-D and #204)
    f. Dewar thermo-flask, 1 L (*e.g.* Fisher Scientific Catalog Number 03-692-155)
    g. Liquid nitrogen
    h. Isopentane (2-methylbutane, certified grade)(*e.g.* Fisher Cat Number O3551-4)
    i. Three-prong beaker tongs (*e.g.* Fisher Scientific Catalog Number 15-212)
    j. Long forceps, 8-12" (*e.g.* Fisher Scientific Catalog Number 10-316B)
    k. Metal beaker, 100 mL (*e.g.* Fisher Scientific Catalog Number 02-583A)
    l. Timer
    m. Fine point Cryomarker (*e.g.* Nalge Nunc Cryomarker Black #6313-0020)
    n. Disposable, sterile plastic transfer pipets (*e.g.* Falcon Cat #357524) or sterilized glass Pasteur pipets (*e.g.* Fisher Scientific Catalog Number 13-678-20A)
    o. Ice bucket
    p. Dry ice
2. For Buccal Cell Collection with Swabs or Brushes
    a. Microcentrifuge
    b. Micropipettor, 1000 µL, with sterile tips
    c. Buccal swabs or brushes (*e.g.* Catch-All Sample Swabs, Epicentre Catalog Number QEC89100)
    d. 1.5 mL centrifuge tubes
    e. Vortex
    f. Sterile forceps (*e.g.* Fisherbrand fine point forceps, Catalog Number 22-327-379)
    g. Scissors
    h. TE buffer (10 mM Tris-HCl, 1mM EDTA-Na_2, pH 8.0, 0.2 µm filtered)

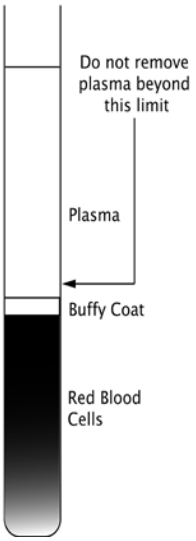
Mark all containers with the patient project-assigned ID labels obtained prior to surgery.

Procedure

A. Blood Sample Processing with Blood Fractionation
    1. Collect 10 mL of blood in a tube containing either EDTA or acid citrate dextrose (ACD) anticoagulant labeled with the HTMCP project-assigned ID.
    2. Prepare an ice bucket with dry ice. Chill one 2 mL cryovial to collect the white blood cells isolated in this procedure. The vial must be identified with the HTMCP case ID freezer-

resistant label from the Project Team (PT). The labels from the PT are obtained prior to surgery (see HTMCP SOP #203A-D).

3. Fractionate the whole blood by centrifuging at 1500-2000 *x g* for 10-15 minutes at room temperature. This will separate the blood into an upper plasma layer, a lower red blood cell (RBC) layer, and a thin interface containing the white blood cells (WBCs) / buffy coat (see figure). Fractionate the blood as soon as possible after collection. **NOTE***: Check the user manual for your centrifuge to determine the speed (rpm) necessary to achieve a force of 1500-2000 x g.*



4. Use a disposable plastic transfer pipet or Pasteur pipet to slowly and carefully aspirate the plasma (upper layer) down to about 1 mm above the buffy coat. Do not disturb the buffy coat. Discard the plasma into a 250 mL flask containing bleach.
5. Gently recover the buffy coat (WBCs) with a fresh disposable pipet, Pasteur pipet, or 1000 µl micropipettor with a sterile tip. Try not to uptake the RBC layer below the buffy coat.
6. Place the recovered buffy coat into the WBC labeled cryovial cooled on ice from step 2.
7. Screw on the cryovial cap **tightly** to prevent isopentane from seeping into the vial.
8. Visually estimate the volume of WBCs recovered using the volume lines on the cryovial and write the information into the datasheet. Buffy coat volume is greater in samples with high WBC counts. Usually you can expect ≤ 0.5 mL total.
9. Proceed to section C, "Freezing Collected Cells."

B. Buccal Cell Collection with Brushes or Swabs

1. Attach the HTMCP case ID freezer-resistant labels for buccal cells obtained from the Project Team to three 2 mL cryovials. Place the vials on dry ice in an ice bucket to chill.
2. To ensure adequate DNA collection, we recommend that a technician rubs the inside of both of the patient's cheeks firmly with a minimum of three swabs or brushes. Each swab or brush should be rubbed for a minimum of 15 seconds on a different location on the cheeks.
3. Immediately after each swab or brush has been used, use scissors to cut the tip of the swab

or brush and place it into one of the labeled 2 mL cryovials.

4. Once all three swab or brush tips have been collected into the cryovials, add 1 mL TE buffer to each vial and screw the caps on tightly and carefully.
5. The swab or brush tips in buffer should then be frozen as described in section C, "Freezing Collected Cells".

C. Freezing Collected Cells

1. Set Up Freezing Station
    - Do not perform snap freezing with bare hands. Wear gloves at all times and heavy duty gloves when working with liquid nitrogen or cooled isopentane.
    - Use extreme caution when dispensing liquid nitrogen.
    a. Fill a small 100 mL metal beaker about 1/4 full with isopentane.
    b. Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
2. Freezing Cells in Cryovials
    a. Using beaker tongs lower the 100 mL metal beaker containing isopentane half-way into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered. When the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.
    b. Using beaker tongs, lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes). Place the beaker on the workbench.
    c. Use long forceps to hold one to three cryovial(s) down into the cooled isopentane. Submerge cryovial(s) for at least 1 minute.
    d. Take out the cryovial(s) containing frozen tissue.
    e. Store frozen cryovial(s) in liquid nitrogen storage tanks or -80°C freezers.

The frozen specimens should be kept frozen ON DRY ICE AT ALL TIMES during transport to and from storage tanks.

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4th Version:	11/7/2013
5th Version:	7/16/2014
Reviewed:	

HTMCP SOP #207: Sample Shipping Guidelines for the HIV+ Tumor Molecular Characterization Project

Introduction

Tumor samples from HIV+ patients are rare and they may be accrued at specific tumor source sites (TSS) at a rate of 3-5 per calendar year. Shipping costs for infectious labeled material in vapor phase liquid nitrogen containers (cryoports) are expensive.

Scope and Purpose

1. To establish a sample shipping guideline standard to be applied to all samples contributed to the HIV+ Tumor Molecular Characterization Project (HTMCP) that balances the need for expeditious transport while maintaining cost efficiency.
2. This procedure applies to all TSSs.

Adopted Standard

- Immediate requests for a cryoport will be made to the Genome Science Center at British Columbia (GSC-BC) coordinator (see contact sheet) when the contributing TSS has in its possession three (3) or more matched tumor-normal tissues.
- However, if fewer than three cases are accrued, and the date of oldest sample resection is more than four (4) months, shipment of this/these sample(s) is warranted.

Questions regarding this protocol should be directed to the Project Team manager (see HTMCP SOP #200A-D).

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HTMCP SOP #208: Shipping Cryoports Containing Frozen Biosamples for Processing and Extraction of Nucleic Acids

Introduction

Cryoports are shipped from the Genome Sciences Center at the British Columbia Cancer Agency (GSC-BC) to the Tissue Source Site (TSS). TSSs are instructed to use this SOP when shipping samples to the GSC-BC.

Scope and Purpose

1. To establish a procedure for personnel in shipping the cryoports.
2. This procedure applies to all laboratory personnel.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200A-D) with the details.

Safety Precautions

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection, and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.
3. Always keep the cryoport in the upright position.

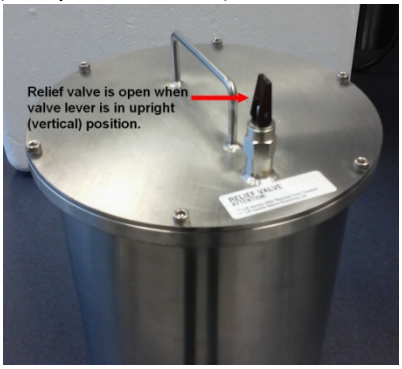
Equipment and Materials

1. Cryoport, obtained in 3 or 4 days in advance from the GSC-BC Coordinator (see HTMCP SOP #200A-D)
2. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat, and closed-toe shoes
3. Shipping documents

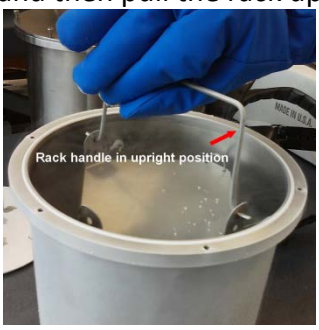
Procedure

1. **All regulatory documents must be put in place before any request for shipping.**

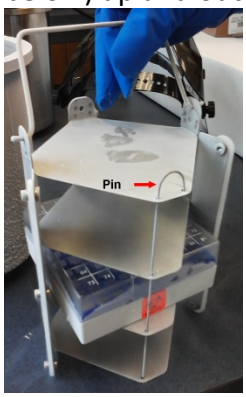
2. Request cryoport from GSC-BC shipping coordinator (see HTMCP SOP #200A-D) according to the guidelines in HTMCP SOP #207.
3. Complete the appropriate shipping forms needed for the sample(s).
4. Complete the sample shipping document with the project-assigned ID obtained prior to surgery, the sample type information, and any comments. Sign and date the form and have a second individual verify the contents of the shipment and sign and date the form.
5. Don personal protection equipment.
6. To unlock the cryoport shipping carton, cut the zip ties securing the two twist latches on the outer lid, then flip the butterfly handles outwards and turn counterclockwise to disengage the latches. Carefully open the cryoport shipping carton lid. The cryoport cork with attached data logger will be visible. It is not necessary to remove the cryoport from the shipping carton in order to access the internal sample canister. Note: **Do not press any buttons on the data logger.**
7. Extract the Allan key from the magnetic holder attached to the inside of the shipping carton by sliding it up and out of the holder.
8. Remove the large ziplock bag attached to the underside of the shipping carton lid. The bag contains the Cryoport Shipping Temperature and Charging Log form, two IATA shipping labels, a courier waybill and/or waybill pouch as needed, a leak-proof biohazard bag, absorbent cloth sheets, and zip ties.
9. Fill out the information on the "TSS Inbound" section of the Cryoport Temperature Log.
   A. The internal temperature of the cryoport is displayed on the data logger.
   B. If the cryoport will not be returned within 24 hours, please record the temperature each subsequent day after arrival in the "Temperature Records" section of the Cryoport Temperature Log.
   C. If the temperature is -190°C or colder, it can be used to ship the samples to the GSC-BC. Alert: If the temperature is warmer than -190°C, please contact the GSC-BC coordinator for instructions before proceeding further.
10. Remove the zip tie securing the cryoport cork lid to the cryoport. Lift the cork up to gain internal access to the cryoport. The top of the inner, sealed, stainless steel canister will be visible. Note: Only remove the canister when you are ready to place your samples inside.
11. Carefully remove the stainless steel canister by grabbing the handle at the top and slowly lifting the canister up and out of the cryoport. Attention: After removing the stainless steel canister from the cryoport, immediately lift the black lever of the relief valve on the top of the canister up into a vertical position to release any pressure/vacuum inside the canister (see photo below).



12. Place the cork back in the cryoport while you perform the following steps. Attention: Be careful that the temperature probe extending from the bottom of the cork goes into the cryoport and does not get trapped between the cork and the side of the cryoport.
    A. Use the Allan key to remove the 6 Allan bolts securing the lid to the stainless steel canister. Be careful not to misplace any of the bolts. Ensure that the relief valve lever is still in the upright position, and lift the lid off the container. The top of the stainless steel rack will be visible.
    B. The rack has a hinged metal handle on top. Swing the handle upright (see photo below) and then pull the rack up to lift it out of the canister.



    C. To access the freezer box, slide the containment pin at the front of the rack (see photo below) up and out of the guide holes, then slide the freezer box out of the rack.

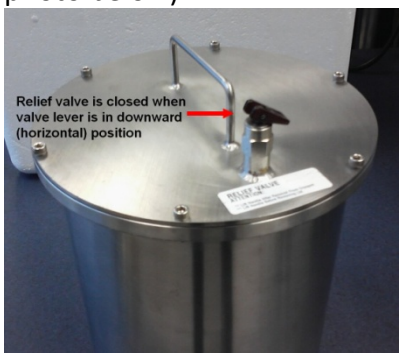


    D. Place the cryovials containing your samples into the cryovial box, then seal the cryovial box inside the supplied biohazard ziplock bag along with 1 or more sheets (folded in half) of the absorbent cloth, as required. Each sheet is capable of absorbing 250mL of liquid. Ensure most of the air is pressed out of the bag before sealing. Fold the excess length of the biohazard bag under one edge of the freezer box (see photo below).

E. Place the cryovial box back into a shelf on the rack, orienting the folded edge of the plastic bag to one side of the rack (see photo above). Replace the containment pin by sliding it down through the top of the rack and the guide holes on each shelf. Ensure the top of the pin goes through the locking guide hole on the top of the rack (see photo below).

F. Use the handles on top of the rack to carefully lower the apparatus back into the stainless steel canister. The fit is quite snug; you may need to slightly adjust the box position as you lower the rack into the canister in order for the box and bag to clear the edges of the canister.

G. Ensure that the top flange of the stainless steel canister and the underside of the canister lid are dry. Place the lid on the canister and align the holes in the lid with the screw holes in the canister. Ensure the relief valve lever is in the upright position, and use the Allan key to secure the lid with the 6 Allan bolts. Once all the bolts are secured, close the relief valve by flipping the lever downward into the horizontal position (see photo below).



13. Carefully lower the stainless steel canister back into the cryoport, and replace the cork. Attention: Be careful that the temperature probe extending from the bottom of the cork goes into the cryoport and does not get trapped between the cork and the side of the cryoport.
14. Align the openings in the side of the cork lid with the openings in the cryoport neck, and secure with one of the supplied zip ties. Cut most of the excess length off of the zip tie.

15. Allow the cryoport temperature to stabilize at -190^{o}C or colder as displayed on the data logger. When the data logger displays a stable temperature reading, record the temperature in the "TSS Outbound" section of the Cryoport Temperature Log.
16. Place the Allan key back into the magnetic holder attached to the inside of the shipping carton. Ensure the Allan key is flush against the magnets and is fully inserted through both slots so the Allan Key does not fall out during transport.
17. Carefully close the shipping carton lid. Engage both of the twist latches by interlocking the catches, turning the butterfly handles clockwise to close down the latch, and then folding handles down so they are flush with the body of the latch. Secure each latch with two zip ties as illustrated by the image on the shipping carton.
18. Attach the provided labels with the IATA mark (UN 3373, Biological Substance, Category B) to opposite sides of the shipping carton, such that the labels are clearly visible and in the upright orientation. Place all shipping documents, including the Sample Shipping Document, the Cryoport Temperature Log, and multiple copies of the Commercial Invoice (5 copies for FedEx; 3 copies on letterhead for World Courier), into the waybill pouch. Seal the pouch. For FedEx shipments, attach the Tie-On tag to a handle on the shipping carton, and secure with a zip tie. World Courier waybill pouches are attached to the shipping carton lid.
19. Notify the shipping carrier for pick-up on the shipping date that has been previously coordinated with the GSC-BC. If an exception is needed, the GSC-BC must be contacted for further instructions and to alert the GSC-BC personnel of any schedule changes.
20. TSS personnel will notify the coordinator by email stating the cryoport is being returned with tissue samples back to the GSC-BC, and providing the tracking number. Also provide an electronic copy of the Sample Shipping Document.
21. The GSC-BC Coordinator will track the cryoport in transit.
22. If there are any exceptions to the normal shipping schedule or in the event of an anticipated shipment delay, the Coordinator will notify the GSC-BC on-call personnel of the potential arrival of samples after normal working hours or on the weekend.
23. Upon receiving the cryoport, the temperature will be recorded and quality control verified by a second individual.
24. Any questions regarding shipments to the GSC-BC should be directed to the GSC-BC Coordinator.

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Adopted:	4/26/2010
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HTMCP SOP #210: Sectioning Tissue for the HIV+ Tumor Molecular Characterization Project

Introduction

Accurate pathological diagnosis of tissue is essential to determine which samples qualify for the HIV+ Tumor Molecular Characterization project. In addition to the diagnosis using formalin fixed tissue from each case, a top and bottom section of each piece of frozen tissue to be used for macromolecule extraction will undergo staining with hematoxylin and eosin (H&E) to visualize gross tissue morphology and confirm the sample contains a minimum of 70% tumor nuclei and a minimum of 80% viable cells. Either the Tissue Source Site (TSS) or Genome Science Center at British Columbia (GSC-BC) must perform this procedure before macromolecule extraction may proceed.

Scope and Purpose

1. To establish a common procedure for tissue sectioning prior to shipment to the Genome Science Center at British Columbia (GSC-BC) across tissue source sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times, and which samples were affected. This information should be given within 48 hours of occurrence to the project team manager (see HTMCP SOP #200A-D).

Safety Precautions

1. Wear personal protective equipment (PPE) such as lab coats and gloves.

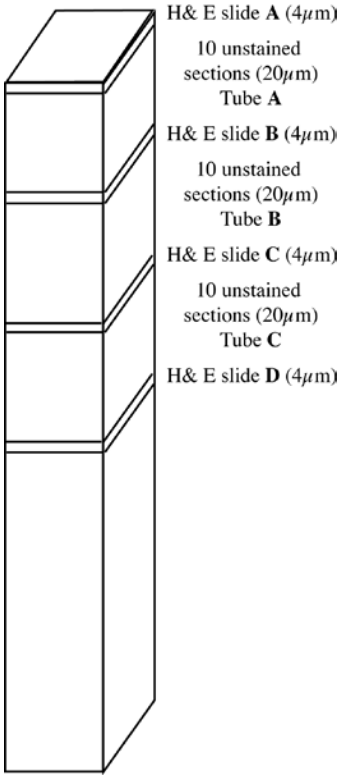
Equipment and Materials

1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Frozen sample
3. OCT Freezing Compound
4. Cryostat
5. Glass slide(s) (such as Corning Glass Slides, 3 x 1” frosted end, # 26003)
6. Cryovials (2mL vials, e. g., ChartBiomed, Part Number 10778828)
7. Freezer resistant labels with project-assigned ID (obtained from Project Team, see HTMCP SOP #203A-D and #204)

MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

Procedure

1. All tube(s) must be kept on dry ice **at all times** and be stored in liquid nitrogen storage tanks until shipment to the GSC-BC can be arranged following the HTMCP shipping guidelines (see HTMCP SOP #207 and #208).
2. Transport the cryovial containing the sample on dry ice to the cryostat.
3. Remove frozen tissue from cryovial with sterilized forceps.
4. Coat the top of the tissue piece with a thin layer of OCT by dipping into the compound held in a small weighing boat or similar container.
5. Obtain a 4 µm section and mount onto a glass slide. Stain with H&E to assess the tissue quality. Label with the project-assigned ID and a capital letter A (see HTMCP SOP #204) and save the section for shipment. **No sample should be shipped if the preliminary % tumor nuclei assessment at the TSS is below the 70% cut-off.**
6. Label a cryovial with the project-assigned ID followed by -01A (see HTMCP SOP #204). Cut ten 20 µm thick sections (see figure below) and put into the labeled cryovial in a beaker of dry ice inside the cryostat. **The number of sections needed is based on a tissue with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required and vice versa (see calculation formula at the end of this SOP to estimate the number of sections needed).**



7. Coat the top of the tissue piece with a thin layer of OCT by dipping into the compound held in a small weighing boat or similar container.

8. Obtain a 4 µm section and mount onto a glass slide. Stain with H&E to assess the tissue quality. Label with the project-assigned ID and a capital letter B (see HTMCP SOP #204) and save the section for shipment.
9. Additional sections (10/tube) may be cut into tubes -01B, -01C, etc. depending on the anticipated future research needs (see HTMCP SOP #204). A 4 µm section must be obtained and stained with H&E to assess the quality of the tissue in between each series of thick sections. These H&E slides must be shipped to the appropriate location.
10. Return the remaining tissue to the liquid nitrogen storage tank.
11. **The blade should be cleaned with alcohol after each case and different parts of the blade used for different cases.**
12. Note that excess OCT must be carefully trimmed away before sectioning as its inclusion will interfere with subsequent RNA extraction.
13. Shipping guidelines for the cryovials containing the frozen sections as well as the H&E sections are in HTMCP SOP #207 and #208. **The frozen specimens must be kept frozen on dry ice at all times during transport to and from storage tanks**.

Estimating the number of 20µm sections needed:
1) Measure, in millimeters, the length and width of the tissue in the block.
2) Use the formula below to estimate the number of 20µm sections needed per cryovial to fulfill tissue requirements. Use that number of sections in step 6 of this protocol.

Number of sections = [Length (mm) x width (mm)] x 10 / 100 mm^2

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HTMCP SOP #211: Disposition Form for Remaining Macromolecules/Tissues Contributed to the HIV+ Tumor Molecular Characterization Project

Introduction

The HIV+ Tumor Molecular Characterization Project (HTMCP) is an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. The project aims to generate large scale, high quality data on the cancers' genome and transcriptome using 2nd generation sequencing technology which means that the changes identified range from large genomic rearrangements, expression profile changes and detection of mutations. The characterization of the latter is mostly performed in other NCI-sponsored projects. The comparison of alterations in transcriptomes and genomes of tumors from HIV^+ and HIV^- individuals may or may not identify a) virus-associated genomic alterations (including mutations) which would indicate if the etiology of the illness is different; and/or b) novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

Tissues to the HTMCP are contributed by a number of international investigators (tissue source site, TSS). A major contributor is the AIDS Malignancy Consortium (AMC), a National Cancer Institute-supported clinical trials group founded in 1995 to support innovative trials for AIDS-associated malignancies. The AMC is composed of 14 Clinical Trials Sites and their affiliates, and is committed to enhancing therapeutic options for patients with HIV-associated malignancies. All samples and macromolecules obtained from cases contributed by AMC members are sent to the AIDS and Cancer Specimen Resource (ACSR, http://acsr.ucsf.edu/dotnetnuke/) for banking.

ACSR is a resource for investigators working in the fields of HIV/AIDS, cancer, virology, immunology, pathology, epidemiology, tumor biology assay development, and many others. It is a biorepository for HIV-infected human biospecimens from a wide spectrum of HIV-related or associated diseases, including cancer, and from appropriate HIV-negative controls. ACSR was established by the NCI in 1994 to acquire, store, and equitably distribute tumor tissues, biological fluids, and associated clinical information from patients with HIV-associated malignancies to the scientific research community-at-large. Availability of such biospecimens facilitates efforts to identify therapeutic targets and gain further insights into the pathogenesis and treatment of cancer in the HIV-infected population.

The ACSR's public access and research facilitation function makes it an ideal location to bank any remaining tissue and/or derived macromolecule after the molecular characterization is completed by the HTMCP.

Scope and Purpose

1. To establish a procedure to follow for the disposition of remaining macromolecules (DNA and/or RNA) and tissue after characterization is completed from cases submitted to the HTMCP.
2. This form must be completed by every TSS and included along with the shipping documents at the time of tissue submission **if the default option of banking at the ACSR is not acceptable**.

Remaining Material Disposition Form

Note: You only need to choose one of the options below if you do not want to send remaining material to ACSR for banking.

If after molecular characterization of case # _____ there is any remaining material (tissue and or macromolecules), these remnants should be (choose one):

☐ Sent back to the TSS (at the TSS's expense)
☐ Destroyed

Name: Date:

Institution:

Signature:

HTMCP SOP #212: Data Release Policy for the HIV+ Tumor Molecular Characterization Project (HTMCP)

Background

Rapidly evolving sequencing and informatics tools are substantially diminishing costs of comprehensive characterization of tumor transcriptomes and tumor genomes. These advances have resulted in detailed information on the repertoire of alterations in tumors. NCI already supports tumor genome characterization projects for several common cancers, as part of the Cancer Genome Characterization Initiative and the Cancer Genome Atlas (TCGA). Comprehensive sequencing of genomes and transcriptomes in cancers that arise in HIV-infected individuals may provide a starting point for a systems biology approach towards understanding differences in etiologies among identical histological subtypes of cancers in HIV+ and HIV- patients. The results obtained could provide important clues to the pathways that either allow tumors to counteract immune surveillance mechanisms or are redundant in the presence of an extrinsic oncogenic influence such as viruses. It is also possible that the comparison of transcriptomes and genomes between tumors from HIV+ and HIV- individuals might identify novel non-human sequences that could suggest the presence of transcripts from hitherto undiscovered viral agents.

This is a "community resource project", with rapid data release to enable accelerated translation to enhance clinical impact. Therefore patenting on the PRIMARY data is discouraged to allow easy access and encourage its use. There is an expectation of a rapid initial "summary" publication by the group once the data are generated.

Two data types will be produced: 1) raw sequences from the tumor/normal genomes and tumor transcriptome; 2) analyzed data from those raw sequences. It is important to acknowledge that algorithms for sequence analysis to identify tumor-specific calls are still in the development stage and thus the results obtained require confirmation.

Confirmation is defined in two ways:

- Verification: assessment of sequence quality before data release (e.g. identifying Illumina artifacts, performing sample swaps, etc.)
- Validation: confirmation of variants identified by the current analytical algorithms by using orthogonal experimental methodology such as Sanger sequencing. Validation will be performed; the scope will depend on the costs and the accuracy of the sequence-calling algorithms available at the specific time. It may be performed either for a subset or all variants found (the details will be developed on real time basis to take advantage of the best approaches). The criteria for selection of a subset of variants for validation will be

developed by the cancer-specific working group based on all empirical data available at decision time.

Policy

The data release policy should be consistent across all NCI-funded large-scale genomic characterization projects. The HIV+ cancers are hard to accrue and therefore the data generation will span over a number of months or years. To best accomplish the goals of the project (generating and analyzing large enough data set to be able to draw statistically and biologically sound conclusions) and the Institute (to facilitate research and reduce redundancy by making primary data available to the scientific community in real time), the project members suggest the following policy:

- Release of analyzed sequences (BAM files) will occur after a sample set (number to be determined) is complete, but not later than 4-6 month after they are generated.
- Table of the validated mutations (MAF) will be deposited to the Data Coordinating Center (DCC) after manuscript describing the findings of the dataset is submitted for publication.

The "Using CGCI Data" site (http://ocg.cancer.gov/programs/cgci/using-cgci-data) includes information about the philosophy of the rapid data release policy. The language will be aligned as much as possible to the one used for TCGA and Therapeutically Applicable Research to Generate Effective Treatments (TARGET).

A HTMCP manuscript could include:

- Commentary detailing the scientific aims and organization of HIV+ tumor molecular characterization project
- Analysis of paired DNA sequencing data for the sample set
- Analysis of the RNA sequencing data for the sample set
- Validation of a subset of variant calls found by either DNA or RNA sequencing of the sample set

To support the continued prompt public release of large-scale genomic data prior to publication, researchers who plan to prepare manuscripts that would be comparable to the analyses described above, and journal editors who receive such manuscripts, are encouraged to coordinate their independent reports with the project's publication schedule described above. This may be done by contacting the Project Team (see below).

Once the first global analysis by the project members is in press, all other researchers are free, and indeed encouraged, to publish results based on integrating HIV+ tumor data with data from other sources. Researchers also are encouraged to use HTMCP data to publish on the development of novel methods to analyze genomic data related to cancer and genotype- phenotype relationships in cancer.

NCI does not consider that deposition of data from the HTMCP, like those from other large-scale genomic projects, into its own or public databases to be the equivalent of publication in a peer-reviewed journal. Therefore, although the data are available to others, the producers still consider

them to be formally unpublished and expect that the data will be used in accord with standard scientific etiquette and practices concerning unpublished data.

Prior to the publication of the initial paper, the HTMCP project requests that authors who use data acknowledge the HTMCP as follows: "The results published here are in whole or part based upon data generated by The HIV+ Tumor Molecular Characterization Project established by the Office of Cancer Genomics and Office of HIV and AIDS malignancies of the NCI. Information about project and the investigators and institutions that constitute the HIV+ Tumor workgroups can be found at http://ocg.cancer.gov/programs/cgci." After initial publication, the paper and website should be referenced.

To ensure protection of genetic privacy for sample donors, data users will have to agree to certain conditions described in the HTMCP Patient Protection Policy and Controlled Access Policy as to how the data will be used. For example, users will have to agree that they will share these data only with others who have also completed a data access agreement and that they will not patent discoveries in a way that prevents others from using the data. This means that reviewers of a manuscript who need to see any controlled-access HTMCP data underlying a result must also agree to these user access conditions before they can see these data.

Meeting presentations of HTMCP data and analyses by project team members are possible and encouraged. We request that the project team members inform the NCI of public meeting oral and poster presentations. The HTMCP Project Team will develop two-three slides that should be used for oral presentations, posters, etc. They will provide a standard method of citing the HTMCP and its many contributors; it is critical that the HTMCP also be properly cited and identified in the meeting abstracts, and language will be provided to accomplish this goal.

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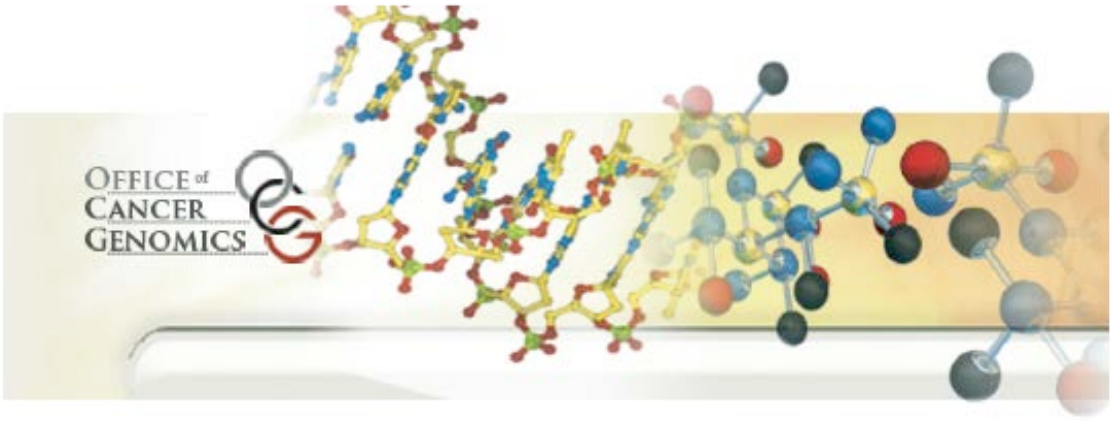
National Cancer Institute



HIV+ Tumor Molecular Characterization Project (HTMCP) Diffuse Large B-cell Lymphoma (DLBCL)-Specific Protocols

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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3rd Version:	11/7/2013
4th Version:	7/16/14
Reviewed:	

HTMCP SOP #200A:
HIV+ Tumor Molecular Characterization Project
Diffuse Large B-cell Lymphoma Contact Sheet

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HTMCP SOP #203A: Prospective Sample Submission Procedure for the HIV+ Diffuse Large B-Cell Lymphoma Characterization Project

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer-related alterations in HIV+ patients and HIV- patients. The HIV+ Tumor Molecular Characterization Project aims to generate large scale, high-quality data on the cancers' genomes and transcriptomes using 2nd and 3rd generation sequencing technology. The data collected from the Diffuse Large B-cell Lymphoma (DLBCL) subproject will allow scientists to identify genetic alterations common to individuals with DLBCL and HIV.

Scope and Purpose

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200A) with the details.

Procedures

A. Before patient accrual begins:
   1. Make sure all the documents required for sample shipment as spelled out in HTMCP SOP #201 are in place before you start case accruals.
   2. You may request project-assigned IDs in advance. Contact OCG (see HTMCP SOP #200A) with your TSS-assigned ID to obtain project-assigned IDs (see HTMCP SOP #204) which you must use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.

3. You may request freezer-resistant labels with the project-assigned IDs in advance. Contact the OCG PT manager (see HTMCP SOP #200A) to obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.

B. Before patient surgery:
   1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.
   2. If you have not done so already, contact OCG with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.
   3. If you have not done so already, contact the OCG PT manager and obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.
   4. Prepare the tissue freezing station and have ready all the materials needed for tissue processing (HTMCP SOP #205).
   5. Inform the research nurse that a 10 mL peripheral blood sample must be obtained from the patient to use as a non-tumoral control (see Appendix A). The buffy coat must be separated from the plasma within two hours of the blood draw from the patient. Store the blood sample in the refrigerator until processing. Time in storage must be reported to the PT manager. The buffy coat sample should be moved immediately to a -80°C or Liquid Nitrogen (LN2) freezer for storage (see HTMCP SOP #206).

C. During patient surgery:
   1. Inform the surgical staff of the tissue requirements for the project (see Appendix A).
   2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   3. Note the time between surgery and freezing in a notebook and send to the PT manager.

D. After surgery:
   1. Process solid tissue as described in the tissue processing protocol (HTMCP SOP #205). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   2. Process the blood sample according to HTMCP SOP #206. Store isolated cells in a -80°C freezer or liquid nitrogen (LN2) storage until shipment.
   3. Obtain a formalin-fixed, paraffin-embedded tissue block or, if not possible, **fifteen (15)** unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. Affix one of the provided freezer-resistant labels to each slide or block.

E. Preparing samples and shipment:
   1. **Optional**: Section frozen tumor sample following the frozen tissue sectioning protocol. Produce a 4 µm frozen section of the top of the tumor sample for initial quality control as described in the tissue processing protocol (HTMCP SOP #210).
   2. When tissue from at least three cases are accrued, or every quarter (see HTMCP SOP #207) contact the Genome Sciences Center at British Columbia Cancer Agency (GSC-BC)

Coordinator (see HTMCP SOP #200A) to schedule a shipment of a cryoport transport vessel to send the cryovials containing frozen tumor sample sections and frozen blood cells.

3. When the cryoport arrives follow the frozen sample shipment protocol (HTMCP SOP #208) and send the frozen samples to GSC-BC. It is expected that most sites will send tissues within to GSC-BC within 24 hours of receiving the cryoport. The timing of shipment should be discussed prior to tissue collection, especially if exceptions are required. Provide both the GSC-BC and PT with tracking number the day of shipment.
4. Send a formalin-fixed, paraffin-embedded tissue block or, if not possible, **fifteen (15)** unstained 4 µm sections obtained from the formalin fixed blocks mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides, to the Pathology Coordinator (see HTMCP SOP #200A). Upon shipment, provide both the Pathology Coordinator and OCG PT with the tracking number of the parcel. If slides are sent, ship in a box designed to hold slides securely to prevent breakage (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).
5. Collect all the **de-identified** clinical data requested in the sample requirements (Appendix A). You will be requested by the OCG project coordinator to send the data electronically to NCH using the appropriate TSS-assigned ID at a later date.

Notes

- A checklist is provided to help you track all the steps required by this process (Appendix B). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained tissue blocks or slides, and clinical data) is not present, the submission is incomplete, the sample cannot be accepted for HTMCP, and reimbursement of costs cannot proceed.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

Appendix A: Sample Requirements

Tissue Requirements

To be accepted to the project, the following conditions have to be met at the tissue level.

- Tissue must come from a patient who has not received neoadjuvant therapy for the tumor type submitted for HTMCP or systemic treatment for any tumor.
- Paired tumor and normal tissue (blood cells) must be available in sufficient quantities (~100 mg of frozen tumor tissue, plus 10 mL of blood).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in liquid nitrogen, but -80°C or lower is acceptable. The form of tissue storage must be recorded.
- Tumors need to have a minimum percent of tumor nuclei of 70% as assessed by H&E on top and bottom of a tissue section physically adjacent to the specimen used for generating the RNA and DNA.
- There must be enough tissue of both to produce a 4 µm thick section from the top for H&E staining, then 10 sections of 20 µm thickness, followed by another 4 µm section to stain by H&E. **The number of sections needed is based on a block with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required. See HTMCP SOP #210 for the formula allowing calculation of number of sections needed.** A core biopsy obtained at the same time as the one produced for pathology might provide sufficient tissue if it is of high tumor content and low necrosis.
- A formalin-fixed paraffin embedded block for pathology consensus review (or at least fifteen unstained 4 µm sections mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides) must exist for the tumor.

Clinical Data Requirements

To be accepted to the project, the following conditions must meet at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) listed on the following pages. Should some of the data fields be missing, please contact the OCG PT manager to get approval for submission. **All patient information must be de-identified.**

These clinical data elements must be reported to NCH as an initial report within two weeks of enrolling the patient. At 12 months and 24 months after the patient's enrollment in HTMCP, an update of the status and clinical condition of each patient needs to be submitted to the NCH. If the patient dies prior to the first year update, the second year update would only serve to confirm the status.

Patients need to be consented in such a way that allows for the use of their tissues for genomic-scale molecular characterization.

Instructions: *The Enrollment Form should be completed for each qualified case in the HIV+ Tumor Characterization Project (HTMCP) study. The Tissue Source Site (TSS) should complete the form for qualified cases upon qualification notice from the Office of Cancer Genomics (OCG).*

Questions regarding this form should be directed to the Clinical Data Collection Operation & Database (CDCOD) or OCG.

Please note the following definitions for the "Unknown" and "Not Evaluated" answer options on this form.

Unknown: This answer option should only be selected if the TSS does not know this information after all efforts to obtain the data have been exhausted. If this answer option is selected for a question that is part of the HTMCP required data set, the TSS must complete a discrepancy note providing a reason why the answer is unknown.

Not Evaluated: This answer option should only be selected by the TSS if it is known that the information being requested cannot be obtained. This could be because the test in question was never performed on the patient or the TSS knows that the information requested was never

Tissue Source Site (TSS): _____TSS Identifier: _____ TSS Unique Patient Identifier: _____

Completed By *(Interviewer Name in OpenClinica)*: _____Completed Date: _____

#	Data Element	Entry Alternatives	Working Instructions
General Information			
*1	Is this a prospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for prospective tissue collection. If the submitted tissue was collected after the date the HTMCP contract was executed, the tissue has been collected prospectively. 3088492
*2	Is this a retrospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for retrospective tissue collection. If the submitted tissue was collected prior to the date the HTMCP contract was executed, the tissue has been collected retrospectively. 3088528
Patient Information			
Demographic Information			
*3	Date of Birth	___ ___ / ___ ___ / ___ ___ ___ ___ (month) (day) (year)	Provide the date the patient was born. 2896950 (month), 2896952 (day), 2896954 (year) *Note: The day of Birth is not required.*
*4	Gender	☐ Female ☐ Male	Provide the patient's gender using the provided categories. 2200604
*5	Race *(check all that apply)*	☐ American Indian or Alaska Native ☐ Asian ☐ White ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ Other (please specify) ☐ Not Evaluated ☐ Unknown	Provide the patient's race using the defined categories. 3009519 American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. Asian: A person having origins in any of the original peoples of the far East, Southeast Asia, or in the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. White: A person having origins in any of the original peoples of the four Europe, the Middle East, or North Africa. Black or African American: A person having origins in any of any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." Native Hawaiian or other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
	Other Race Only complete if "other" is selected in #5.	_____	If the patient's race was not defined in the previous question, provide the patient's race. 2192205

#	Data Element	Entry Alternatives	Working Instructions
6	Ethnicity	☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Not Evaluated ☐ Unknown	Provide the patient's ethnicity using the defined categories. 2192217 Not Hispanic or Latino: A person not meeting the definition of Hispanic or Latino. Hispanic or Latino: A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
7	Height *(at time of diagnosis)*	_____(cm)	Provide the patient's height (centimeters) at the time the patient was diagnosed with the tumor submitted for HTMCP. 649
8	Weight *(at time of diagnosis)*	_____(kg)	Provide the patient's weight (kilograms) at the time the patient was diagnosed with the tumor submitted for HTMCP. 651
Survival Information			
*9	Vital Status *(at date of last contact)*	☐ Living ☐ Deceased	Indicate whether the patient was living or deceased at the date of last contact. 5
*10	Date of Last Contact	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient is living, provide the date of last contact with the patient (as reported by the patient, medical provider, family member, or caregiver). 2897020 (month), 2897022 (day), 2897024 (year) *Do not answer if patient is deceased.* *Note: The day of Last Contact is not required.*
*11	Date of Last Known Alive	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Indicate the last date the patient was known to be alive, regardless of whether the patient, medical provider, family member or caregiver was contacted. 2975722 (month), 2975724 (day), 2975726 (year) *Note: The day of Last Known Alive is not required.*
*12	Date of Death	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient is deceased, provide the month of death. 2897026, (month) 2897028 (day), 2897030 (year) *Note: The day of Death is not required.*
6	Cause of Death Only complete if patient is deceased.	☐ Cancer Related ☐ Non-Cancer Related ☐ Unknown ☐ Other (please specify)	Indicate the patient's cause of death. 2554674
7	Other Cause of Death Only complete if "other" is selected in #6.	_____	If the patient's cause of death was not included in the provided list, specify the patient's cause of death. 2004150
Patient Status (Regarding Submitted Tumor)			
*13	Did the patient receive neo-adjuvant therapy for the tumor submitted for HTMCP?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient received treatment (radiation, pharmaceutical, or both) prior to the procurement of the sample submitted for TCGA. 3382737 *If the answer to this question is "yes", the submitted case is excluded.*
*14	Tumor Status *(at time of last contact or death)*	☐ Tumor free ☐ With tumor ☐ Unknown	Indicate whether the patient was tumor/disease free (i.e. free of the malignancy that yielded the sample submitted for the HTMCP study) at the date of last contact or death. 2759550
15	Performance Status: Eastern Cooperative Oncology Group	☐ 0: Asymptomatic ☐ 1: Symptomatic, but fully ambulatory ☐ 2: Symptomatic, in bed less than 50% of day ☐ 3: Symptomatic, in bed more than 50% of day, but not bed-ridden ☐ 4: Bed-ridden ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time of diagnosis. 88
16	Performance Status: Karnofsky Score	☐ 100: Normal, no complaints, no evidence of disease ☐ 90: Able to carry on normal activity; minor signs or symptoms of disease	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time of diagnosis. 2003853

#	Data Element	Entry Alternatives	Working Instructions
		☐ 80: Normal activity with effort; some signs or symptoms of disease ☐ 70: Cares for self, unable to carry on normal activity or to do active work ☐ 60: Requires occasional assistance ☐ 50: Requires considerable assistance and frequent medical care ☐ 40: Disabled, requires special care and assistance ☐ 30: Severely disabled, hospitalization indicated. Death not imminent ☐ 20: Very sick, hospitalization ☐ 10: Moribund, fatal processes progressing rapidly ☐ 0: Dead ☐ Unknown ☐ Not Evaluated	
17	Performance Status Score: Timing	☐ Preoperative ☐ Post-operative (no adjuvant therapy) ☐ Pre-adjuvant Therapy ☐ Post-adjuvant Therapy ☐ Unknown	Indicate the timing of the performance status(es) provided in the previous question(s). 2792763
18	Tumor Response	☐ Progressive Disease ☐ Stable Disease ☐ Partial Response ☐ Complete Response	Indicate the patient's measure of success after their primary treatment for the tumor submitted for HTMCP. Treatment includes surgery and adjuvant therapies. 2786727
*9	Adjuvant (Post-Operative) Radiation Therapy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had adjuvant/ post-operative radiation therapy *for the tumor submitted for HTMCP.* 2005312
*10	Adjuvant (Post-Operative) Pharmaceutical Therapy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had adjuvant/ post-operative pharmaceutical therapy *for the tumor submitted for HTMCP*. 3397567
12	Results of PET Scan Performed within 2 Months after Treatment	☐ Positive ☐ Negative ☐ Indeterminate ☐ Not Performed	Provide the results of the PET Scan which was performed to identify the absence or presence of disease within two months after the completion of the first course of treatment. 2603749
Smoking History			
25	Tobacco Smoking History Indicator *(at time of diagnosis)*	☐ 1: Lifelong Non-Smoker ☐ 2: Current Smoker ☐ 3: Current Reformed Smoker for > 15 years ☐ 4: Current Reformed Smoker for <= 15 years ☐ 5: Current Reformed Smoker (duration not specified) ☐ Smoking Status not Documented	Indicate the patient's history of tobacco smoking as well as their current smoking status using the defined categories. If the patient is a lifelong non-smoker, skip the additional smoking questions. 2181650
26	Age of Onset Tobacco History Indicator	____ ____ years	Provide the age in years when the patient began smoking cigarettes. 2178045
27	Year of Quiting Tobacco Smoking	____ ____ ____ ____ (YYYY)	Provide the year the patient quit smoking, if applicable. 2228610
28	Number of Pack Years Smoked *(at time of diagnosis)*	____ ____ ____ ____ pack years	Provide the number of pack years thepatient smoked. This is calculated using the number of cigarettes smoked per day times the number f years smoked, divided by 20. For example, if the patient smoked 5 cigarettes per day times 10 years divided by 20, the patient would have 2.5 pack years (e.g. 5x10/20=2.5). 2955385
Patient History of Disease			

#	Data Element	Entry Alternatives	Working Instructions
HIV Status			
*19	Is this patient HIV positive?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient is HIV positive. 2180464
*20	Date of HIV Diagnosis (if known)	____ ____ / ____ ____ / ____ ____ ____ (month) (day) (year)	Provide the month the patient was diagnosed with HIV. 3579640 (month), 3579644 (day), 3579643 (year) *Note: The day of HIV Diagnosis is not required.*
21	Nadir CD4 Counts	_____ (cells/mm^3)	Provide the patient's Nadir CD4 counts, which are the lowest CD4 counts the patient has had. 2684395
*22	CD4 Counts at Diagnosis of the Submitted Malignancy	_____ (cells/mm^3)	Provide the patient's CD4 Counts at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922654
*23	HIV RNA load at Diagnosis of Submitted Malignancy	_____	Provide the HIV RNA load (also known as the "viral load") at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922674
24	Prior AIDS Defining Conditions	☐ Candidiasis of bronchi, trachea or lungs ☐ Candidiasis, esophageal ☐ CMV other than liver, spleen or nodes, onset at age >1month ☐ CMV retinitis ☐ Coccidioidomycosis, disseminated or extrapulmonary ☐ Cryptococcosis, extrapulmonary ☐ Cryptosporidiosis, chronic intestinal ☐ Encephalopathy, HIV-related ☐ Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis or esophagitis (onset at age > 1 month) ☐ Histoplasmosis, disseminated or extrapulmonary ☐ Isosporiasis, chronic intestinal (> 1 mon) ☐ Mycobacterium avium complex or Mycobacterium kansasii disseminated or extrapulmonary ☐ Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary ☐ Mycobacterium, other species or unidentified species, disseminated or extrapulmonary ☐ Nocardiosis ☐ Pneumocystis jirovecii pneumonia ☐ Pneumonia, recurrent ☐ Progressive multifocal leukoencephalopathy ☐ Salmonella septicemia, recurrent ☐ Toxoplasmosis of the brain, onset at age >1month ☐ Wasting syndrome, due to HIV	Prior to the malignancy submitted for the HTMCP study, provide any AIDS defining conditions. 2679581
	Co-Infections *(serology*	**Test** **Results**	Using the list provided, indicate whether the patient had any co-infections by providing the results of each of the tests

#	Data Element	Entry Alternatives	Working Instructions
	data/viral load if available)		listed.
		25. HBV	2180456
		26. HCV	2695021
		27. HPV	2230033
		28. KSHV/HHV8	3335773
*29	HAART Treatment Prior to Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment prior to the diagnosis of the malignancy submitted for the HTMCP study. 3335156
*30	HAART Treatment at Time of Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment at the time of the diagnosis of the malignancy submitted for the HTMCP study. 2922679
31	CDC HIV Risk Group(s)	☐ Homosexual or bisexual contact ☐ Heterosexual contact ☐ IV drug user ☐ Transfusion recipient ☐ Hemophiliac ☐ Other	Indicate whether the patient has a history of any of the listed HIV Risk Groups as defined by the Center for Disease Control (CDC). 2542215
Prior Malignancies			
*32	Has this patient at any time in their life had a prior diagnosis of a malignant neoplasm?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient was, at any time in their life, diagnosed with a malignancy prior to the diagnosis of the specimen submitted for HTMCP. 61396 *If the answer to this question is "yes", the submitted case is excluded. This exclusion does not apply if the patient only has a history of non-melanoma skin cancer OR in situ carcinoma.*
	Type of Prior Malignancies Only complete if "yes" is selected in #32.	_____	If the patient has had a prior diagnosis of a malignant neoplasm, provide the type of prior malignancy. 2718428
Prior Immunological Disease			
33	Patient History of Prior Immunological Disease	☐ Rheumatoid Arthritis ☐ Sjogren's Syndrome ☐ Systemic Lupus Erythematous ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Hasimoto's Thyroiditis ☐ Other (please specify) ☐ Unknown	Indicate whether the patient has a history of any of the listed immunological diseases. 3233628
	Other History of Prior Immunological Disease Only complete if "other" is selected in #33.	_____	If the patient has a history of immuniological disease and the disease is not listed in the previous question, provide the name of the disease(s). 3233629
34	Patient History of Prior Immunosuppressive Therapy for Immunological Disease	☐ Methotrexate ☐ Azathioprine ☐ Unknown ☐ Anti-TNF therapy ☐ Other (please specify) ☐ Cyclophosphamide	If the patient received immunosuppressive therapy for the immunological disease selected in the previous question, provide the type of immunosuppressive therapy given. 3233638
	Other History of Prior Immunosuppresive Therapy for Immunological Disease Only complete if "other" is selected in #34.	_____	If the patient has a history of immunosuppressive therapy for immunological disease and the disease is not listed in the previous question, provide the name of the disease(s). 2873928
Prior Infectious Disease			
35	Patient History of Relevant Prior Infectious Disease	☐ Hepatitis B ☐ Hepatitis C ☐ H. Pylori ☐ Other (please specify) ☐ Unknown	Indicate whether the patient has a history of any of the listed infectious disease. 3233645

#	Data Element	Entry Alternatives	Working Instructions
	Patient History of Other Relevant Infectious Disease Only complete if "other" is selected in #35.	_____	If the patient has a history of relevant prior disease that was not included in the list, provide the infectious disease. 3233643
Pathologic Information			
*36	Histological Subtype	☐ Diffuse Large B-cell Lymphoma (DLBCL) NOS (any anatomic site, nodal or extra nodal) ☐Primary Mediastinal (thymic) Large B-cell Lymphoma ☐ Primary DLBCL of the CNS ☐ Primary cutaneous DLBCL, leg type ☐ EBV Positive DLBCL of the Elderly ☐ DLBCL Associated with Chronic Inflammation	Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3081934
37	Percent Follicular Component	☐ <10% ☐ >= 10%	Using the pathology report, indicate the percentage of the follicular component within the diffuse large B-cell lymphoma sample that was removed from the patient. 3232840
*38	Site of Nodal Involvement at Diagnosis *(Please check all that apply)*	☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral ☐ Ililac ☐ Iliac-common ☐ Iliac-external ☐ Mediastinal ☐ Mesenteric ☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Supraclavicular ☐ Submandibular ☐ No Known Nodal Involvement	Using the patient's medical record check all applicable boxes to identify the lymph node chain(s) that were involved by diffuse large B-cell lymphoma at the time of initial diagnosis. 2180591 *To select multiple sites of involvement, press the control button and select the sites of involvement. Your selections should be highlighted after you've selected.*
*39	Site(s) of Extranodal Involvement At Diagnosis *(Please check all that apply)*	☐ Adrenal ☐ Bone ☐ Bone Marrow ☐ Brest ☐ Peripheral Blood ☐ Skin ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* **ENT & Eye** ☐ Intraocular ☐ Larynx ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Oropharynx ☐ Parotid Gland ☐ Peri-orbital Soft Tissue ☐ Salivary Gland ☐ Sinus ☐ Thyroid **Central Nervous System** ☐ Brain ☐ Epidural ☐ Lepomeninges **Gastrointestinal/ Abdominal** ☐ Ascites/ Peritoneum ☐ Appendix ☐ Colon ☐ Esophagus ☐ Liver ☐ Pancreas ☐ Rectum ☐ Small Intestine ☐ Stomach **Genito-urinary Tract** ☐ Epididymis ☐ Kidney ☐ Ovary ☐ Prostate ☐ Testes ☐ Uterus **Mediastinal/ Intra-thoracic** ☐ Heart ☐ Lung ☐ Mediastinal Soft Tissue ☐ Pericardium ☐ Pleura ☐ Other, please specify ☐ No Known Extranodal Involvement	Using the patient's medical record check all applicable boxes to identify the anatomic location of all site(s) of extranodal involvement by diffuse large B-cell lymphoma at the time of initial diagnosis. 2735776 *To select multiple sites of involvement, press the control button and select the sites of involvement. Your selections should be highlighted after you've selected.*
	Other Extranodal Involvement at Diagnosis *(For Primary Clinical Involvement)* Only complete if "other" is	_____	If all extranodal sites of involvement are not included in the list provided, please indicate any sites of extranodal involvement. 3234303

#	Data Element	Entry Alternatives		Working Instructions
	selected in #39.			
40	Number of Extranodal Sites of Involvement Above *(to calculate the IPI)*	_____		Provide the total number of extranodal sites with lymphoma involvement. Use the previous three questions to determine this number. This information, along with other data provided, will be used by the Analysis Working Group (AWG) to calculate the International Prognostic Index (IPI). 3233242
41	Maximum Tumor Bulk *(Dimension)*	_____ (cm)		After review of the entire medical record, record the length of the largest dimension/ diameter of a tumor, regardless of anatomical plane. 64215
*42	Anatomic Site of Maximum Tumor Bulk *(Select one anatomic site from listing above)*	☐ Adrenal ☐ Bone ☐ Bone Marrow ☐ Brest ☐ Peripheral Blood ☐ Skin ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* **Genito-urinary Tract** ☐ Epididymis ☐ Kidney ☐ Ovary ☐ Prostate ☐ Testes ☐ Uterus **ENT & Eye** ☐ Intraocular ☐ Larynx ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Oropharynx ☐ Parotid Gland ☐ Peri-orbital Soft Tissue ☐ Salivary Gland ☐ Sinus ☐ Thyroid **Mediastinal/ Intra-thoracic** ☐ Heart ☐ Lung ☐ Mediastinal Soft Tissue ☐ Pericardium ☐ Pleura ☐ Other, please specify ☐ No Known Extranodal Involvement	**Gastrointestinal/ Abdominal** ☐ Ascites/ Peritoneum ☐ Appendix ☐ Colon ☐ Esophagus ☐ Liver ☐ Pancreas ☐ Rectum ☐ Small Intestine ☐ Stomach **Central Nervous System** ☐ Brain ☐ Epidural ☐ Lepomeninges **Lymph Nodes** ☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral ☐ Ililac ☐ Iliac-common ☐ Iliac-external ☐ Mediastinal ☐ Mesenteric ☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Supraclavicular ☐ Submandibular ☐ No Known Nodal Involvement	Using the list of sites in numbers 43 and 44, provide the anatomic site of the maximum tumor bulk. 3233300
Pathologic Diagnosis and Surgical Resection				
*43	Date of Initial Pathologic Diagnosis	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)		Provide the date the patient was initially diagnosed with the malignancy submitted for HTMCP. This may or may not be the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 2896956 (month), 2896958 (day), 2896960 (year) *Note: The day of Initial Pathologic Diagnosis is not required.*
44	Method of Initial Pathologic Diagnosis	☐ Cytology ☐ Biopsy ☐ Surgical Resection		Provide the method of the initial pathologic diagnosis. This is the method used on the date provided above. 2757941

#	Data Element	Entry Alternatives	Working Instructions
		☐ Other (please specify) ☐ Unknown	
	Other Method of Initial Pathologic Diagnosis Only complete if "other" is selected in #44.	_____	If the method of initial pathologic diagnosis is not included in the list above, provide the method used. 2757948
45	Date of Surgical Resection	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 3008197 (month), 3008195 (day), 3008199 (year)
Lymph Node Status			
62	Were Lymph Nodes Examined at the Time of Primary Resection?	☐ Yes ☐ No ☐ Unknown	Indicate whether any lymph nodes were examined at the time of the primary resection. 2200396
3	Number of Lymph Nodes Examined	_____	Provide the number of lymph nodes examined, if one or more lymph nodes were removed. 3
4	Number of Lymph Nodes Positive by H&E light microscopy	_____	Provide the number of lymph nodes positive through hematoxylin and eosin (H&E) staining and light microscopy. 3086388
5	Number of Lymph Nodes Positive by IHC Keratin Staining only	_____	Provide the number of lymph nodes positive through keratin immunohistochemistry (IHC) staining. 3086383
6	Pathologic Positive Lymph Node Location(s) *(Check all that apply)*	☐ Pelvic (external iliac, internal iliac, obturator) ☐ Common iliac ☐ Paraaortic ☐ Supraclavicular ☐ Unknown ☐ Other, specify	Using the patient's pathology/laboratory report, provide the location(s) of any positive lymph nodes. 3151519
7	Other Positive Lymph Node	_____	If the location of positive lymph nodes was not included in the list provide, please provide the location of positive lymph nodes. 3151522
Staging and Histology of Bone Marrow			
*46	Clinical Tumor Stage	**Stage** / **Clinical (CS)** ☐ Stage I — ☐ A ☐ B ☐ E ☐ Stage II — ☐ A ☐ B ☐ E ☐ Stage III — ☐ A ☐ B ☐ E ☐ Stage IV — ☐ A ☐ B ☐ E	Using the Ann Arbor criteria, provide the clinical stage that was used to treat the patient. 3440332 **A**: Absence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **B**: Presence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **E**: Presence of lymphoma in extranodal sites.
*47	Pathological Tumor Stage	**Stage** / **Pathologic (PS)** ☐ Stage I — ☐ A ☐ B ☐ E ☐ Stage II — ☐ A ☐ B ☐ E ☐ Stage III — ☐ A ☐ B ☐ E ☐ Stage IV — ☐ A ☐ B ☐ E	Using the Ann Arbor criteria, provide the pathologic stage that was used to treat the patient. 3065862 **A**: Absence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **B**: Presence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **E**: Presence of lymphoma in extranodal sites.
48	Presence of Malignant Cells in Bone Marrow by Histology	☐ Yes ☐ No ☐ Unknown	Indicate if malignant cells are histologically Confirmed in the patient's bone marrow. 2180550
49	Histology of Bone Marrow Samples	☐ Concordant Histology ☐ Disconcordant Histology ☐ Unknown	If malignant cells are present in the bone marrow at the time of initial staging workup, determine if the histologic diagnosis of the bone marrow is concordant with the previously diagnosed DLBCL. 3233401
Tests Performed			
LDH Level (at the time of staging)			

#	Data Element	Entry Alternatives	Working Instructions
*50	LDH Level	_____(IU)	Record the result of the LDH lab test performed during the staging workup. 2798766
*51	LDH Level Upper Limit for Normal at Facility	_____(IU)	Record the upper limit of the normal range of the LDH lab test performed at the reporting facility. 2953115
Genetic Testing			
52	Immunophenotyping	(+) (-) Indeterminant CD19 ☐ ☐ ☐ CD10 > 30% ☐ ☐ ☐ BCL2 ☐ ☐ ☐ P53 > 20% ☐ ☐ ☐ CD20 ☐ ☐ ☐ MUM1 > 30% ☐ ☐ ☐ CD138 ☐ ☐ ☐ CD22 ☐ ☐ ☐ BCL6 > 30% ☐ ☐ ☐ CD23 ☐ ☐ ☐ CD79a ☐ ☐ ☐ PAX5 ☐ ☐ ☐ CD5 ☐ ☐ ☐ HHV8 ☐ ☐ ☐ CD30 ☐ ☐ ☐ Cytoplasmic lg ☐ ☐ ☐ CD15 ☐ ☐ ☐ Surface lg ☐ ☐ ☐ EBER ☐ ☐ ☐ Cyclin D1 ☐ ☐ ☐ ALK ☐ ☐ ☐	Indicate all tests performed for immunophenotypic analysis in order to classify clonal subgroups. 3234614, 3234626
53	B-cell Immunophenotype Methodology	☐ IHC ☐ Flow Cytometry ☐ Unknown	If B-cell genotype was performed, indicate the testing method used. 64540
54	Immunophenotyping MIB-1 *(Percent Positive; 4+ Scale)*	☐ 0-25% ☐ 51-75% ☐ 26-50% ☐ 76-100%	Provide the percentage range of MIB-1 positive cells identified through immunophenotypic analysis. 3233414
55	Methodology Used to Determine B-Cell Genotype	☐ PCR ☐ Southern ☐ Not Performed	If B-cell genotype was performed, indicate the testing method used. 3233449
56	B-Cell Genotype: IgH	☐ Clonal ☐ Non-Clonal ☐ Not Performed	If B-cell genotype was performed, indicate the results of the IgH. 3233560
57	B-Cell Genotype: IgK	☐ Clonal ☐ Non-Clonal ☐ Not Performed	If B-cell genotype was performed, indicate the results of the IgK. 3233565
Genetic Abnormalities			
58	Genetic Abnormalities	N T G A L O C-MYC ☐ ☐ ☐ ☐ ☐ ☐ BLC2 ☐ ☐ ☐ ☐ ☐ ☐ BCL6 ☐ ☐ ☐ ☐ ☐ ☐ ALK ☐ ☐ ☐ ☐ ☐ ☐ C-REL ☐ ☐ ☐ ☐ ☐ ☐ 9p21 ☐ ☐ ☐ ☐ ☐ ☐ CCND1 ☐ ☐ ☐ ☐ ☐ ☐ MALT1 ☐ ☐ ☐ ☐ ☐ ☐	Indicate all genetic abnormalities for which the patient was tested. 3234675, 3234680 N = Normal T = Translocation G = Gain L = Loss A = Amplification O = Other
	Other Genetic	N T G A L O	Specify any other genetic abnormalities not in the provided

#	Data Element	Entry Alternatives	Working Instructions
	Abnormalities *(please specify)* Only complete if "other" is selected in #58.	_____ ☐ ☐ ☐ ☐ ☐ ☐ _____ ☐ ☐ ☐ ☐ ☐ ☐ _____ ☐ ☐ ☐ ☐ ☐ ☐ _____ ☐ ☐ ☐ ☐ ☐ ☐	list for which the patient was tested. 3234685
	Methodology Used to Identify Genetic Abnormalities Only complete if patient had a genetic abnormality.	1 2 3 4 C-MYC ☐ ☐ ☐ ☐ BLC2 ☐ ☐ ☐ ☐ BCL6 ☐ ☐ ☐ ☐ ALK ☐ ☐ ☐ ☐ C-REL ☐ ☐ ☐ ☐ 9p21 ☐ ☐ ☐ ☐ CCND1 ☐ ☐ ☐ ☐ MALT1 ☐ ☐ ☐ ☐	If the patient was tested for a specific genetic abnormality, indicate the testing method used to perform each analysis. 3234684 Methodology Code: 1 = PCR 2 = Southern Blot 3 = FISH 4 = Cytogenetic
	Other Methodology Used to Identify Genetic Abnormalities Only complete if "other" is selected in #59.	_____	Specify any other genetic abnormality testing performed that is not in the provided list.
59	Methodology Used to Determine EBV Status of Malignant Cells	☐ EBER in situ Hybridization ☐ LMP Immunohistochemistry ☐ EBV PCR	If the patient's EBV status was positive, provide the testing method used to determine the EBV status of the malignant cells. 3233656
60	EBV Status of Malignant Cells	☐ Positive ☐ Not Performed ☐ Negative	Provide the result of the lab test to detect the presence of Epstein/Barr Virus antibody in the patient. 2003961
61	If EBV status is positive, provide the percent positive. *(does not include background positives)*	_____(%)	If the patient's EBV status was positive, provide the percentage of EBV positive malignant cells. Do not include the number of background positives. 3233649
New Tumor Event Information *Complete this section if the patient had a new tumor event. If the patient did not have a new tumor event (or if the TSS does not know) indicate this in the question below, and the remainder of this section can be skipped.* Note: The New Tumor Event section on OpenClinica can be completed multiple times, if the patient had multiple New Tumor Events.			
*62	New Tumor Event After Initial Treatment?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had a new tumor event (e.g. metastatic, recurrent, or new primary tumor) after the date of initial diagnosis. 3121376
63	Type of New Tumor Event	☐ Locoregional/Recurrence ☐ Distant Metastasis ☐ New Primary Tumor	Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis or a new primary tumor. 3119721
64	Site of New Tumor Event	**Nodal Involvement** ☐ Axillary ☐ Mesenteric ☐ Cervical ☐ Occipital ☐ Epitrochlear ☐ Paraaortic ☐ Femoral ☐ Parotid ☐ Hilar ☐ Popliteal ☐ Iliac-common ☐ Retroperitone ☐ Iliac-external ☐ Splenic ☐ Mediastinal ☐ Supraclavicular ☐ Submandibular	Indicate the site of this new tumor event. 3108271

#	Data Element	Entry Alternatives	Working Instructions
		Extranodal Involvement ☐ Adrenal ☐ Bone ☐ Bone Marrow ☐ Brest ☐ Peripheral Blood ☐ Skin ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* **ENT & Eye** ☐ Intraocular ☐ Larynx ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Oropharynx ☐ Parotid Gland ☐ Peri-orbital Soft Tissue ☐ Salivary Gland ☐ Sinus ☐ Thyroid **Central Nervous System** ☐ Brain ☐ Epidural ☐ Lepomeninges **Gastrointetinal/ Abdominal** ☐ Ascites/ Peritoneum ☐ Appendix ☐ Colon ☐ Esophagus ☐ Liver ☐ Pancreas ☐ Rectum ☐ Small Intestine ☐ Stomach **Genito-urinary Tract** ☐ Epididymis ☐ Kidney ☐ Ovary ☐ Prostate ☐ Testes ☐ Uterus **Mediastinal/ Intra-thoracic** ☐ Heart ☐ Lung ☐ Mediastinal Soft Tissue ☐ Pericardium ☐ Pleura	
65	Other Site of New Tumor Event Only complete if "other" is selected in #5.	_____	If the patient had a new tumor event and the site of this tumor was not included in the provided list, describe the site. 3128033
*66	Date of New Tumor Event	___ ___ / (month) ___ ___ / (day) ___ ___ ___ ___ (year)	If the patient had a new tumor event, provide the date of diagnosis for this new tumor event. 3104044
67	Was Site of First Progression Biopsied?	☐ Yes ☐ No ☐ Unknown	If the patient has had progression of disease, indicate whether the site of first progression was biopsied. 2716366
68	If Biopsied, What was the Histologic Type?	☐ Diffuse Large B-Cell Lymphoma ☐ Other (please specify)	Indicate the histologic diagnosis (type) of the tissue biopsied for the first progression of the malignant lymphoma. 3282652
69	Other Histologic Type Only complete if "other" is selected in #5.	_____	If the first site of malignant lymphoma progresson is not DLBCL, specify the other histologic diagnosis (type) of the tissue biopsied for the first progression of the malignant lymphoma. 3282653
*1	Is this Patient Lost to Follow-up?	☐ Yes ☐ No	Indicate whether the patient is lost to follow-up, as defined by the ACoS Commission on Cancer. This only includes cases where updated follow-up information has not been collected within the past 15 months and all efforts to contact the patient have been exhausted (this includes reviewing the Social Security death index). If the patient is lost to follow-up, the remaining questions can be left unanswered. 61333 *If the patient is **deceased** and a HTMCP follow-up form has not yet been completed, the answer to this question should be "no," and the remaining applicable questions should be completed.*
70	**General Comments**		

#	Data Element	Entry Alternatives	Working Instructions

Principal Investigator (*Printed Name*)

Principal Investigator (*Signature*) Date

I acknowledge that the above information provided by my institution is true and correct and has been quality controlled.

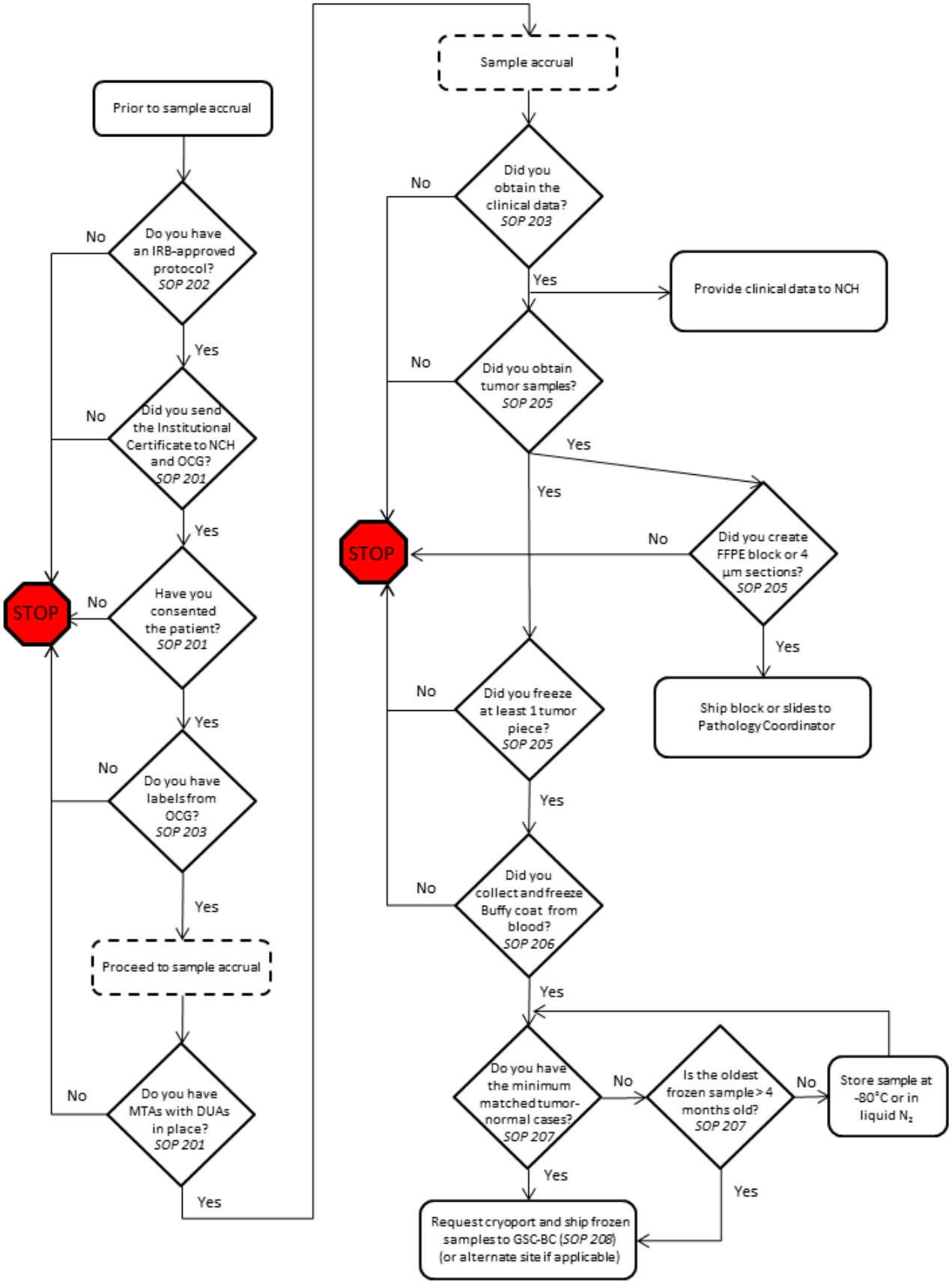
Appendix B: Checklist of Task Completion for Sample Submission

Date:
Institution:
Operator:

- Do you have an IRB-approved protocol?
- Have you sent your Institutional Certification to the Project Team and NCH?
- Have you consented the patient?
- Have you obtained the project-assigned ID and labels from the Project Team?
- Do you have at least one frozen tissue section (≤ 100 mg each) in individual cryovials? Are the cryovials labeled with **only** the freezer-resistant labels from the Project Team?
- Do you have frozen non-tumoral cells? Are they labeled with the freezer-resistant labels from the Project Team?
- Do you have a formalin-fixed paraffin embedded (FFPE) tissue block (or sixteen [16] unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides)? Are they labeled with the freezer-resistant labels from the Project Team?
- Have you sent the FFPE tissue block or unstained sections for central pathology review? Have you received notification from OCG that the samples qualify for study inclusion?
- Have you ordered a cryoport?
- Do you have the clinical data elements required by the project? (Appendix A). Have you received notification from OCG to send the clinical data elements electronically to NCH following molecular QC of the samples?

You may ship samples ONLY once all of the questions above are answered "YES."

Follow the flowchart on the next page for additional guidance.


Prior to sample accrual
Do you have an IRB-approved protocol? SOP 202
No
Yes
Did you send the Institutional Certificate to NCH and OCG? SOP 201
No
Yes
STOP
Have you consented the patient? SOP 201
No
Yes
Do you have labels from OCG? SOP 203
No
Yes
Proceed to sample accrual
Do you have MTAs with DUAs in place? SOP 201
No
Yes
Sample accrual
Did you obtain the clinical data? SOP 203
No
Yes
Provide clinical data to NCH
Did you obtain tumor samples? SOP 205
No
Yes
STOP
Did you create FFPE block or 4 µm sections? SOP 205
No
Yes
Ship block or slides to Pathology Coordinator
Did you freeze at least 1 tumor piece? SOP 205
No
Yes
Did you collect and freeze Buffy coat from blood? SOP 206
No
Yes
Do you have the minimum matched tumor-normal cases? SOP 207
No
Is the oldest frozen sample > 4 months old? SOP 207
No
Store sample at -80°C or in liquid N2
Yes
Yes
Request cryoport and ship frozen samples to GSC-BC (SOP 208) (or alternate site if applicable)

Status	Date
Adopted:	9/1/2010
2nd Version:	4/7/2011
3rd Version:	5/25/2012
4th Version:	11/7/2013
4th Version:	7/16/2014

HTMCP SOP #209A: Centralized Pathology Review Process for HIV+ Diffuse Large B-Cell Lymphoma Characterization Project

Introduction

Pathological diagnosis of tumors can be impacted by the subjective nature of the process as well as the subjective definition of the criteria used in the assessment. To assure that samples meet the tissue requirements for the HIV+ Tumor Molecular Characterization Project (HTMCP) and are diagnosed as Diffuse Large B-cell Lymphoma (DLBCL), a Pathology Review Committee (PRC) of five board-certified pathologists is established. The review of tissues by a group minimizes the subjectivity that is unavoidable in pathology reviews and allows an efficient resolution of discrepancies.

Scope and Purpose

1. To establish a standard procedure for the centralized pathology review of tissue submitted to the HTMCP.

Equipment and Materials

1. A formalin-fixed paraffin-embedded (FFPE) diagnostic block (preferred) OR a minimum of fifteen (15) unstained 4 µm thick sections from the formalin-fixed paraffin-embedded (FFPE) diagnostic block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. These blocks/sections will be provided by the tissue source site (TSS) contributing the case and should be labeled with freezer-resistant labels containing the project-assigned ID (obtained from the Project Team; see HTMCP SOP #203A and 204).
2. Bioimagene or Aperio Slide Scanner

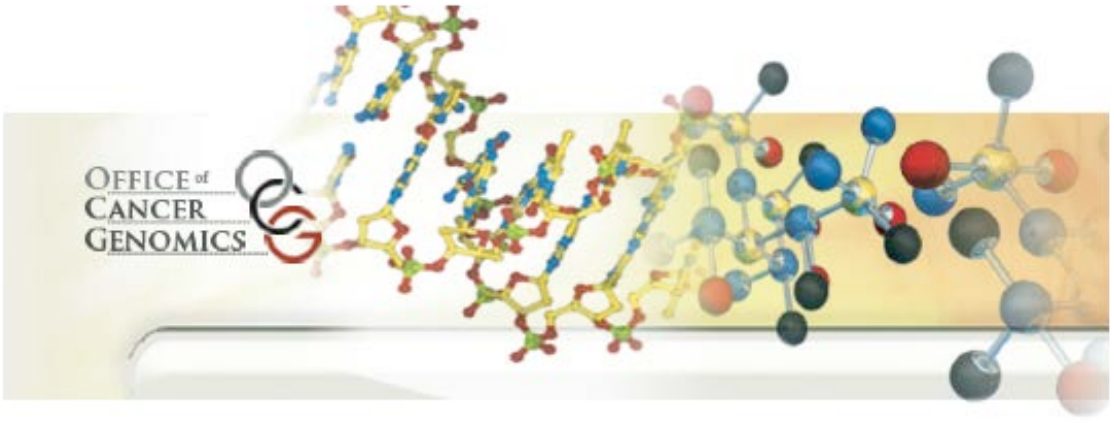
Procedure

A. Preparation for review:
   1. All members of a centralized pathology board obtain their PathXchange credentials by going to the following website: http://www.pathxchange.org/user/register
   2. Once the credentials are secured, they should be communicated to the Office of Cancer Genomics (OCG) Project Team (PT) manager (see HTMCP SOP #200A).

3. Immediately upon arrival to the Pathology Review Lab (PRL), the Pathology Coordinator will verify that all blocks/slides submitted are labeled with the same project-assigned ID for each case.
4. Pathology coordinator will send the appropriate number of slides to the histology service to perform hematoxylin & eosin (H&E) as well as necessary immunohistochemical (IHC) and *in situ* hybridization protocols. The processing should take no longer than 2 weeks.
   (1) IHC to be performed include: **CD3, CD10, CD20, BCL6, MUM1, BCL2, Ki67, TP53 , CD79a**
   (2) In situ hybridization will be performed: **EBER**
5. Once all processing is completed, the Pathology Coordinator will:
   (1) scan the H&E and IHC slides on the Bioimagene system
   (2) deposit images of the slides and a blank review form in the PathXchange website (http://www.pathxchange.org) within group HTMCP DLBCL
6. The Pathology Coordinator will send an e-mail to the members of the pathology review core (PRC) (with copy to the PT manager) informing them that materials for review have been deposited in a folder. This communication must specify the number and name of files, as well as the project-assigned ID(s) for the case(s) under review.
7. This deposition and communication must occur within 48 hours of scanning the slides by the Pathology Coordinator.

B. Review:
1. Within three days of receipt of the e-mail from the Pathology Coordinator, all members of the PRC will return their pathology review form to the Pathology Coordinator via e-mail.
2. The tumors will be classified using the WHO classification.
3. If a consensus is reached and the case passes the specified criteria the pathology coordinator will create a final pathology report and submit it to the Office of Cancer Genomics and the Genome Science Center at British Columbia (GSC-BC) within 4 days. The OCG Project Team manager will complete the Pathology Report form on OpenClinica. Steps 1-3 will take 2 weeks total.
4. Cases for which the tissue is inadequate for diagnosis (*e.g.* tumor nuclei below 70%, degraded tissue) or for which the diagnosis is not Diffuse Large B-cell Lymphoma will be labeled as such and taken out of the study.
5. Cases for which the members of the PRC do not agree on a diagnosis will undergo an additional review by the PRC to reach a consensus. This consensus review will be convened by the Pathology Coordinator. The schedule of such consensus reviews will be dictated by the following:
   - When six or more discordant cases have been accrued, a consensus review panel must be convened.
   - If there are fewer than six discordant cases, but the oldest accrued case is more than three months old, a consensus review panel must be convened.

National Cancer Institute



HIV+ Tumor Molecular Characterization Project (HTMCP) Lung Tumor-Specific Protocols

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Status	Date
Adopted:	9/14/2010
2nd Version:	11/7/2013
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Reviewed:	

HTMCP SOP #200B:
HIV+ Tumor Molecular Characterization Project
Lung Tumor Contact Sheet

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HTMCP SOP #203B: Prospective Sample Submission Procedure for the HIV+ Lung Tumor Characterization Project

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer-related alterations in HIV+ patients and HIV- patients. The HIV+ Tumor Molecular Characterization Project aims to generate large scale, high-quality data on the cancers' genomes and transcriptomes using 2nd and 3rd generation sequencing technology. The data collected from the lung cancer characterization subproject will allow scientists to identify genetic alterations common to individuals with lung cancer and HIV.

Scope and Purpose

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200B) with the details.

Procedures

A. Before patient accrual begins:
   1. Make sure all the documents required for sample shipment as spelled out in HTMCP SOP #201 are in place before you start case accruals.
   2. You may request project-assigned IDs in advance. Contact OCG (see HTMCP SOP #200B) with your TSS-assigned ID to obtain project-assigned IDs (see HTMCP SOP #204) which you must use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.

3. You may request freezer-resistant labels with the project-assigned IDs in advance. Contact the OCG PT manager (see HTMCP SOP #200B) to obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.

B. Before patient surgery:
   1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.
   2. If you have not done so already, contact OCG with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.
   3. If you have not done so already, contact the OCG PT manager and obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.
   4. Prepare the tissue freezing station and have ready all the materials needed for tissue processing (HTMCP SOP #205).
   5. Inform the research nurse that a 10 mL peripheral blood sample must be obtained from the patient to use as a non-tumoral control (see Appendix A). The buffy coat must be separated from the plasma within two hours of the blood draw from the patient. Store the blood sample in the refrigerator until processing. Time in storage must be reported to the PT manager. The buffy coat sample should be moved immediately to a -80°C or Liquid Nitrogen (LN2) freezer for storage (see HTMCP SOP #206).

C. During patient surgery:
   1. Inform the surgical staff of the tissue requirements for the project (see Appendix A).
   2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   3. Note the time between surgery and freezing in a notebook and send to the PT manager.

D. After surgery:
   1. Process solid tissue as described in the tissue processing protocol (HTMCP SOP #205). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   2. Process the blood sample according to HTMCP SOP #206. Store isolated cells in a -80°C freezer or liquid nitrogen (LN2) storage until shipment.
   3. Obtain a formalin-fixed, paraffin-embedded tissue block or, if not possible, **five (5)** unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. Affix one of the provided freezer-resistant labels to each slide or block.

E. Preparing samples and shipment:
   1. **Optional**: Section frozen tumor sample following the frozen tissue sectioning protocol. Produce a 4 µm frozen section of the top of the tumor sample for initial quality control as described in the tissue processing protocol (HTMCP SOP #210).
   2. When tissue from at least three cases are accrued, or every quarter (see HTMCP SOP #207) contact the Genome Sciences Center at British Columbia Cancer Agency (GSC-BC)

Coordinator (see HTMCP SOP #200B) to schedule a shipment of a cryoport transport vessel to send the cryovials containing frozen tumor sample sections and frozen blood cells.

3. When the cryoport arrives follow the frozen sample shipment protocol (HTMCP SOP #208) and send the frozen samples to GSC-BC. It is expected that most sites will send tissues within to GSC-BC within 24 hours of receiving the cryoport. The timing of shipment should be discussed prior to tissue collection, especially if exceptions are required. Provide both the GSC-BC and PT with tracking number the day of shipment.
4. Send a formalin-fixed, paraffin-embedded tissue block or, if not possible, **five (5)** unstained 4 µm sections obtained from the formalin fixed blocks mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides, to the Pathology Coordinator (see HTMCP SOP #200B). Upon shipment, provide both the Pathology Coordinator and OCG PT with the tracking number of the parcel. If slides are sent, ship in a box designed to hold slides securely to prevent breakage (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).
5. Collect all the **de-identified** clinical data requested in the sample requirements (Appendix A). You will be requested by the OCG project coordinator to send the data electronically to the NCH using the appropriate TSS-assigned ID at a later date.

Notes

- A checklist is provided to help you track all the steps required by this process (Appendix B). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained tissue blocks or slides, and clinical data) is not present, the submission is incomplete, the sample cannot be accepted for HTMCP, and reimbursement of costs cannot proceed.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

Appendix A: Sample Requirements

Tissue Requirements

To be accepted to the project, the following conditions have to be met at the tissue level.

- Tissue must come from a patient who has not received neoadjuvant therapy for the tumor type submitted for HTMCP or systemic treatment for any tumor.
- Paired tumor and normal tissue (blood cells) must be available in sufficient quantities (~100 mg of frozen tumor tissue, plus 10 mL of blood).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in liquid nitrogen, but -80°C or lower is acceptable. The form of tissue storage must be recorded.
- Tumors need to have a minimum percent of tumor nuclei of 70% as assessed by H&E on top and bottom of a tissue section physically adjacent to the specimen used for generating the RNA and DNA.
- There must be enough tissue of both to produce a 4 µm thick section from the top for H&E staining, then 10 sections of 20 µm thickness, followed by another 4 µm section to stain by H&E. **The number of sections needed is based on a block with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required. See HTMCP SOP #210 for the formula allowing calculation of number of sections needed.** A core biopsy obtained at the same time as the one produced for pathology might provide sufficient tissue if it is of high tumor content and low necrosis.
- A formalin-fixed paraffin-embedded block for pathology consensus review (or at least five [5] unstained 4 µm sections mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides) must exist for the tumor.

Clinical Data Requirements

To be accepted to the project, the following conditions must meet at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) listed on the following pages. Should some of the data fields be missing, please contact the OCG PT manager to get approval for submission. **All patient information must be de-identified.**

These clinical data elements must be reported to NCH as an initial report within two weeks of enrolling the patient. At 12 months and 24 months after the patient's enrollment in HTMCP, an update of the status and clinical condition of each patient needs to be submitted to NCH. If the patient dies prior to the first year update, the second year update would only serve to confirm the status.

Patients need to be consented in such a way that allows for the use of their tissues for genomic-scale molecular characterization.

HTMCP – Lung Tumor Enrollment Form

Instructions: The Clinical Data needed to complete this Enrollment Form should be collected for each patient with a lung tumor in the HIV+ Tumor Molecular Characterization Project (HTMCP) prior to acquisition of tissues. Upon qualification notice from the Office of Cancer Genomics (OCG), the Tissue Source Site (TSS) should complete this Enrollment form for each qualified case within 60 days. Questions regarding this form should be directed to the Nationwide Children's Hospital (NCH) or OCG.

Please note the definitions for "Unknown" and "Not Evaluated" on this form.

Unknown: This should only be selected if the TSS does not know this information after all efforts to obtain the data have been exhausted. If this answer is selected for a question that is part of the required data set, the TSS must complete a discrepancy note providing a reason why it is unknown.

Not Evaluated: This answer option should only be selected by the TSS if it is known that the information being requested cannot be obtained. This could be because the test in question was never performed on the patient or the TSS knows that the information requested was never disclosed.

Tissue Source Site (TSS): _____TSS ID: _____ TSS Unique Patient ID: _____
Completed by (interviewer name in OpenClinica): _____
Completed Date: ___ ___/___ ___ /___ ___ ___ ___

#	Data Element	Entry Alternatives	Working Instructions
1	Is this a prospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for prospective tissue collection. If the submitted tissue was collected after the date the HTMCP contract was executed, the tissue has been collected prospectively. 3088492
2	Is this a retrospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for retrospective tissue collection. If the submitted tissue was collected prior to the date the HTMCP contract was executed, the tissue has been collected retrospectively. 3088528
*3	Date of Birth	__ __/ __ __/ __ __ __ __ month day year	Provide the date the patient was born. 2896950 (month), 2896952 (day), 2896954 (year) *Note: The day of Birth is not required.*
*4	Gender	☐ Female ☐ Male	Provide the patient's gender using the provided categories. 2200604

#	Data Element	Entry Alternatives	Working Instructions
5	Race *(check all that apply)*	☐ American Indian or Alaska Native ☐ Asian ☐ White ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ Other (please specify) ☐ Not Evaluated ☐ Unknown	Provide the patient's race using the defined categories. 3009519 American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. Asian: A person having origins in any of the original peoples of the far East, Southeast Asia, or in the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. White: A person having origins in any of the original peoples of the four Europe, the Middle East, or North Africa. Black or African American: A person having origins in any of any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.” Native Hawaiian or other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
6	Other Race	_____	If the patient’s race was not defined in the previous question, provide the patient’s race. 2192205

#	Data Element	Entry Alternatives	Working Instructions
7	Ethnicity	☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Not Evaluated ☐ Unknown	Provide the patient's ethnicity using the defined categories. 2192217 Not Hispanic or Latino: A person not meeting the definition of Hispanic or Latino. Hispanic or Latino: A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
8	Height *(at time of diagnosis)*	_____(cm)	Provide the patient's height (centimeters) at the time the patient was diagnosed with the tumor submitted for HTMCP. 649
9	Weight *(at time of diagnosis)*	_____(kg)	Provide the patient's weight (kilograms) at the time the patient was diagnosed with the tumor submitted for HTMCP. 651
*10	Tobacco Smoking History Indicator	☐ 1: Lifelong Non-Smoker ☐ 2: Current Smoker ☐ 3: Current Reformed Smoker for > 15 years ☐ 4: Current Reformed Smoker for <= 15 years ☐ 5: Current Reformed Smoker (duration not specified) ☐ Smoking Status not Documented	Indicate the patient's history of tobacco smoking as well as their current smoking status using the defined categories. If the patient is a lifelong non-smoker, skip the additional smoking questions. 2181650
11	Age of Onset Tobacco History Indicator	_____ _____ years	Provide the age in years when the patient began smoking cigarettes. 2178045
12	Year of Quitting Tobacco Smoking	_____ _____ _____ _____ (YYYY)	Provide the year the patient quit smoking. 2228610

#	Data Element	Entry Alternatives	Working Instructions
13	Number of Pack Years Smoked	____ ____ ____ ____ pack years	Provide the number of pack years the patient smoked. This is calculated using the number of cigarettes smoked per day times the number f years smoked, divided by 20. For example, if the patient smoked 5 cigarettes per day times 10 years divided by 20, the patient would have 2.5 pack years (e.g. 5x10/20=2.5). 2955385
*14	Vital Status *(at date of last contact)*	☐ Living ☐ Deceased	Indicate whether the patient was living or deceased at the date of last contact. 5
*15	Date of Last Contact	__ __/ __ __/ __ __ __ __ month day year	If the patient is living, provide the date of last contact with the patient (as reported by the patient, medical provider, family member, or caregiver). 2897020 (month), 2897022 (day), 2897024 (year) *Note: The day of Last Contact is not required.*
*16	Date of Last Known Alive	__ __/ __ __/ __ __ __ __ month day year	Indicate the last date the patient was known to be alive, regardless of whether the patient, medical provider, family member or caregiver was contacted. 2975722 (month), 2975724 (day), 2975726 (year) Do not answer if patient is deceased. *Note: The day of Last Known Alive is not required.*
*17	Date of Death	__ __/ __ __/ __ __ __ __ month day year	If the patient is deceased, provide the date of death. 2897026, (month) 2897028 (day), 2897030 (year) *Note: The day of Death is not required.*

#	Data Element	Entry Alternatives	Working Instructions
18	Did the patient receive neo-adjuvant therapy for the tumor submitted for HTMCP?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient received treatment (radiation, pharmaceutical, or both) prior to the procurement o the sample submitted for TCGA. 3382737 *If the answer to this question is "yes", the submitted case is excluded.*
*19	Tumor Status *(at time of last contact or death)*	☐ Tumor free ☐ With tumor ☐ Unknown	Indicate whether the patient was tumor/disease free (i.e. free of the malignancy that yielded the sample submitted for the HTMCP study) at the date of last contact or death. 2759550
20	Performance Status: Eastern Cooperative Oncology Group Score	☐ 0: Asymptomatic ☐ 1: Symptomatic, but fully ambulatory ☐ 2: Symptomatic, in bed less than 50% of day ☐ 3: Symptomatic, in bed more than 50% of day, but no bed-ridden ☐ 4: Bed-ridden ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time it was evaluated, as selected in the "Performance Status: Timing" question below. 88

#	Data Element	Entry Alternatives	Working Instructions
21	Performance Status: Karnofsky Score	☐ 100: Normal, no complaints, no evidence of disease ☐ 90: Able to carry on normal activity; minor signs or symptoms of disease ☐ 80: Normal activity with effort; some signs or symptoms of disease ☐ 70: Cares for self, unable to carry on normal activity or to do active work ☐ 60: Requires occasional assistance ☐ 50: Requires considerable assistance and frequent medical care ☐ 40: Disabled, requires special care and assistance ☐ 30: Severely disabled, hospitalization indicated. Death not imminent ☐ 20: Very sick, hospitalization ☐ 10: Moribund, fatal processes progressing rapidly ☐ 0: Dead ☐ Unknown ☐ Not Evaluated	Provide the Karnofsky performance status of the patient at the time it was evaluated, as selected in the "Performance Status: Timing" question below. 2003853
22	Performance Status: Timing	☐ Preoperative ☐ Pre-adjuvant Therapy ☐ Post-adjuvant Therapy ☐ Unknown	Indicate the timing of the performance status(es) provided in the previous question(s). 2792763
*23	Is this patient HIV positive?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient is HIV positive. 2180464
*24	Date of HIV Diagnosis (if known)	__ __/ __ __/ __ __ __ __ month day year	Provide the month the patient was diagnosed with HIV. 3579640 (month), 3579644 (day), 3579643 (year) *Note: The day of HIV Diagnosis is not required.*
25	Nadir CD4 Counts	_____(cells/mm^3)	Provide the patient's Nadir CD4 counts, which are the lowest CD4 counts the patient has had. 2684395

#	Data Element	Entry Alternatives	Working Instructions
26	CD4 Counts at Diagnosis of the Submitted Malignancy	_____ (cells/mm^3)	Provide the patient's CD4 Counts at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922654
*27	HIV RNA load at Diagnosis of Submitted Malignancy	_____	Provide the HIV RNA load (also known as the "viral load") at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922674

#	Data Element	Entry Alternatives	Working Instructions
28	Prior AIDS Defining Conditions	☐ Candidiasis of bronchi, trachea or lungs ☐ Candidiasis, esophageal ☐ CMV other than liver, spleen or nodes, onset at age >1month ☐ CMV retinitis ☐ Coccidioidomycosis, disseminated or extrapulmonary ☐ Cryptococcosis, extrapulmonary ☐ Cryptosporidiosis, chronic intestinal ☐ Encephalopathy, HIV-related ☐ Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis or esophagitis (onset at age > 1 month) ☐ Histoplasmosis, disseminated or extrapulmonary ☐ Isosporiasis, chronic intestinal (> 1 mon) ☐ Mycobacterium avium complex or Mycobacterium kansasii disseminated or extrapulmonary ☐ Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary ☐ Mycobacterium, other species or unidentified species, disseminated or extrapulmonary ☐ Nocardiosis ☐ Pneumocystis jirovecii pneumonia ☐ Pneumonia, recurrent ☐ Progressive multifocal leukoencephalopathy ☐ Salmonella septicemia, recurrent ☐ Toxoplasmosis of the brain, onset at age >1month ☐ Wasting syndrome, due to HIV	Prior to the malignancy submitted for the HTMCP study, provide any AIDS defining conditions 2679581

#	Data Element	Entry Alternatives	Working Instructions
29	CoInfections *(serology data/viral load if available)*	**Test Results**	Indicate whether the patient had any co-infections by providing the results of each of the tests listed.
		HBV	2180456
		HCV	2695021
		HPV	2230033
		KSHV/ HHV8	3335773
*30	HAART Treatment Prior to Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment prior to the diagnosis of the malignancy submitted for the HTMCP study. 3335156
*31	HAART Treatment at Time of Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment at the time of the diagnosis of the malignancy submitted for the HTMCP study. 2922679
32	CDC HIV Risk Group(s)	☐ Homosexual or bisexual contact ☐ Heterosexual contact ☐ IV drug user ☐ Transfusion recipient ☐ Hemophiliac ☐ Other	Indicate whether the patient has a history of any of the listed HIV Risk Groups as defined by the Center for Disease Control (CDC). 2542215
*33	Has this patient at any time in their life had a prior diagnosis of a malignant neoplasm?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient was, at any time in their life, diagnosed with a malignancy prior to the diagnosis of the specimen submitted for HTMCP. 61396 If the answer to this question is "yes", the submitted case is excluded. This exclusion does not apply if the patient only has a history of non-melanoma skin cancer OR in situ carcinoma.
34	Type of Prior Malignancies	_____	If the patient has had a prior diagnosis of a malignant neoplasm, provide the type of prior malignancy. 2718428

#	Data Element	Entry Alternatives	Working Instructions
35	Patient History of Prior Immunological Disease	☐ Rheumatoid Arthritis ☐ Sjogren's Syndrome ☐ Systemic Lupus Erythematous ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Hasimoto's Thyroiditis ☐ Other ☐ Unknown	Indicate whether the patient has a history of any of the listed immunological diseases. 3233628
36	Patient History of Prior Immunosup-pressive Therapy for Immunological Disease	☐ Methotrexate ☐ Cyclo-phosphamide ☐ Azathioprine ☐ Anti-TNF therapy ☐ Other ☐ Unknown	If the patient received immunosuppressive therapy for the immunological disease selected in the previous question, provide the type of immunosuppressive therapy given. 3233638
37	Patient History of Relevant Prior Infectious Disease	☐ Hepatitis B ☐ Hepatitis C ☐ H. Pylori ☐ Other ☐ Unknown	Indicate whether the patient has a history of any of the listed infectious disease. 3233645
38	Patient History of Other Relevant Infectious Disease	_____	If the patient has a history of relevant prior disease that was not included in the list, provide the infectious disease. 3233643

#	Data Element	Entry Alternatives	Working Instructions
*39	Histological Subtype	**Squamous Cell Carcinoma** ☐ Papillary Squamous Cell Carcinoma ☐ Clear Cell Squamous Cell Carcinoma ☐ Small Cell Squamous Cell Carcinoma ☐ Basaloid Squamous Cell Carcinoma ☐ Squamous Cell Carcinoma (NOS) **Adenocarcinoma** ☐ Adenocarcinoma, Mixed Subtype ☐ Acinar Adenocarcinoma ☐ Papillary Adenocarcinoma ☐ Bronchioloalveolar Carcinoma, Mucinous ☐ Bronchioloalveolar Carcinoma, Non-Mucinous ☐ Solid Pattern Predominant Adenocarcinoma ☐ Micropapillary Adenocarcinoma ☐ Fetal Adenocarcinoma ☐ Mucinous Cytadenocarcinoma ☐ Mucinous (Colloid) Adenocarcinoma ☐ Signet Ring Adenocarcinoma ☐ Clear Cell Adenocarcinoma ☐ Adenocarcinoma (NOS)	Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3081934
*40	Organ of Origin	☐ Lung	Using the patient's pathology/ laboratory report, select the organ where the disease originated. 2735776
*41	Laterality	☐ Right ☐ Left ☐ Bilateral	Using the patient's pathology/ laboratory report, select the laterality of the disease. Include all areas of invasion. 827
*42	Anatomic Organ Subdivision *(Check all that apply)*	☐ Upper Lobe ☐ Middle Lobe *(right only)* ☐ Lower Lobe ☐ Bronchus ☐ Mediastinal ☐ Other (please specify)	Using the patient's pathology/laboratory report, select the anatomic organ subdivision(s) of the disease. Include all areas of invasion. 2008006

#	Data Element	Entry Alternatives	Working Instructions
43	Other Anatomic Organ Subdivision	_____	If the anatomic organ subdivision was not included in the provided, indicate the anatomic organ subdivision of the disease. 3407703
*44	Date of Initial Pathologic Diagnosis	__ __/ __ __/ __ __ __ __ month day year	Provide the date the patient was initially diagnosed with the malignancy submitted for HTMCP. This may or may not be the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 2896956 *Note: The day of Initial Pathologic Diagnosis is not required.*
*45	Method of Initial Pathologic Diagnosis	☐ Cytology ☐ Fine Needle Aspiration Biopsy ☐ Incisional Biopsy ☐ Excisional Biopsy ☐ Tumor Resection ☐ Other (please specify) ☐ Unknown	Provide the method of the initial pathologic diagnosis. This is the method used on the date provided above. 2757941
46	Other Method of Initial Pathologic Diagnosis	_____	If the method of initial pathologic diagnosis is not included in the list above, provide the method used. 2757948
47	Date of Surgical Resection	__ __/ __ __/ __ __ __ __ month day year	Provide the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 3008197 (month), 3008195 (day), 3008199 (year)
48	Residual Tumor	☐ RX: Margins not assessed ☐ R0: Negative margins ☐ R1: Microscopic positive margins ☐ R2: Macroscopic positive margins ☐ Unknown	Using the defined categories, indicate the patient's residual tumor margins after their final surgery. 2608702

#	Data Element	Entry Alternatives		Working Instructions
*49	Primary Tumor (pT)	**Clinical** ☐ TX ☐ T0 ☐ T1 ☐ T1a ☐ T1b ☐ T2 ☐ T2a ☐ T2b ☐ T3 ☐ T4	**Pathologic** ☐ TX ☐ T0 ☐ T1 ☐ T1a ☐ T1b ☐ T2 ☐ T2a ☐ T2b ☐ T3 ☐ T4	Using the patient's medical records, select the primary tumor category (T) used to determine the patient's final AJCC stage. 3440328 (clinical), 3045435 (pathologic) Clinical and/or pathologic staging can be selected, but pathologic staging is preferred.
*50	Regional Lymph Nodes (pN)	**Clinical** ☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3	**Pathologic** ☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3	Using the patient's medical records, select the patient's regional lymph node category (N) used to determine the patient's final AJCC stage. 3440330 (clinical), 3203106 (pathologic) Clinical and/or pathologic staging can be selected, but pathologic staging is preferred.
*51	Distant Metastasis (M)	**Clinical** ☐ MX ☐ M0 ☐ M1 ☐ M1a ☐ M1b	**Pathologic** ☐ MX ☐ M0 ☐ M1 ☐ M1a ☐ M1b	Using the patient's medical records, select the patient's distant metastasis category (M) used to determine the patient's final AJCC stage. 3440331 (clinical), 3045439 (pathologic) Clinical and/or pathologic staging can be selected, but pathologic staging is preferred.
*52	Overall Stage	**Clinical** ☐ Stage I ☐ Stage IA ☐ Stage IB ☐ Stage II ☐ Stage IIA ☐ Stage IIB ☐ Stage III ☐ Stage IIIA ☐ Stage IIIB ☐ Stage IV	**Pathologic** ☐ Stage I ☐ Stage IA ☐ Stage IB ☐ Stage II ☐ Stage IIA ☐ Stage IIB ☐ Stage III ☐ Stage IIIA ☐ Stage IIIB ☐ Stage IV	Using the patient's medical records, select the final AJCC stage. 3440332 (clinical), 3203222 (pathologic) Clinical and/or pathologic staging can be selected, but pathologic staging is preferred.

#	Data Element	Entry Alternatives	Working Instructions
*53	AJCC Staging Edition Used to Stage the Patient	☐ 1st Edition (1978-1983) ☐ 2nd Edition (1984-1988) ☐ 3rd Edition (1989-1992) ☐ 4th Edition (1993-1997) ☐ 5th Edition (1998-2002) ☐ 6th Edition (2003-2009) ☐ 7th Edition (2010-present) ☐ Unknown	Please select the AJCCC cancer staging edition used to determine the T, N, M, and stage provided. 2798766

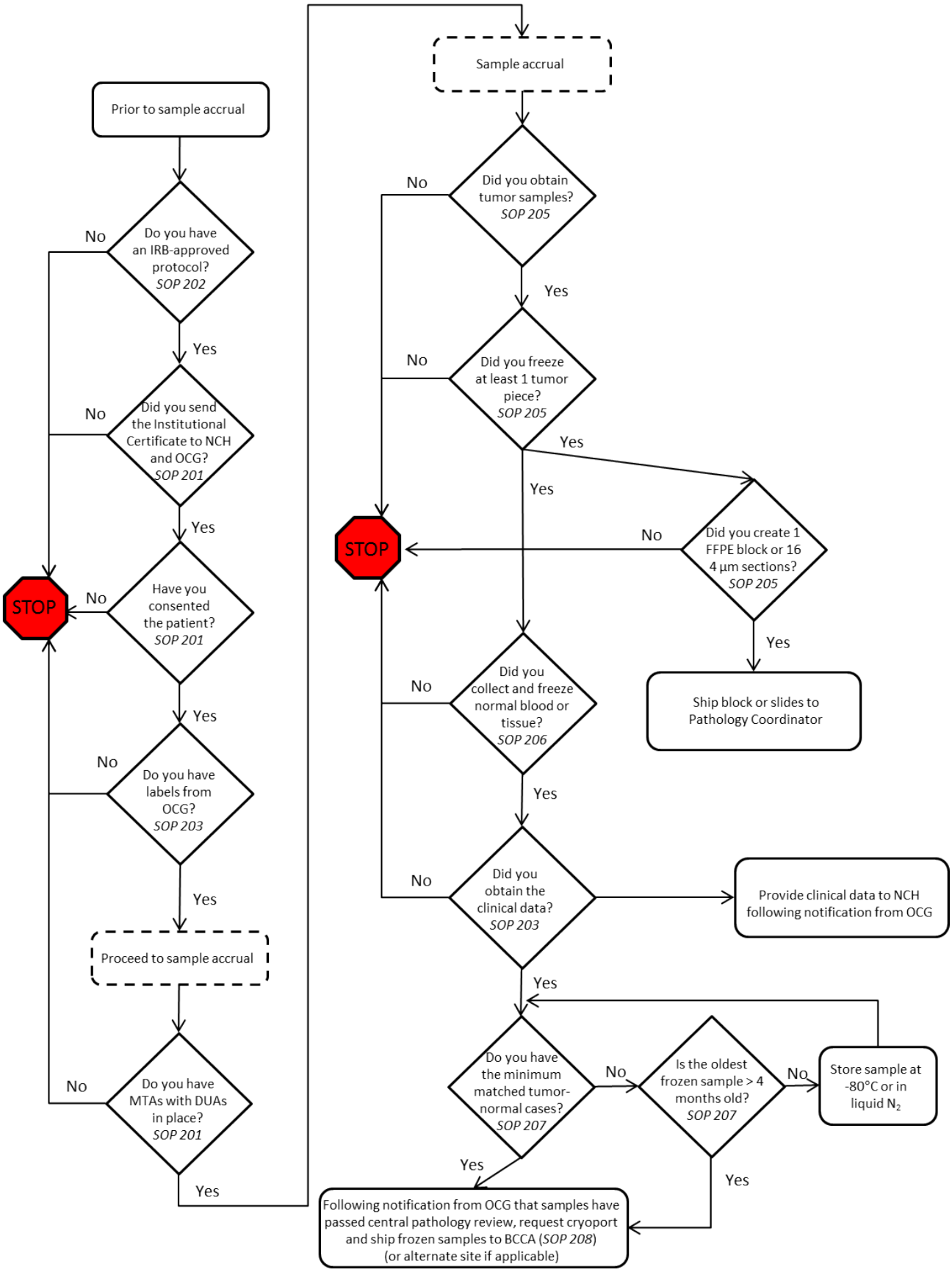
Appendix B: Checklist of Task Completion for Sample Submission

Date:
Institution:
Operator:

- Do you have an IRB-approved protocol?
- Have you sent your Institutional Certification to the Project Team and NCH?
- Have you consented the patient?
- Have you obtained the project-assigned ID and labels from the Project Team?
- Do you have at least one frozen tissue section (≤ 100 mg each) in individual cryovials? Are the cryovials labeled with **only** the freezer-resistant labels from the Project Team?
- Do you have frozen non-tumoral cells? Are they labeled with the freezer-resistant labels from the Project Team?
- Do you have a formalin-fixed paraffin embedded (FFPE) tissue block (or sixteen [16] unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides)? Are they labeled with the freezer-resistant labels from the Project Team?
- Have you sent the FFPE tissue block or unstained sections for central pathology review? Have you received notification from OCG that the samples qualify for study inclusion?
- Have you ordered a cryoport?
- Do you have the clinical data elements required by the project? (Appendix A). Have you received notification from OCG to send the clinical data elements electronically to NCH following molecular QC of the samples?

You may ship samples ONLY once all of the questions above are answered "YES."

Follow the flowchart on the next page for additional guidance.


Prior to sample accrual
Do you have an IRB-approved protocol? SOP 202
No
Yes
Did you send the Institutional Certificate to NCH and OCG? SOP 201
No
Yes
STOP
Have you consented the patient? SOP 201
No
Yes
Do you have labels from OCG? SOP 203
No
Yes
Proceed to sample accrual
Do you have MTAs with DUAs in place? SOP 201
No
Yes
Sample accrual
Did you obtain tumor samples? SOP 205
No
Yes
Did you freeze at least 1 tumor piece? SOP 205
No
Yes
STOP
Did you create 1 FFPE block or 16 4 µm sections? SOP 205
No
Yes
Ship block or slides to Pathology Coordinator
Did you collect and freeze normal blood or tissue? SOP 206
No
Yes
Did you obtain the clinical data? SOP 203
No
Yes
Provide clinical data to NCH following notification from OCG
Do you have the minimum matched tumor-normal cases? SOP 207
No
Yes
Is the oldest frozen sample > 4 months old? SOP 207
No
Yes
Store sample at -80°C or in liquid N_2
Following notification from OCG that samples have passed central pathology review, request cryoport and ship frozen samples to BCCA (SOP 208) (or alternate site if applicable)

Status	Date
Adopted:	9/14/2010
2nd Version:	4/7/2011
3rd Version:	5/25/2012
4th Version:	11/7/2013
Reviewed:	

HTMCP SOP #209B: Centralized Pathology Review Process for HIV+ Lung Tumor Characterization Project

Introduction

Pathological diagnosis of tumors can be impacted by the subjective nature of the process as well as the subjective definition of the criteria used in the assessment. To ensure that samples entering the sequencing pipeline of the HIV+ Tumor Characterization Project (HTMCP) meet the tissue requirements and are diagnosed as Lung Cancer, a Pathology Review Committee (PRC) of three board-certified pathologists is established. The review of tissues by a group minimizes the subjectivity that is unavoidable in pathology reviews and allows an efficient resolution of discrepancies.

Scope and Purpose

1. To establish a standard procedure to follow for the centralized pathology review of tissue submitted to the HIV+ Tumor Characterization Project.

Equipment and Materials

1. A formalin-fixed paraffin-embedded (FFPE) diagnostic block (preferred) OR a minimum of five (5) unstained 4 µm thick sections from the formalin-fixed paraffin-embedded (FFPE) diagnostic block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. These blocks/sections will be provided by the tissue source site (TSS) contributing the case and should be labeled with freezer-resistant labels containing the project-assigned ID (obtained from the Project Team; see HTMCP SOP #203B and 204).
2. Bioimagene or Aperio Slide Scanner

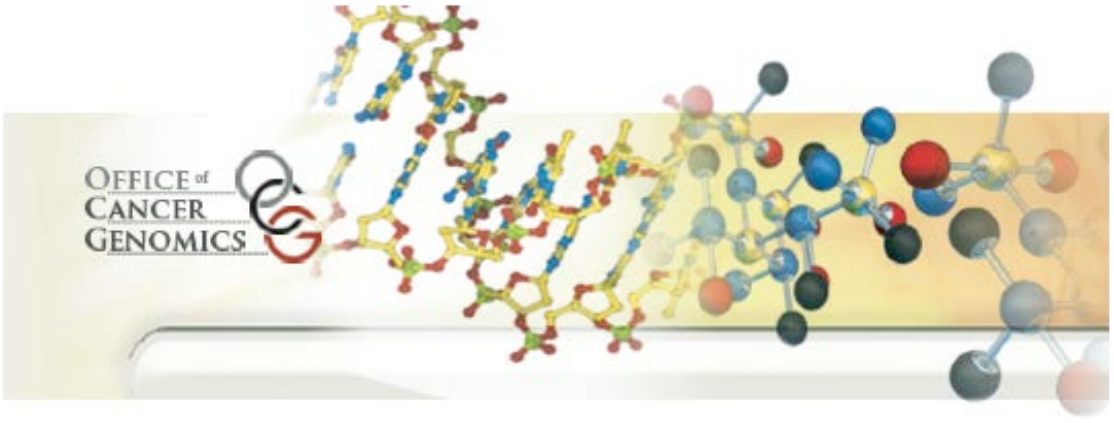
Procedure

A. Preparation for review:
   1. All members of the centralized pathology board obtain their PathXchange credentials by going to the following website: http://www.pathxchange.org/user/register
   2. Once the credentials are secured, they should be communicated to the Office of Cancer Genomics (OCG) Project Team (PT) manager (see HTMCP SOP #200B).
   3. Immediately upon arrival to the Pathology Review Lab (PRL), the Pathology Coordinator will verify that all blocks/slides and reports submitted are labeled with the same project-assigned ID for each case.

4. Pathology coordinator will send the appropriate number of slides to the histology service to perform hematoxylin & eosin (H&E) as well as necessary immunohistochemical (IHC) and *in situ* hybridization protocols. The processing should take no longer than 2 weeks.
   (1) IHC to be performed include: **TTF-1, p63**
   (2) *In situ* hybridization will be performed: **ALK FISH/HPV**.
5. Once all processing is completed, the Pathology Coordinator will:
   (1) scan the H&E and IHC slides on the Bioimagene system
   (2) deposit images of the slides and a blank review form in the PathXchange website (http://www.pathxchange.org) within group HTMCP Lung
6. The Pathology Coordinator will send an e-mail to the members of the pathology review core (PRC) (with copy to the PT manager) informing them that materials for review have been deposited in a folder. This communication must specify the number and name of files, as well as the project-assigned ID(s) for the case(s) under review.
7. This deposition and communication must occur within 48 hours of scanning the slides by the Pathology Coordinator.

B. Review:
1. Within three days of receipt of the e-mail from the Pathology Coordinator, all members of the PRC will return their pathology review form to the Pathology Coordinator via e-mail.
2. The tumors will be classified using the WHO classification.
3. If a consensus is reached and the case passes the specified criteria the pathology coordinator will create a final pathology report and submit it to the Office of Cancer Genomics and the Genome Science Center at British Columbia (GSC-BC) within 4 days. The OCG Project Team manager will complete the Pathology Report form on OpenClinica. Steps 1-3 will take 2 weeks total.
4. Cases for which the tissue is inadequate for diagnosis (*e.g.* tumor nuclei below 70%, degraded tissue) or for which the diagnosis is not lung cancer will be labeled as such and taken out of the study.
5. Cases for which the members of the PRC do not agree on a diagnosis will undergo an additional review by the PRC to reach a consensus. This consensus review will be convened by the Pathology Coordinator. The schedule of such consensus reviews will be dictated by the following:
   - When six or more discordant cases have been accrued, a consensus review panel must be convened.
   - If there are fewer than six discordant cases, but the oldest accrued case is more than three months old, a consensus review panel must be convened.

National Cancer Institute



HIV+ Tumor Molecular Characterization Project (HTMCP) Cervical Tumor-Specific Protocols

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Status	Date
Adopted:	9/14/2010
2nd Version:	11/7/2013
3rd Version:	7/16/2014
4th Version:	
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HTMCP SOP #200C:
HIV+ Tumor Molecular Characterization Project
Cervical Tumor Contact Sheet

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Status	Date
Adopted:	5/25/2012
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3rd Version:	7/16/2014
4th Version:	
Reviewed:	

HTMCP SOP #203C: Prospective Sample Submission Procedure for the HIV+ Cervical Tumor Characterization Project

Introduction

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer-related alterations in HIV+ patients and HIV- patients. The HIV+ Tumor Molecular Characterization Project aims to generate large scale, high-quality data on the cancers' genomes and transcriptomes using 2nd and 3rd generation sequencing technology. The data collected from the cervical cancer characterization subproject will allow scientists to identify genetic alterations common to individuals with cervical cancer and HIV.

Scope and Purpose

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating the nature of the deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) manager by sending an email (see HTMCP SOP #200C) with the details.

Procedures

A. Before patient accrual begins:
   1. Make sure all the documents required for sample shipment as spelled out in HTMCP SOP #100 are in place before you start case accruals.
   2. You may request project-assigned IDs in advance. Contact OCG (see HTMCP SOP #200C) with your TSS-assigned ID to obtain project-assigned IDs (see HTMCP SOP #204) which you must use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.

3. You may request freezer-resistant labels with the project-assigned IDs in advance. Contact the OCG PT manager (see HTMCP SOP #200C) to obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.

B. Before patient surgery:
   1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.
   2. If you have not done so already, contact OCG with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.
   3. If you have not done so already, contact the OCG PT manager and obtain freezer-resistant labels that you will use to mark all containers/slides carrying materials for the project.
   4. Prepare the tissue freezing station and have ready all the materials needed for tissue processing (HTMCP SOP #205).
   5. Inform the research nurse that a 10 mL peripheral blood sample must be obtained from the patient to use as a non-tumoral control (see Appendix A). The buffy coat must be separated from the plasma within two hours of the blood draw from the patient. Store the blood sample in the refrigerator until processing. Time in storage must be reported to the PT manager. The buffy coat sample should be moved immediately to a -80°C or Liquid Nitrogen (LN2) freezer for storage (see HTMCP SOP #206).

C. During patient surgery:
   1. Inform the surgical staff of the tissue requirements for the project (see Appendix A).
   2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   3. Note the time between surgery and freezing in a notebook and send to the PT manager.

D. After surgery:
   1. Process solid tissue as described in the tissue processing protocol (HTMCP SOP #205). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
   2. Process the blood sample according to HTMCP SOP #206. Store isolated cells in a -80°C freezer or liquid nitrogen (LN2) storage until shipment.
   3. Obtain a formalin-fixed, paraffin-embedded tissue block or, if not possible, **five (5)** unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. Affix one of the provided freezer-resistant labels to each slide or block.

E. Preparing samples and shipment:
   1. **Optional**: Section frozen tumor sample following the frozen tissue sectioning protocol. Produce a 4 µm frozen section of the top of the tumor sample for initial quality control as described in the tissue processing protocol (HTMCP SOP #210).
   2. When tissue from at least three cases are accrued, or every quarter (see HTMCP SOP #207) contact the Genome Sciences Center at British Columbia Cancer Agency (GSC-BC)

Coordinator (see HTMCP SOP #200C) to schedule a shipment of a cryoport transport vessel to send the cryovials containing frozen tumor sample sections and frozen blood cells.

3. When the cryoport arrives follow the frozen sample shipment protocol (HTMCP SOP #208) and send the frozen samples to GSC-BC. It is expected that most sites will send tissues within to GSC-BC within 24 hours of receiving the cryoport. The timing of shipment should be discussed prior to tissue collection, especially if exceptions are required. Provide both the GSC-BC and PT with tracking number the day of shipment.
4. Send a formalin-fixed, paraffin-embedded tissue block or, if not possible, **five (5)** unstained 4 µm sections obtained from the formalin fixed blocks mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides, to the Pathology Coordinator (see HTMCP SOP #200C). Upon shipment, provide both the Pathology Coordinator and OCG PT with the tracking number of the parcel. If slides are sent, ship in a box designed to hold slides securely to prevent breakage (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).
5. Collect all the **de-identified** clinical data requested in the sample requirements (Appendix A). You will be requested by the OCG project coordinator to send the data electronically to OCG using the appropriate TSS-assigned ID at a later date.

Notes

- A checklist is provided to help you track all the steps required by this process (Appendix B). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained tissue blocks or slides, and clinical data) is not present, the submission is incomplete, the sample cannot be accepted for HTMCP, and reimbursement of costs cannot proceed.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

Appendix A: Sample Requirements

Tissue Requirements

To be accepted to the project, the following conditions have to be met at the tissue level.

- Tissue must come from a patient who has not received neoadjuvant therapy for the tumor type submitted for HTMCP or systemic treatment for any tumor.
- Paired tumor and normal tissue (blood cells) must be available in sufficient quantities (~100 mg of frozen tumor tissue, plus 10 mL of blood).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in liquid nitrogen, but -80°C or lower is acceptable. The form of tissue storage must be recorded.
- Tumors need to have a minimum percent of tumor nuclei of 70% as assessed by H&E on top and bottom of a tissue section physically adjacent to the specimen used for generating the RNA and DNA.
- There must be enough tissue of both to produce a 4 µm thick section from the top for H&E staining, then 10 sections of 20 µm thickness, followed by another 4 µm section to stain by H&E. **The number of sections needed is based on a block with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required. See HTMCP SOP #210 for the formula allowing calculation of number of sections needed.** A core biopsy obtained at the same time as the one produced for pathology might provide sufficient tissue if it is of high tumor content and low necrosis.
- A formalin-fixed paraffin-embedded block for pathology consensus review (or at least five [5] unstained 4 µm sections mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides) must exist for the tumor.

Clinical Data Requirements

To be accepted to the project, the following conditions must meet at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) listed on the following pages. Should some of the data fields be missing, please contact the OCG PT manager to get approval for submission. **All patient information must be de-identified.**

These clinical data elements must be reported to NCH as an initial report within two weeks of enrolling the patient. At 12 months and 24 months after the patient's enrollment in HTMCP, an update of the status and clinical condition of each patient needs to be submitted to NCH. If the patient dies prior to the first year update, the second year update would only serve to confirm the status.

Patients need to be consented in such a way that allows for the use of their tissues for genomic-scale molecular characterization.

Instructions: *The Enrollment Form should be completed for each qualified case in the HIV+ Tumor Characterization Project (HTMCP) study. The Tissue Source Site (TSS) should complete the form for qualified cases upon qualification notice from the Office of Cancer Genomics (OCG).*

Questions regarding this form should be directed to the Clinical Data Collection Operation & Database (CDCOD) or OCG.

Please note the following definitions for the "Unknown" and "Not Evaluated" answer options on this form.

Unknown: This answer option should only be selected if the TSS does not know this information after all efforts to obtain the data have been exhausted. If this answer option is selected for a question that is part of the HTMCP required data set, the TSS must complete a discrepancy note providing a reason why the answer is unknown.

Not Evaluated: This answer option should only be selected by the TSS if it is known that the information being requested cannot be obtained. This could be because the test in question was never performed on the patient or the TSS knows that the information requested was never disclosed.

Tissue Source Site (TSS): _____TSS Identifier: _____ TSS Unique Patient Identifier: _____

Completed By *(Interviewer Name in OpenClinica)*: _____Completed Date: _____

#	Data Element	Entry Alternatives	Working Instructions
General Information			
*1	Is this a prospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for prospective tissue collection. If the submitted tissue was collected after the date the HTMCP contract was executed, the tissue has been collected prospectively. 3088492
*2	Is this a retrospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for retrospective tissue collection. If the submitted tissue was collected prior to the date the HTMCP contract was executed, the tissue has been collected retrospectively. 3088528
Patient Information			
Demographic Information			
*3	Date of Birth	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the date the patient was born. 2896950 (month), 2896952 (day), 2896954 (year)
*4	Gender	☐ Female ☐ Male	Provide the patient's gender using the provided categories. 2200604
5	Menopause Status *(at time of diagnosis)*	☐ Premenopausal *<6 months since LMP AND no prior bilateral oophorectomy AND not on estrogen replacement* ☐ Perimenopausal *6-12 months since last menstrual period* ☐ Postmenopausal *Prior bilateral oophorectomy OR > 12 months since LMP with no prior ooporectomy* ☐ Indeterminate or Unknown ☐ Not Evaluated	Using the patient's medical records, indicate their menopause satus at the time the patient was diagnosed with the malignancy submitted for HTMCP. 2957270
*6	Race	☐ American Indian or Alaska Native ☐ Asian ☐ White ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ Other (please specify) ☐ Not Evaluated ☐ Unknown	Provide the patient's race using the defined categories. 3009519 American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. Asian: A person having origins in any of the original peoples of the far East, Southeast Asia, or in the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. White: A person having origins in any of the original peoples of the four Europe, the Middle East, or North Africa. Black or African American: A person having origins in any of any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

#	Data Element	Entry Alternatives	Working Instructions
			Native Hawaiian or other Pacific Islander:A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
7	Other Race Only complete if "other" is selected in #6.	_____	If the patient's race was not defined in the previous question, provide the patient's race. 2192205
8	Ethnicity	☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Not Evaluated ☐ Unknown	Provide the patient's ethnicity using the defined categories. 2192217 Not Hispanic or Latino: A person not meeting the definition of Hispanic or Latino. Hispanic or Latino: A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. Not Evaluated: Not provided or available Unknown: Could not be determined or unsure
9	Height *(at time of diagnosis)*	_____(cm)	Provide the patient's height (centimeters) at the time the patient was diagnosed with the tumor submitted for HTMCP. 649
10	Weight *(at time of diagnosis)*	_____(kg)	Provide the patient's weight (kilograms) at the time the patient was diagnosed with the tumor submitted for HTMCP. 651
History of Pregnancies and Contraceptive Use			
11	Hormonal Contraceptive Use	☐ Current User ☐ Never Used ☐ Former User ☐ Unknown	Indicate whether the patient has used or is currently using hormonal contraceptives. 3104217
12	Total Number of Pregnancies	_____	Provide the total number of times the patient conceived and became pregnant. This should include all of the pregnancies under the question "Number of Pregnancies by Outcome Type" and current pregnancies. 2005341
13	Number of Pregnancies by Outcome Type *(Complete all that apply)*	**Pregnancy Type** / **Number of Pregnancies**	
		Live Birth *(single or multiple births)* _____	Provide the number of times the patient had successful pregnancies that resulted in the live birth of at least one child. 2005342
		Miscarriage _____	Provide the number of times the patient conceived and became pregnant, but did not carry fetus to term due to natural occurrences or problems during the pregnancy. 2180637
		Induced Abortion _____	Provide the number of times the patient conceived and became pregnant, but did not carry fetus to term due to medical intervention to end the pregnancy. 2180648
		Ectopic Pregnancy _____	Provide the number of times the patient conceived and become pregnant, but did not carry the fetus to term due to an ectopic pregnancy. 2261915
		Stillbirth *(early fetal death)* _____	Indicate the number of times the patient conceived and become pregnant, but the pregnancy ended with stillbirth. 2183304
		Unknown _____	Provide the number of times the patient was known to be pregnant, but the outcome of the pregnancy was unknown.
14	Pregnant at Time of Diagnosis	☐ Yes ☐ No	Indicate whether the patient was pregnant at the time of initial diagnosis. 3012573
Survival Information			
*15	Vital Status *(at date of last contact)*	☐ Living ☐ Deceased	Indicate whether the patient was living or deceased at the date of last contact.

#	Data Element	Entry Alternatives	Working Instructions
			5
*16	Date of Last Contact	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient is living, provide the date of last contact with the patient (as reported by the patient, medical provider, family member, or caregiver). 2897020 (month), 2897022 (day), 2897024 (year) *Do not answer if patient is deceased.*
*17	Date of Last Known Alive	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Indicate the last date the patient was known to be alive, regardless of whether the patient, medical provider, family member or caregiver was contacted. 2975722 (month), 2975724 (day), 2975726 (year)
*18	Date of Death	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient is deceased, provide the month of death. 2897026, (month) 2897028 (day), 2897030 (year)
19	Cause of Death	☐ Cervical Cancer ☐ Unknown ☐ Other (please specify)	Indicate the patient's cause of death. 2554674
20	Other Cause of Death Only complete if "other" is selected in #6.	_____	If the patient's cause of death was not included in the provided list, specify the patient's cause of death. 2004150
Patient Status (Regarding Submitted Tumor)			
*21	Did the patient receive neo-adjuvant therapy for the tumor submitted for HTMCP?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient received treatment (radiation, pharmaceutical, or both) prior to the procurement o the sample submitted for TCGA. 3382737 *If the answer to this question is "yes", the submitted case is excluded.*
*22	Tumor Status *(at time of last contact)*	☐ Tumor free ☐ With tumor ☐ Unknown	Indicate whether the patient was tumor/disease free (i.e. free of the malignancy that yielded the sample submitted for the HTMCP study) at the date of last contact or death. 2759550
23	Performance Status: Eastern Cooperative Oncology Group	☐ 0: Asymptomatic ☐ 1: Symptomatic, but fully ambulatory ☐ 2: Symptomatic, in bed less than 50% of day ☐ 3: Symptomatic, in bed more than 50% of day, but no bed-ridden ☐ 4: Bed-ridden ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time of diagnosis. 2003853
24	Performance Status: Eastern Cooperative Oncology Group	☐ 100: Normal, no complaints, no evidence of disease ☐ 90: Able to carry on normal activity; minor signs or symptoms of disease ☐ 80: Normal activity with effort; some signs or symptoms of disease ☐ 70: Cares for self, unable to carry on normal activity or to do active work ☐ 60: Requires occasional assistance ☐ 50: Requires considerable assistance and frequent medical care ☐ 40: Disabled, requires special care and assistance ☐ 30: Severely disabled, hospitalization indicated. Death not imminent ☐ 20: Very sick, hospitalization ☐ 10: Moribund, fatal processes progressing rapidly ☐ 0: Dead ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time of diagnosis. 88
25	Performance Status Score: Timing	☐ Preoperative ☐ Pre-adjuvant Therapy ☐ Post-adjuvant Therapy	Inidcate the timeing of the performance status(es) provided in the previous question(s). 2792763

#	Data Element	Entry Alternatives	Working Instructions
		☐ Unknown	
26	Tumor Response	☐ Progressive Disease ☐ Stable Disease ☐ Partial Response ☐ Complete Response	Indicate the patient's measure of success after their primary treatment including surgery and adjuvant therapies. 2786727
27	Adjuvant (Post-Operative) Radiation Therapy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had adjuvant/ post-operative radiation therapy *for the tumor submitted for HTMCP.* 2005312
28	Adjuvant (Post-Operative) Pharmaceutical Therapy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had adjuvant/ post-operative pharmaceutical therapy *for the tumor submitted for HTMCP*. 3397567
Smoking History			
29	Tobacco Smoking History Indicator *(at time of diagnosis)*	☐ 1: Lifelong Non-Smoker ☐ 2: Current Smoker ☐ 3: Current Reformed Smoker for > 15 years ☐ 4: Current Reformed Smoker for <= 15 years ☐ 5: Current Reformed Smoker (duration not specified) ☐ Smoking Status not Documented	Indicate the patient's history of tobacco smoking as well as their current smoking status using the defined categories. If the patient is a lifelong non-smoker, skip the additional smoking questions. 2181650
30	Age of Onset Tobacco History Indicator	____ ____ years	Provide the age in years when the patient began smoking cigarettes. 2178045
31	Year of Quiting Tobacco Smoking	____ ____ ____ ____ (YYYY)	Provide the year the patient quit smoking, if applicable. 2228610
32	Number of Pack Years Smoked *(at time of diagnosis)*	____ ____ ____ ____ pack years	Provide the number of pack years thepatient smoked. This is calculated using the number of cigarettes smoked per day times the number f years smoked, divided by 20. For example, if the patient smoked 5 cigarettes per day times 10 years divided by 20, the patient would have 2.5 pack years (e.g. 5x10/20=2.5). 2955385
Patient History of Disease			
HIV Status			
*33	Is this patient HIV positive?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient is HIV positive. 2180464
*34	Date of HIV Diagnosis (if known)	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the month the patient was diagnosed with HIV. 3579640 (month), 3579644 (day), 3579643 (year)
35	Nadir CD4 Counts	_____ (cells/mm^3)	Provide the patient's Nadir CD4 counts, which are the lowest CD4 counts the patient has had. 2684395
*36	CD4 Counts at Diagnosis of the Submitted Malignancy	_____ (cells/mm^3)	Provide the patient's CD4 Counts at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922654
*37	HIV RNA load at Diagnosis of Submitted Malignancy	_____	Provide the HIV RNA load (also known as the "viral load") at the time the patient was diagnosed with the malignancy submitted for the HTMCP study. 2922674

#	Data Element	Entry Alternatives	Working Instructions
38	Prior AIDS Defining Conditions	☐ Candidiasis of bronchi, trachea or lungs ☐ Candidiasis, esophageal ☐ CMV other than liver, spleen or nodes, onset at age >1month ☐ CMV retinitis ☐ Coccidioidomycosis, disseminated or extrapulmonary ☐ Cryptococcosis, extrapulmonary ☐ Cryptosporidiosis, chronic intestinal ☐ Encephalopathy, HIV-related ☐ Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis or esophagitis (onset at age > 1 month) ☐ Histoplasmosis, disseminated or extrapulmonary ☐ Isosporiasis, chronic intestinal (> 1 mon) ☐ Mycobacterium avium complex or Mycobacterium kansasii disseminated or extrapulmonary ☐ Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary ☐ Mycobacterium, other species or unidentified species, disseminated or extrapulmonary ☐ Nocardiosis ☐ Pneumocystis jirovecii pneumonia ☐ Pneumonia, recurrent ☐ Progressive multifocal leukoencephalopathy ☐ Salmonella septicemia, recurrent ☐ Toxoplasmosis of the brain, onset at age >1month ☐ Wasting syndrome, due to HIV	Prior to the malignancy submitted for the HTMCP study, provide any AIDS defining conditions. 2679581
39	Co-Infections *(serology data/viral load if available)*	**Test** **Results**	Using the list provided, indicate whether the patient had any co-infections by providing the results of each of the tests listed.
		☐HBV	2180456
		☐HCV	2695021
		☐HPV	2230033
		☐KSHV/HHV8	3335773
*40	HAART Treatment Prior to Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment prior to the diagnosis of the malignancy submitted for the HTMCP study. 3335156
*41	HAART Treatment at Time of Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment at the time of the diagnosis of the malignancy submitted for the HTMCP study. 2922679
42	CDC HIV Risk Group(s)	☐ Homosexual or bisexual contact ☐ Heterosexual contact ☐ IV drug user ☐ Transfusion recipient ☐ Hemophiliac ☐ Other	Indicate whether the patient has a history of any of the listed HIV Risk Groups as defined by the Center for Disease Control (CDC). 2542215
Prior Malignancies			

#	Data Element	Entry Alternatives	Working Instructions
43	Has this patient at any time in their life had a prior diagnosis of a malignant neoplasm?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient was, at any time in their life, diagnosed with a malignancy prior to the diagnosis of the specimen submitted for HTMCP. 61396 *If the answer to this question is "yes", the submitted case is excluded. This exclusion does not apply if the patient only has a history of non-melanoma skin cancer OR in situ carcinoma.*
44	Type of Prior Malignancies Only complete if "yes" is selected in #41.	_____	If the patient has had a prior diagnosis of a malignant neoplasm, provide the type of prior malignancy. 2718428
Prior Immunological Disease			
45	Patient History of Prior Immunological Disease	☐ Rheumatoid Arthritis ☐ Sjogren's Syndrome ☐ Systemic Lupus Erythematous ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Hasimoto's Thyroiditis ☐ Other ☐ Unknown	Indicate whether the patient has a history of any of the listed immunological diseases. 3233628
46	Other History of Prior Immunological Disease Only complete if "other" is selected in #42.	_____	If the patient has a history of immuniological disease and the disease is not listed in the previous question, provide the name of the disease(s). 3233629
47	Patient History of Prior Immunosuppressive Therapy for Immunological Disease	☐ Methotrexate ☐ Cyclophosphamide ☐ Azathioprine ☐ Anti-TNF therapy ☐ Other ☐ Unknown	If the patient received immunosuppressive therapy for the immunological disease selected in the previous question, provide the type of immunosuppressive therapy given. 3233638
48	Other History of Prior Immunosuppresive Therapy for Immunological Disease Only complete if "other" is selected in #43.	_____	If the patient has a history of immunosuppressive therapy for immunological disease and the disease is not listed in the previous question, provide the name of the disease(s). 2873928
Prior Infectious Disease			
49	Patient History of Relevant Prior Infectious Disease	☐ Hepatitis B ☐ Hepatitis C ☐ H. Pylori ☐ Malaria ☐ Other ☐ Unknown	Indicate whether the patient has a history of any of the listed infectious disease. 3233642
50	Patient History of Other Relevant Infectious Disease Only complete if "other" is selected in #44.	_____	If the patient has a history of relevant prior disease that was not includeded in the list, provide the infectious disease. 3233643
Pathologic Information			
*51	Histological Subtype	☐ Cervical Squamous Cell Carcinoma ☐ Endocervical type of Adenocarcinoma ☐ Endocervical Adenocarcinoma of the Usual Type ☐ Mucin-depleted Adenocarcinoma ☐ Endometrioid Adenocarcinoma of Endocervix	Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3081934
52	Keratinization in Squamous Cell Carcinoma	☐ Keratinizing squamous cell carcinoma ☐ Non-keratinizing squamous cell carcinoma	If the patient had squamous cell carcinoma, indicate whether the tumor has any keratinizing squamous cell carcinoma using the patient's pathology/laboratory report. Keratinizing tumors have at least one well-formed keratin pearl. All other patters are non-keratinizing. 3151599
*53	Primary Site of Disease	☐ Cervix	Using the patient's pathology/laboratory report, select the organ where the disease originated. 2735776
54	Tumor Grade	☐ G1 Well Differentiated	Using the patient's pathology/laboratory report, select the tumor grade.

#	Data Element	Entry Alternatives	Working Instructions
		☐ G2 Moderately Differentiated ☐ G3 Poorly Differentiated ☐ G4 Undifferentiated ☐ GX Grade cannot be assessed	2785839
Pathologic Diagnosis and Surgical Resection			
*55	Date of Initial Pathologic Diagnosis	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the date the patient was initially diagnosed with the malignancy submitted for HTMCP. This may or may not be the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 2896956
*56	Method of Initial Pathologic Diagnosis	☐ Cytology ☐ Biopsy (cervical, CT-guided or other) ☐ Cone Biopsy / LEEP ☐ Lymph Node Sampling or Dissection ☐ Other (please specify) ☐ Unknown	Provide the method of the initial pathologic diagnosis. This is the method used on the date provided above. 2757941
57	Other Method of Initial Pathologic Diagnosis Only complete if "other" is selected in #50.	_____	If the method of initial pathologic diagnosis is not included in the list above, provide the method used. 2757948
58	Date of Surgical Resection	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the date of the surgical resection that yielded the tumor sample submitted for HTMCP. 3008197 (month), 3008195 (day), 3008199 (year)
59	If hysterectomy was performed, what type was it?	☐ Hysterectomy not performed ☐ Simple ☐ Radical (modified or not modified) ☐ Other, specify	Indicate whether a hysterectomy was performed at diagnosis. If a hysterectomy was performed, indicate the type. 2647164
60	Other Type of Hysterectomy Only complete if "other" is selected in #52.	_____	If the type of hysterectomy performed was not included in the list provided, please provide the type of hysterectomy performed. 3151506
61	If hysterectomy was performed, were there involved pathologic margins?	☐ Macroscopic parametrial involvement ☐ Microscopic parametrial involvement ☐ Positive bladder margin ☐ Positive vaginal margin ☐ Unknown ☐ Other, specify	If a hysterectomy was performed, provide the patient's margin involvement after surgery. 3151541
62	Other Involved Pathologic Margins Only complete if "other" is selected in #55.	_____	If the margin involvement was not included in the provided list, describe the pathologic margins. 3151544
63	Pelvic Extension Comment	_____	Using the patient's pathology/laboratory report, provide comments regarding any tumor extension to the pelvic wall. 3151605
64	Pathologic Lymphovascular Invasion	☐ Present ☐ Absent ☐ Unknown	Using the patient's pathology/laboratory report, indicate the presence or absents of pathologic lymphovascular invasion. 2008052
65	Corpus Involvement	☐ Present ☐ Absent ☐ Unknown	The corpus uteri is the part of the uterus above the isthmus, comprising about two thirds of the non-pregnant organ. To have a connection by participation or association or use; sharing in an activity or process. 3151610
Lymph Node Status			
66	Were Lymph Nodes Examined at the Time of Primary Resection?	☐ Yes ☐ No ☐ Unknown	Indicate whether any lymph nodes were examined at the time of the primary resection. 2200396
67	Number of Lymph Nodes Examined	_____	Provide the number of lymph nodes examined, if one or more lymph nodes were removed. 3
68	Number of Lymph Nodes Positive by H&E	_____	Provide the number of lymph nodes positive through hematoxylin and eosin (H&E) staining and light microscopy. 3086388

#	Data Element	Entry Alternatives	Working Instructions
	light microscopy		
69	Number of Lymph Nodes Positive by IHC Keratin Staining only	_____	Provide the number of lymph nodes positive through keratin immunohistochemistry (IHC) staining. 3086383
70	Pathologic Positive Lymph Node Location(s) *(Check all that apply)*	☐ Pelvic (external iliac, internal iliac, obturator) ☐ Common iliac ☐ Paraaortic ☐ Supraclavicular ☐ Unknown ☐ Other, specify	Using the patient's pathology/laboratory report, provide the location(s) of any positive lymph nodes. 3151519
71	Other Positive Lymph Node	_____	If the location of positive lymph nodes was not included in the list provide, please provide the location of positive lymph nodes. 3151522
AJCC and FIGO Staging			
*72	AJCC Primary Tumor (T)	**Clinical** ☐ TX ☐ T2 ☐ T0 ☐ T2a ☐ Tis ☐ T2a1 ☐ T1 ☐ T2a2 ☐ T1a ☐ T2b ☐ T1a1 ☐ T3 ☐ T1a2 ☐ T3a ☐ T1b ☐ T3b ☐ T1b1 ☐ T4 ☐ T1b2 **Pathologic** ☐ TX ☐ T2 ☐ T0 ☐ T2a ☐ Tis ☐ T2a1 ☐ T1 ☐ T2a2 ☐ T1a ☐ T2b ☐ T1a1 ☐ T3 ☐ T1a2 ☐ T3a ☐ T1b ☐ T3b ☐ T1b1 ☐ T4 ☐ T1b2	Using the patient's medical records, select the primary tumor category (T) used to determine the patient's final AJCC stage. 3440328 (clinical), 3045435 (pathologic)
*73	AJCC Regional Lymph Nodes (N)	**Clinical** ☐ NX ☐ N0 ☐ N1 **Pathologic** ☐ NX ☐ N0 ☐ N1	Using the patient's medical records, select the patient's regional lymph node category (N) used to determine the patient's final AJCC stage. 3440330 (clinical), 3203106 (pathologic)
*74	AJCC Distant Metastasis (M)	**Clinical** ☐ MX ☐ M0 ☐ M1 **Pathologic** ☐ MX ☐ M0 ☐ M1	Using the patient's medical records, select the patient's distant metastasis category (M) used to determine the patient's final AJCC stage. 3440331 (clinical), 3045439 (pathologic)
*75	AJCC Staging Edition Used to Determine the T, N, and M values	☐ 1st Edition (1978-1983) ☐ 2nd Edition (1984-1988) ☐ 3rd Edition (1989-1992) ☐ 4th Edition (1993-1997) ☐ 5th Edition (1998-2002) ☐ 6th Edition (2003-2009) ☐ 7th Edition (2010-present) ☐ Unknown	Please selected the AJCCC cancer staging edition used to determine the T, N, M, and stage provided. 2798766
*76	FIGO Stage	☐ Stage I ☐ Stage IA ☐ Stage IA1 ☐ Stage IA2 ☐ Stage IB ☐ Stage IB1 ☐ Stage IB2 ☐ Stage II ☐ Stage IIA ☐ Stage IIA1 ☐ Stage IIA2 ☐ Stage IIB ☐ Stage III ☐ Stage IIIA ☐ Stage IIIB ☐ Stage IV ☐ Stage IVA ☐ Stage IVB	Using the patient's pathology/laboratory report, provide the FIGO stage given to the patient at the time of diagnosis. 3225684
*77	FIGO Staging System *(Publication Date Used for Staging)*	☐ 1988 ☐ 1995 ☐ 2009	Using the patient's pathology/laboratory report, provide the FIGO staging system used to stage the patient. 3114049

#	Data Element	Entry Alternatives	Working Instructions
Tests Performed			
FED-PET or PET/CT			
78	Date of FED-PET or PET/CT	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient's medical records indicate the patient had a FED-PT or PET/CT, provide the date of the procedure. 3151498 (month), 3151499 (day), 3151500 (year)
79	Cervix Standardized Update Value (SUV)	_____	If the patient's medical records indicate the patient had a FED-PT or PET/CT, provide the patient's cervix SUV. 3151615
80	FED-PET or PET/CT Results *Check all that apply*	**Test** / **Outcome**: *Present* / *Absent* / *Unknown* Pelvic Nodes Paraortic Nodes Supraclavicular Nodes Parametrium Bladder Extra-Pelvic Met Disease	If the patient's medical records indicate the patient had a FED-PT or PET/CT, provide the results for each applicable anatomic site. 3151497
Magnetic Resonance Imaging (MRI)			
81	Date of MRI	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient's medical records indicate the patient had an MRI, provide the date of the MRI. 3151491 (month), 3151492 (day), 3151493 (year)
82	MRI Results *Check all that apply*	**Test** / **Outcome**: *Present* / *Absent* / *Unknown* Pelvic Nodes Paraortic Nodes Supraclavicular Nodes Parametrium Bladder Extra-Pelvic Met Disease	If the patient's medical records indicate the patient had an MRI, provide the results for each applicable anatomic site. 3151441
X-ray Computed Tomography (CT Scan)			
83	Date of CT Scan	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient's medical records indicate the patient had a CT scan, provide the date of the CT scan. 3151134 (month), 3151132 (day), 3151133 (year)
84	CT Scan Results *Check all that apply*	**Test** / **Outcome**: *Present* / *Absent* / *Unknown* Pelvic Nodes Paraortic Nodes Supraclavicular Nodes Parametrium Bladder Extra-Pelvic Met Disease	If the patient's medical records indicate the patient had an CT scan, provide the results for each applicable anatomic site. 2932340
Tumor Marker Analysis			
85	HPV Positive Type *Check all that apply*	☐ HPV 16 ☐ HPV 18 ☐ Other HPV Type (please specify) ☐ None	If the patient's medical records indicate a positive diagnosis of the human papillomavirus (HPV), provide the HPV type found to be positive for this patient. 2922649
86	Other HPV Type Only complete if "other" is selected in #71.	_____	If the patient's medical records indicate a positive diagnosis of the human papillomavirus (HPV) and the type is not included in the provided list, describe the HPV type found to be positive for this patient. 3166168
87	Method of HPV Typing	☐ PCR ☐ Qiagen – digene #2 ☐ Roche – linear array ☐ Other (please specify)	Indicate the method used for HPV typing. 3151457
88	Other Method of HPV Typing Only complete if "other" is	_____	If the method used for HPV typing is not included in the provided list, describe the HPV typing method used. 3151460

#	Data Element	Entry Alternatives	Working Instructions
	selected in #73.		
89	PCR Primer Pairs	☐ MY09/MY11 ☐ PGMY09/PGMY11 ☐ Roche – linear array ☐ SPF10-LiPA ☐ GP5+/GP6+ ☐ Other (please specify)	Indicate the PCR primar pairs used. 3151487
90	Other PCR Primer Pairs Only complete if "other" is selected in #75.	_____	If the method used for PCR primer pairs used are not included in the provided list, describe the PCR primer pairs used. 3151490
91	Squamous Cellular Carcinoma Antigen (SCCA) Tumor Marker	_____	Provide the patient's squamous cellular carcinoma antigen (SCCA) tumor marker results. 3151234
92	Date of SCCA Performed	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	Provide the date SCCA was performed. 3151235(month), 3151236 (day), 3151237 (year)
93	Is this Patient Lost to Follow-up?	☐ Yes ☐ No	Indicate whether the patient is lost to follow-up, as defined by the ACoS Commission on Cancer. This only includes cases where updated follow-up information has not been collected within the past 15 months and all efforts to contact the patient have been exhausted (this includes reviewing the Social Security death index). If the patient is lost to follow-up, the remaining questions can be left unanswered. 61333 *If the patient is **deceased** and a HTMCP follow-up form has not yet been completed, the answer to this question should be "no," and the remaining applicable questions should be completed.*
New Tumor Event Information *Complete this section if the patient had a new tumor event. If the patient did not have a new tumor event (or if the TSS does not know) indicate this in the question below, and the remainder of this section can be skipped.* Note: The New Tumor Event section on OpenClinica can be completed multiple times, if the patient had multiple New Tumor Events.			
*94	New Tumor Event After Initial Treatment?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had a new tumor event (e.g. metastatic, recurrent, or new primary tumor) after the date of initial diagnosis. 3121376
95	Type of New Tumor Event	☐ Locoregional/Recurrence ☐ Distant Metastasis ☐ New Primary Tumor	Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis or a new primary tumor. 3119721
96	Site of New Tumor Event	☐ Anus ☐ Cervix ☐ Head & Neck ☐ Lung ☐ Vulvar ☐ Other (please specify)	Indicate the site of this new tumor event. 3108271
	Other Site of New Tumor Event	_____	If the patient had a new tumor event and the site of this tumor was not included in the provided list, describe the site. 3128033
*97	Date of New Tumor Event	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient had a new tumor event, provide the date of diagnosis for this new tumor event. 3104044 (month), 3104042 (day), 3104046 (year)
98	Method of Pathologic Diagnosis of New Tumor Event	☐ Cytology ☐ Tumor Resection ☐ Other (please specify)	If the patient has had progression of disease, indicate whether the site of first progression was biopsied. 2716366
99	Other Method of Pathologic Diagnosis for New Tumor Event	_____	If the pathologic method used to diagnose the new tumor event is not included in the provided list, specify the method used. 3151116
100	Additional Surgery for New Tumor Event	☐ Yes ☐ No ☐ Unknown	Using the patient's medical records, indicate whether the patient had surgery for the new tumor event in question. 3427611

#	Data Element	Entry Alternatives	Working Instructions
101	Date of Additional Surgery for New Tumor Event	____ ____ / ____ ____ / ____ ____ ____ (month) (day) (year)	If the patient had surgery for the new tumor event, provide the date this surgery was performed. 3427612 (month), 3427613 (day), 3427614 (year)
102	Residual Tumor *After surgery for New Tumor Event*	☐ RX: The presence of residual tumor or margin status cannot be assessed. ☐ R0: No residual tumor and negative microscopic margins in resected specimen. ☐ R1: Microscopic residual tumor. No gross residual disease but positive microscopic margins. ☐ R2: Macroscopic residual tumor. Grossly visible residual disease.	Using the patient's pathology/laboratory report, select the residual tumor status after the surgical resection for the new tumor event. 3104061
103	Additional treatment for New Tumor Event: *Radiation Therapy*	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received radiation treatment for this new tumor event. 3427615
104	Additional treatment for New Tumor Event: *Pharmaceutical Therapy*	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient received pharmaceutical treatment for this new tumor event. 3427616
*105	Is this Patient Lost to Follow-up?	☐ Yes ☐ No	Indicate whether the patient is lost to follow-up, as defined by the ACoS Commission on Cancer. This only includes cases where updated follow-up information has not been collected within the past 15 months and all efforts to contact the patient have been exhausted (this includes reviewing the Social Security death index). If the patient is lost to follow-up, the remaining questions can be left unanswered. 61333 *If the patient is **deceased** and a HTMCP follow-up form has not yet been completed, the answer to this question should be "no," and the remaining applicable questions should be completed.*
	General Comments		

Principal Investigator (*Printed Name*)

Principal Investigator (*Signature*) Date

I acknowledge that the above information provided by my institution is true and correct and has been quality controlled.

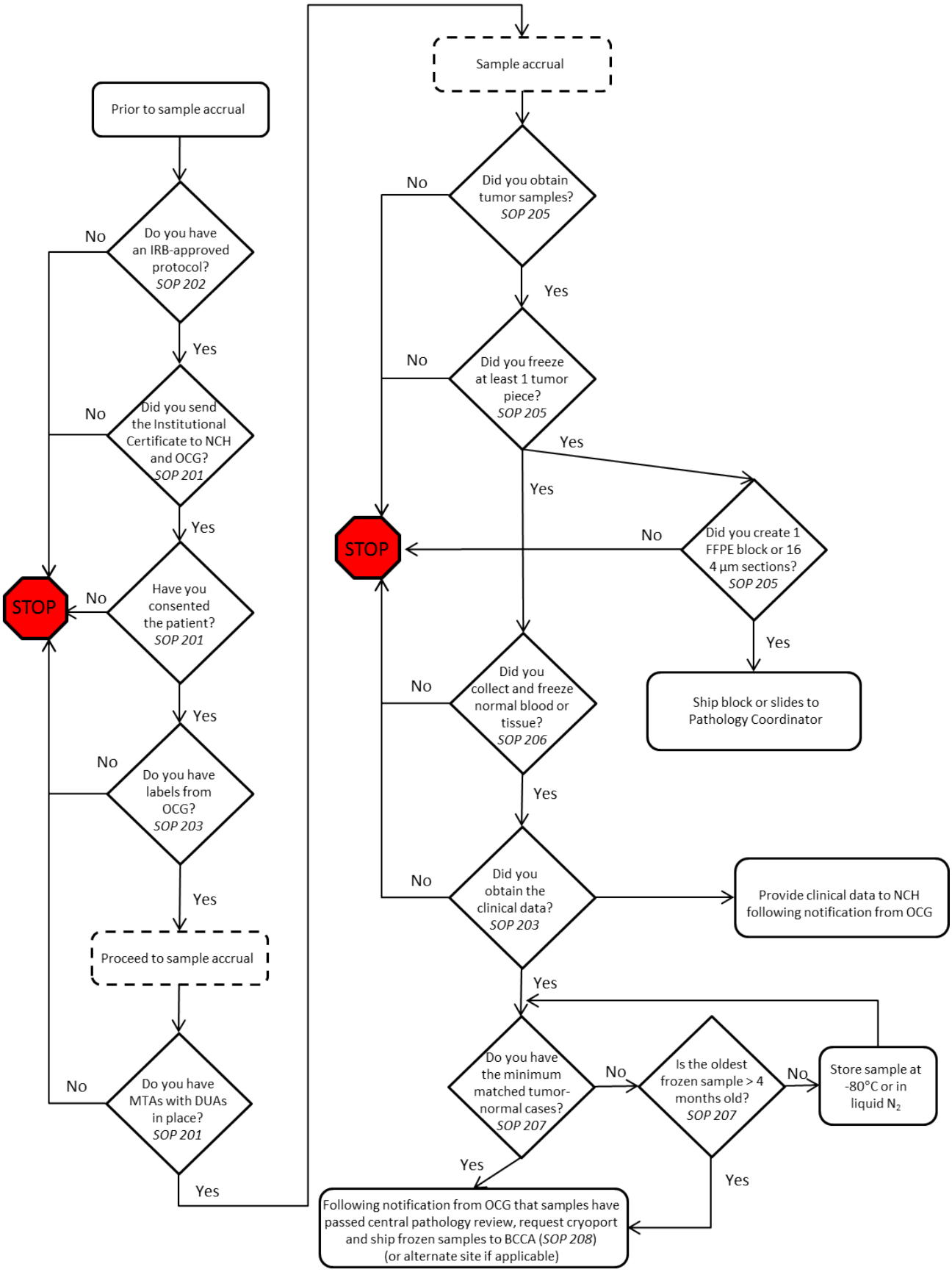
Appendix B: Checklist of Task Completion for Sample Submission

Date:
Institution:
Operator:

- Do you have an IRB-approved protocol?
- Have you sent your Institutional Certification to the Project Team and NCH?
- Have you consented the patient?
- Have you obtained the project-assigned ID and labels from the Project Team?
- Do you have at least one frozen tissue section (≤ 100 mg each) in individual cryovials? Are the cryovials labeled with **only** the freezer-resistant labels from the Project Team?
- Do you have frozen non-tumoral cells? Are they labeled with the freezer-resistant labels from the Project Team?
- Do you have a formalin-fixed paraffin embedded (FFPE) tissue block (or sixteen [16] unstained 4 µm sections from the formalin-fixed block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides)? Are they labeled with the freezer-resistant labels from the Project Team?
- Have you sent the FFPE tissue block or unstained sections for central pathology review? Have you received notification from OCG that the samples qualify for study inclusion?
- Have you ordered a cryoport?
- Do you have the clinical data elements required by the project? (Appendix A). Have you received notification from OCG to send the clinical data elements electronically to NCH following molecular QC of the samples?

You may ship samples ONLY once all of the questions above are answered "YES."

Follow the flowchart on the next page for additional guidance.


Prior to sample accrual
Do you have an IRB-approved protocol? SOP 202
No
Yes
Did you send the Institutional Certificate to NCH and OCG? SOP 201
No
Yes
STOP
Have you consented the patient? SOP 201
No
Yes
Do you have labels from OCG? SOP 203
No
Yes
Proceed to sample accrual
Do you have MTAs with DUAs in place? SOP 201
No
Yes
Sample accrual
Did you obtain tumor samples? SOP 205
No
Yes
Did you freeze at least 1 tumor piece? SOP 205
No
Yes
STOP
Did you create 1 FFPE block or 16 4 µm sections? SOP 205
No
Yes
Ship block or slides to Pathology Coordinator
Did you collect and freeze normal blood or tissue? SOP 206
No
Yes
Did you obtain the clinical data? SOP 203
No
Yes
Provide clinical data to NCH following notification from OCG
Do you have the minimum matched tumor-normal cases? SOP 207
No
Is the oldest frozen sample > 4 months old? SOP 207
No
Store sample at -80°C or in liquid N_2
Yes
Yes
Following notification from OCG that samples have passed central pathology review, request cryoport and ship frozen samples to BCCA (SOP 208) (or alternate site if applicable)

Status	Date
Adopted:	5/25/2012
2nd Version:	11/7/2013
3rd Version:	7/16/2014
4th Version:	
Reviewed:	

HTMCP SOP #209C: Centralized Pathology Review Process for HIV+ Cervical Tumor Characterization Project

Introduction

Pathological diagnosis of tumors can be impacted by the subjective nature of the process as well as the subjective definition of the criteria used in the assessment. To assure that samples meet the tissue requirements for the HIV+ Tumor Molecular Characterization Project (HTMCP) and are diagnosed as Cervical Cancer, a Pathology Review Committee (PRC) of three board-certified pathologists is established. The review of tissues by a group minimizes the subjectivity that is unavoidable in pathology reviews and allows an efficient resolution of discrepancies.

Scope and Purpose

1. To establish a standard procedure to follow for the centralized pathology review of tissue submitted to the HIV+ Tumor Characterization Project.

Equipment and Materials

1. A formalin-fixed paraffin-embedded (FFPE) diagnostic block (preferred) OR a minimum of five (5) unstained 4 µm thick sections from the formalin-fixed paraffin-embedded (FFPE) diagnostic block mounted on adhesive (*e.g.* poly-L-lysine or APTS) coated glass slides. These blocks/sections will be provided by the tissue source site (TSS) contributing the case and should be labeled with freezer-resistant labels containing the project-assigned ID (obtained from the Project Team; see HTMCP SOP #203C and 204).
2. Bioimagene or Aperio Slide Scanner

Procedure

A. Preparation for review:
   1. All members of a centralized pathology board obtain their PathXchange credentials by going to the following website: http://www.pathxchange.org/user/register
   2. Once the credentials are secured, they should be communicated to the Office of Cancer Genomics (OCG) Project Team (PT) manager (see HTMCP SOP #200C).
   3. Immediately upon arrival to the Pathology Review Lab (PRL), the Pathology Coordinator will verify that all blocks/slides submitted are labeled with the same project-assigned ID for each case.

4. Pathology coordinator will send the appropriate number of slides or block to the histology service to perform hematoxylin & eosin (H&E) as well as necessary immunohistochemical (IHC).
    - IHC to be performed include: **p16**. In cases of adenocarcinoma where an endometrial origin is suspected, **Vimentin, Estrogen Receptor, Carcinoembryonic Antigen (CEA) levels will be assessed by IHC.**
5. Once all the processing is completed, the Pathology Coordinator will:
    (1) scan the H&E and IHC slides on the Bioimagene system
    (2) deposit images of the slides and a blank review form in the PathXchange website (http://www.pathxchange.org) within group HTMCP Cervical
    - The processing and scanning should take no longer than 14 days from receipt of blocks/slides.
6. The Pathology Coordinator will send an e-mail to the members of the pathology review core (PRC) (with copy to the PT manager) informing them that materials for review have been deposited in a folder. This communication must specify the number and name of files, as well as the project-assigned ID(s) for the case(s) under review.
    - This deposition and communication must occur within 48 hours of scanning the slides by the Pathology Coordinator.

B. Review:
1. Within three days of receipt of the e-mail from the Pathology Coordinator, all members of the PRC will return their pathology review form to the Pathology Coordinator via e-mail.
2. The tumors will be classified using the WHO classification.
3. If a consensus is reached and the case passes the specified criteria the pathology coordinator will create a final pathology report and submit it to the Office of Cancer Genomics and the Genome Science Center at British Columbia (GSC-BC) within 4 days. The OCG Project Team manager will complete the Pathology Report form on OpenClinica. Steps 1-3 will take 2 weeks total.
4. Cases for which the tissue is inadequate for diagnosis (*e.g.* tumor nuclei below 70%, degraded tissue) or for which the diagnosis is not cervical carcinoma will be labeled as such and taken out of the study.
5. Cases for which the members of the PRC do not agree on a diagnosis will undergo an additional review by the PRC to reach a consensus. This consensus review will be convened by the Pathology Coordinator. The schedule of such consensus reviews will be dictated by the following:
    - When six or more discordant cases have been accrued, a consensus review panel must be convened.
    - If there are fewer than six discordant cases, but the oldest accrued case is more than three months old, a consensus review panel must be convened.