H-30755- INCORPORATION OF GENOMIC SEQUENCING INTO PEDIATRIC CANCER CARE

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.

Cancer is a disease caused by changes (mutations) in the genetic code of a cell that allow it to divide and spread in in an uncontrolled way. Some of these mutations are present in every cell of the body ("inherited mutations") and can be identified from a blood sample, while others are acquired over time in the specific cells that form the cancer ("tumor mutations"). Whole exome sequencing (sequencing of all protein-coding genes) is now available as a clinical test that can be performed for diagnostic purposes on patient material. Exome sequencing is not experimental, but most children with cancer do not have it done as part of their regular cancer care.

We plan to use exome sequencing to analyze the inherited and tumor mutations occurring in newly-diagnosed central nervous system (CNS) and non-CNS solid tumor patients at Texas Children's Cancer Center and Vannie Cook Cancer Center. This CLIA-certified test will be performed in a clinical laboratory (the Baylor College of Medicine Whole Genome Laboratory; WGL) and the results will be placed into each patient's electronic medical record and provided to their treating oncologist. The oncologist will have the opportunity to discuss the results with the study investigators and will disclose the results to the patient's parents (with a study genetic counselor) and utilize the results in their patient's care as they judge medically appropriate. We will then evaluate how often these exome sequencing data impact decisions about cancer risk or treatment at tumor recurrence. In addition, we will study the psychosocial and ethical aspects of incorporating exome sequencing data into patient care and the communication of these data between oncologists and parents.

This research study is funded by NIH.

Purpose

The overall goal of this study is to integrate CLIA-certified germline and tumor exome sequencing information obtained at the time of diagnosis into the care of sequentially diagnosed childhood cancer patients with central nervous system (CNS) tumors and non-CNS solid tumors at the Texas Children's Cancer Center and Vannie Cook Cancer Center. We will follow patients for two years after diagnosis and assess the impact of whole exome sequence data on clinical decision making by studying physician and patient-centered outcomes in the context of two critical clinical questions:

(1) How does the availability of tumor exome sequence data at the time of recurrence affect the treatment plans recommended by oncologists and chosen by parents?

(2) How does the availability of inherited exome sequence data affect cancer surveillance screening for patients and both genetic testing and surveillance screening for family members?

In addition to generating important data on the clinical utility of whole exome sequencing for pediatric cancer care, this project will provide the clinical framework for the examination of the ethical and psychosocial implications of such an approach. Because you are a pediatric oncologist who will be caring for children and families enrolled on the study, we are inviting you to participate in

surveys and interviews about the impact of exome sequencing.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center.

You are being asked to participate as a board-eligible/board-certified pediatric oncologist and member of either the solid tumor team or neuro-oncology team of the Texas Children's Cancer Center or Vannie Cook Cancer Center. We will provide you a copy of the full protocol which outlines the protocol that patients of the TCCC and the VCCC will be participating in for you to read prior to consenting to join the study. We estimate at most 24 oncologists will join over the four year time period of the grant. For physicians who join the study the following study procedures will occur:

A. Initial education session. All physicians participating in the study will receive educational sessions on the nature of tumor and inherited mutation exome reports from study investigators. It is expected that these sessions will be scheduled during regularly scheduled team meetings and will last approximately 30-40 minutes.

B. Provision of exome reports. For any TCCC or VCCC patient enrolled in this study both a blood and tumor sample will be sent to the Whole Genome Laboratory at BCM for exome analysis as described in the study protocol. Physicians will receive two separate exome sequencing reports (one reporting the inherited mutations detected and one reporting the tumor mutations detected) from the WGL. We expect the reports to be received approximately 3 months after sample submission.

1. Inherited mutation report description. After review by American Board of Medical Genetics certified laboratory directors, the validated and annotated inherited mutation data for each patient will be used to populate a clinical report which will be included in the electronic medical record (EMR). All patients will receive a Focused Report which will include the following cancer and non-cancer related medically-actionable germline variants:

i. Deleterious Mutations in Disease Genes Related to Cancer Susceptibility (example: known germline p53 mutation causing Li-Fraumeni syndrome)
ii. Variants of Unknown Clinical Significance in Disease Genes Related to Cancer Susceptibility (example: missense mutation in p53 not previously described)
iii. Medically Actionable Deleterious Mutations in Disease Genes Unrelated to Cancer Susceptibility (example: germline mutation in fibrillin which is associated with Marfarn syndrome and risk of aortic aneurysm)
iv. Pharmacogenetic Profile Variant Alleles (example: variant which impacts response to anti-platelet agents)

Participation in this study provides parents the option of opting in or out of the following information included in the focused report:

v. Carrier Status for Recessive Mendelian Disorders (known mutations only)
(example: CFTR mutation associated with carrier status for cystic fibrosis)

2. Tumor mutation report description. After review by American Board of Medical Genetics or American Board of Molecular Pathology certified laboratory directors, the validated and annotated tumor mutation data for each patient will then be used to populate a clinical report which lists all of the mutations identified in that patient's tumor which will be included in the electronic medical record (EMR). This report will include annotation such as:
i. whether there is a known FDA-approved drug which specifically targets this mutated gene
ii. whether the mutated gene is a member of a core cancer pathway
iii. whether the gene and/or specific genomic position of the somatic mutation has previously been reported as mutated in the Catalogue of Somatic Mutations in Cancer (COSMIC) database
iv. whether the presence of this mutation is frequently or rarely seen in this tumor type.

3. Review of report information. Once the inherited mutation and tumor mutation reports for a patient have been generated by the WGL, these reports will be discussed with you (prior to disclosure to parents) by the study principal investigators Dr. Plon (inherited mutation report) and Dr. Parsons (tumor mutation report). These discussions will likely occur at weekly team meetings but can also be arranged separately at your convenience.

D. Sharing of genomic data with families. You will then share the two reports with the patient's family in the TCCC or VCCC clinic. A genetic counselor will participate in the meetings in which inherited mutation data are disclosed to the families. There will initially be separate meetings to disclose the two sets of results; however, these meetings will be combined after the first year of the study if the participating oncologists and study investigators determine that disclosure of both sets of results in a single meeting is feasible and preferable for the families. The meetings will be scheduled to coincide with planned TCCC or VCCC clinic visits whenever possible in order to minimize additional clinic trips and inconvenience to families. The charges for any specific study disclosure visit will be paid by the study.

These sessions will be audiorecorded in order to learn how to improve communication about exome sequencing results between oncologists and patient families. The methods used to analyze the communication are described in detail in the protocol provided.

E. Oncologist interviews and surveys.

1. General interviews. If you participate in the study you will be interviewed by study investigators at three different time points during the study in order to assess the types of exome data that you believe are important for families at the time of cancer diagnosis and the values or prior experiences that you use to make such clinical judgments. The first ("pre-disclosure") interview will be conducted after the education session with study staff and before you receive exome data from a study patient. The second ("post-disclosure") interview for TCCC oncologists will be conducted after you have disclosed germline and tumor exome sequencing results to at least 5 sets of parents. For VCCC oncologists, this second interview will be conducted after you have disclosed germline and tumor exome sequencing results to at least 2 sets of parents. The third ("follow-up") interview will

be conducted 12 months after the second interview. Both the second and third interview will also focus on getting your opinion about how the process might be improved to better meet patients', parents', and oncologists' needs. Each of these three interviews is expected to take approximately 60 minutes. Vannie Cook Cancer Center oncologists will be included in the above mentioned interviews (at all three timepoints), and these interviews will be scheduled with the same considerations. However, these interviews (at each timepoint) will be conducted preferably via videoconferences but if necessary will be conducted via teleconferences for the VCCC oncologists.

2. Patient-specific surveys about treatment plans in event of tumor recurrence.
For each patient entered into the study we will conduct the following surveys. Within one month of diagnosis but before the receipt of your patient's exome sequencing results, you will be surveyed about the treatment options that you would recommend in the theoretical event of tumor recurrence. This will be accomplished by providing you an updated and curated list of open clinical trials for recurrent CNS and non-CNS solid tumors, including the drugs utilized in each trial and the putative mechanism of action for any molecularly-targeted drugs. We will also provide an updated and curated list of currently-available FDA-approved molecularly-targeted agents and asked if you would consider the use of any of these agents in the hypothetical scenario of tumor recurrence (outside of the context of a clinical trial). We will ask you to rank the top three clinical options (including no treatment, palliative treatment) that you would recommend for your patient in the hypothetical scenario of tumor recurrence. Only one oncologist will be asked to complete the survey for anygiven patient. Within one month of receiving and reviewing the exome sequence data, we will ask again to rank the top three clinical options recommended in the context of tumor recurrence. Completing these surveys will be completed by paper or online and do not require a meeting with study staff.

3. Assessment of the impact of tumor whole exome sequence data on the treatment plans recommended by oncologists and chosen by parents in the event of tumor recurrence. For your patients whose tumors do recur, we will monitor by inspection of the medical record what treatment options you describe in the note and what option the family chooses, and classify as either: non-cancer directed palliative therapy, standard chemotherapy and/or radiation therapy, non-protocol driven therapeutic option or enrollment on a specific clinical trial. If a clinical trial is chosen, the putative mechanism of action for each molecularly-targeted drug used in the trial will be recorded. Within one month after the the treatment decision at recurrence is made we will ask you about what data you used to decide upon the choices to discuss with the family, and in particular whether the tumor exome data was helpful in decision making as a qualitative assessment.

Who will have access to study data?

Recordings and transcripts will be coded using standard qualitative methods. Coders trained in the coding methods will listen to audio-recordings and following the transcript, look for clinician utterances that (a) present genomic information, (b) check on parent's understanding of genomic information, (c) attempt to clarify genomic information, (d) solicit parent's concerns and opinions about genomic information, and (e) acknowledge uncertainty about whether somatic information may be useful in treatment decisions at relapse, and (f) state whether germline genomic information will be useful in decisions about cancer screening/testing of family members.

Similarly, coders will listen and follow transcripts to identify parents utterances that (a) ask questions about genomic information, (b) state their opinions, concerns, and understanding of genomic information, (c) discuss uncertainty about genomic information, and (d) express any preference for using data for cancer screening or testing of family members.

Each clinician and parent will be assigned a numeric identifier. Only the projects leaders will have access to the master list of names and identifiers. Names of clinicians, parents, and patients will be erased from the audio-recordings and excluded from the transcripts. Thus, coders analyzing the transcripts and recordings will have no exposure to identifying information. Publications will identify respondents only in generic terms, e.g., “pediatric oncologist” or “parent of child with brain tumor.” The master list of names and identifiers will be destroyed when data analysis is complete.

Can I change my mind after I consent to participate in the study?

You can withdraw from this study for any reason at any time. If you decide to withdraw from the study we will ask you to complete the initial provision of the exome reports to any families already consented to the study but will not include you in additional subjects.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning sickle cell anemia
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Photographs, videotapes, and/or audiotapes of you

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, Vannie Cook Cancer Center, and NIH: NATIONAL INSTITUTES OF HEALTH and their representatives.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research does not involve treatment. Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center may not condition (withhold or refuse) treating you on whether you sign this Authorization.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NIH: NATIONAL INSTITUTES OF HEALTH and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, Baylor College of Medicine, Doctors Hospital at Renaissance , TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, Texas A&M University, and Vannie Cook Cancer Center may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Sharon Plon
1102 Bates St., FC 1200
Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts
There are no physical risks of the study for the oncologists.

Other risks:
1. Loss of privacy (interview/survey data)
2. Stress and anxiety related to explaining exome sequencing data to parents (the uncertain clinical significance of the results could make these conversations difficult).

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits
The benefits of participating in this study may be: You may benefit from learning more about exome sequencing, its clinical applications, and how to discuss this data with patients.

It is not known whether exome sequencing to identify inherited and tumor mutations occurring in children with cancer will reveal findings that are of potential clinical benefit to your patients and their families. Your patients may have no direct benefit from your participation in this study. However, participation may provide clinically relevant information of several types:

1. The inherited mutation report may provide information about patient risk of developing other cancers or the risk of other diseases for which treatments may be available. This information may also be relevant for close family members as well.

2. The tumor mutation report may provide information that you may use when making decisions about future treatment of your patient's cancer or very rarely about current treatment.

The study will allow the investigators to better understand how cancers develop and how cancer might respond to various treatments and how to use this new type of genetic testing in caring for children with cancer and thus may benefit your other patients in the future. We expect that analysis of physician – patient communication will provide better understanding of how to convey complex genomic information to parents and to incorporate this information when caring for patients with cancer. However, you may receive no benefit from participating.

Alternatives
You may choose to not participate in this study.

Subject Costs and Payments

You will not be paid for participating in this study. However, all of the costs of sample collection and exome sequencing will be paid for by the study. In addition, neither patients nor their insurance companies will be billed for the additional clinic visits necessary as part of the study. These visits will be billed to the study.

There will be no costs or payments to physicians participating in the study. All of the costs of sample collection and exome sequencing will be paid for by the study. In addition, neither patients nor their insurance companies will be billed for the additional clinic visits necessary as part of the study. These visits will be billed to the study.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, SHARON E PLON, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: SHARON E PLON at 832-824-4251. After hours call (832) 824-2099 and ask to page Dr. Plon or Dr. Parsons

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

National Institutes of Health and the National Cancer Institute may have access to your records for research purposes. Coded information may be provided to the NIH/NCI such as Patient ID, Patient Zip code, Patient country code and Patient Birth date (month/year). However, in the event of an audit NIH/NCI might have access to more information that is part of your research record.

H-30755- INCORPORATION OF GENOMIC SEQUENCING INTO PEDIATRIC CANCER CARE

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date