Individualized Cancer Therapy (iCat) Recommendation for Patients with Recurrent, Refractory, or High Risk Solid Tumors

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## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Abstract</td>
<td>3</td>
</tr>
<tr>
<td>2.0 Background/Rationale</td>
<td>3</td>
</tr>
<tr>
<td>3.0 Objectives/Study Aims</td>
<td>6</td>
</tr>
<tr>
<td>4.0 Study Design and Schema</td>
<td>8</td>
</tr>
<tr>
<td>5.0 Eligibility</td>
<td>9</td>
</tr>
<tr>
<td>6.0 Subject Enrollment</td>
<td>9</td>
</tr>
<tr>
<td>7.0 Clinical Data Collection</td>
<td>12</td>
</tr>
<tr>
<td>8.0 Biospecimen Collection and Processing</td>
<td>16</td>
</tr>
<tr>
<td>9.0 Tumor Profiling and iCat Recommendation</td>
<td>18</td>
</tr>
<tr>
<td>10.0 Exploratory Tumor Profiling</td>
<td>20</td>
</tr>
<tr>
<td>11.0 Specimen Bank and Data Bank Management, Access and Oversight</td>
<td>21</td>
</tr>
<tr>
<td>12.0 Data Analysis and Statistical Considerations</td>
<td>23</td>
</tr>
<tr>
<td>13.0 References</td>
<td>27</td>
</tr>
</tbody>
</table>

### Appendices

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix 1</td>
<td>List of Targeted Therapies</td>
<td>29</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>iCat Assessment Tools 1-5</td>
<td>30</td>
</tr>
<tr>
<td>Appendix 3</td>
<td>Immunohistochemistry Panel</td>
<td>76</td>
</tr>
<tr>
<td>Appendix 4</td>
<td>Data and Safety Monitoring Plan</td>
<td>77</td>
</tr>
<tr>
<td>Appendix 5</td>
<td>Specimen Handling Manual</td>
<td>91</td>
</tr>
<tr>
<td>Appendix 6</td>
<td>Letter to Treating Oncologists (Assessment Tool 1)</td>
<td>93</td>
</tr>
<tr>
<td>Appendix 7</td>
<td>Letter to Treating Oncologists (Assessment Tool 2)</td>
<td>94</td>
</tr>
<tr>
<td>Appendix 8</td>
<td>Letter to Treating Oncologists (Assessment Tool 3)</td>
<td>95</td>
</tr>
<tr>
<td>Appendix 9</td>
<td>Letter to Questionnaire Respondents (Parents)</td>
<td>96</td>
</tr>
<tr>
<td>Appendix 10</td>
<td>Letter to Questionnaire Respondents (Young Adult)</td>
<td>98</td>
</tr>
<tr>
<td>Appendix 11</td>
<td>Parent Pilot Testing Script</td>
<td>100</td>
</tr>
<tr>
<td>Appendix 12</td>
<td>Young Adult Pilot Testing Script</td>
<td>103</td>
</tr>
</tbody>
</table>
1.0 ABSTRACT

Our hypothesis is that it will be feasible to identify an actionable alteration and make a treatment recommendation for pediatric participants with recurrent solid tumors. This protocol will 1) Bank tumor specimens from pediatric participants with recurrent / refractory / high risk pediatric solid tumors 2) Identify the actionable alteration(s) present in the cancer of each enrolled child and provide them with a treatment recommendation based on the identified actionable alteration(s) (iCat recommendation); 3) Determine whether a personalized approach to cancer therapy is feasible in participants with recurrent / refractory / high risk solid tumors using currently available clinically applicable tumor profiling technologies; 4) Capture data regarding the efficacy of treatment based on an iCat recommendation; 5) Explore the use of new technologies for clinical profiling of tumor samples and; 6) Collect data on the perspectives of patients and families on tumor genomic data and treatment recommendations based on this data. Broader implications of these objectives include 1) defining which cancer promoting alterations occur in pediatric solid tumors, facilitating rational selection of targeted therapy for further study; and 2) testing a clinical research paradigm for rigorous academic study of personalized cancer medicine.

2.0 BACKGROUND/RATIONALE

2.1 PROBLEM AND RATIONALE

Typical practice in pediatric patients with recurrent or refractory solid tumors for which there are no standard treatment options is to offer participation in a phase I study. The phase I study(ies) offered are typically selected based on availability of the trial rather than on a strong biologic rationale. Perhaps this haphazard approach to selection is responsible for an overall objective response rate in pediatric phase I trials of only 9.6%1. The vast majority of pediatric patients with recurrent / refractory / high risk solid tumors will, unfortunately, die of their disease and innovative treatment approaches are urgently needed.

As genomic tumor profiling technologies become more advanced and more available, tumors will be increasingly tested for actionable alterations despite the fact that, outside of a few histologies, the clinical utility of that testing is unknown. Clinical research paradigms evaluating the feasibility of testing a wide range cancers, outside of those for which personalized cancer medicine has become standard of care, are desperately needed. This study is a first step into rigorous clinical investigation of large scale tumor profiling. The results, whether positive or negative, will inform the design of future clinical investigation of personalized cancer medicine in many types of cancer.

2.2 BACKGROUND

2.2.1 Individualized Cancer Therapy: A Treatment Paradigm with Demonstrated Successes

Incorporating iCat into treatment of pediatric solid tumors has the potential to result in significant therapeutic advances. Well known targeted therapy success stories such as the use of imatinib in Chronic Myelogenous Leukemia (CML) and Gastrointestinal Stromal Tumor (GIST)2 and trastuzumab in ERBB2-positive breast cancer3 clearly demonstrate that targeted therapy, utilized either alone or in combination with chemotherapy, can have a significant impact on outcome. At the same time, the experience with targeting Epidermal Growth Factor Receptor (EGFR) in non-small cell lung cancer, in which patients whose tumors are driven by mutations in EGFR have dramatic responses to EGFR inhibition while those lacking such mutations do not respond, has demonstrated the need for an individualized approach in which treatment is based on the presence of an aberration rather than on diagnosis in tumors with biologic heterogeneity4.
2.2.2 Presence of Targetable Alterations in Pediatric Solid Tumors

Traditional candidate gene sequencing approaches have led to the discovery of mutations in the \textit{ALK} gene in approximately 8\% of neuroblastomas and \textit{FGFR4} gene mutations in rhabdomyosarcomas\textsuperscript{5,6}. However, candidate gene sequencing is a slow and laborious way in which to discover mutations in tumors that can potentially be targeted by a drug (oncogenic mutations). Advances in gene sequencing technology and bioinformatics have facilitated more extensive sequencing of tumors for a large number of oncogenic mutations. Utilizing one of these platforms, OncoMap, developed at the Dana-Farber Cancer Institute, an oncogenic mutation was identified in over 15\% of pediatric low grade gliomas\textsuperscript{7}. Tumors may also contain an actionable alteration as a result of high levels of expression of non-mutated proteins that are amenable to drug inhibition. High levels of protein expression in tumors may be due to gene amplification, epigenetic mechanisms, translocations or cell context. In breast cancer\textsuperscript{3,8}, large B cell lymphoma\textsuperscript{9}, neuroblastoma and other cancers, targeting this type of alteration has resulted in improved outcomes\textsuperscript{10}. Although there is some data to suggest that tumors acquire genetic, epigenetic and proteomic changes during progression\textsuperscript{11-13}, it is not clear whether this will be the case in pediatric solid tumors.

2.2.3 Technologies for Identification of Targetable Alterations in Individual Tumors

Standard technologies utilized to characterize tumors for diagnostic purposes and basic research include cytogenetics, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) and candidate gene sequencing. Several newer technologies permit more extensive tumor characterization than has previously been possible. OncoMap is a platform developed by Drs. Laura MacConaill and Levi Garraway at the Dana-Farber Cancer Institute\textsuperscript{7}. With this platform, tumors can be evaluated for the presence of up to 1,000 previously described oncogenic mutations in 113 genes. Oncomap can be performed utilizing DNA derived from either frozen or paraffin embedded (FFPE) tumor. Sensitivity and specificity of Oncomap is 93.8\% and 100\% in fresh frozen tissue and 89.3\% and 99.4\% in FFPE-derived DNA making it suitable for clinical use. OncoMap has been adapted to a CLIA (Clinical Laboratories Improvement Amendments) certified lab within the Center for Advanced Molecular Diagnostics (CAMD) at the Brigham and Women’s Hospital.

Claritas Genomics, (formerly the DNA laboratory in Department of Laboratory Medicine at Boston Children’s Hospital) performs CLIA certified comparative genomic hybridization (CGH) arrays on DNA from blood\textsuperscript{14}. Several groups have demonstrated the ability to perform high quality array CGH from FFPE clinical specimens\textsuperscript{15,16}. Members of Claritas and other collaborating CLIA certified laboratories have been utilizing DNA from FFPE tumors for array CGH with success.

The mission of the Center for Cancer Genome Discovery (CCGD) at Dana-Farber Cancer Institute is to develop new technologies for the analysis of cancer genomes and to utilize these technologies for translational and clinical investigation. Next generation sequencing technologies using both the 454 and Illumina-Solexa platforms are available through the CCGD. Via the CCGD we have access to a high-throughput next-generation sequencing platform that uses exome capture to target sequencing to cancer-related genes. Sequencing from paraffin embedded clinical samples has been successful using this platform.

2.2.4 Availability of “Targeted” Therapies

As a result of active cooperative group phase I programs, a number of targeted drugs are both commercially available (approved by the FDA) and have a maximal tolerated dose (MTD) or a generally accepted dose determined in pediatric patients. These drugs are suitable for use in patients with recurrent, refractory solid tumors without standard treatment options that would be curative or would significantly prolong life. Currently, these targeted drugs, listed in appendix 1, include seven tyrosine kinase inhibitors (TKIs) targeting 13 different tyrosine kinases, and 3 antibodies targeting 3 different receptor tyrosine kinases.
2.2.5  **Clinical Research Paradigms for Investigation of Personalized Cancer Medicine**

With respect to personalized medicine, each cancer generally falls into one of two categories. In the first category an actionable alteration is known to be present in at least a proportion of patients with the specific disease and that actionable alteration has been demonstrated, via basic investigation in functional disease models and in clinical trials, to be a central oncogenic event. Examples of diseases falling into this first category include GIST, CML, and ERBB-2 positive breast cancer. In this category of cancers, a personalized approach to cancer therapy is standard of care. In the second category, it is not known whether there are actionable alterations present or an actionable alteration has been identified but the actionable alteration has not yet been convincingly demonstrated to be a central oncogenic event. Failure to obtain convincing evidence that an actionable alteration is a central oncogenic event occurs for a number of reasons including: lack of appropriate functional models, lack of time elapsed for required investigation since the discovery of the actionable alteration or inability to perform clinical trials due to a limited patient population. Many cancers occurring in adults and most pediatric solid tumors are in this second category. Technologic advances such as OncoMap permit testing for actionable alterations in this second category of tumors using clinical tumor specimens (those acquired during routine care) in CLIA certified laboratories. A major problem in this second category of tumors is whether to test tumors for actionable alterations and, when an actionable alteration is identified, how therapy based on the presence of the actionable alteration should be incorporated into clinical care.

As genomic tumor profiling technologies become more advanced and more available, tumors in this second category will be increasingly tested for actionable alterations despite the fact that the clinical utility of that testing is unknown. Testing for actionable alterations in cancers in this second category is driven by the marked success of personalized cancer medicine in the first category of cancers and an assumption that similar success will result from personalized therapy in the second category of cancers. Thus, clinical research paradigms evaluating the feasibility of testing cancers in this second category for actionable alterations and the impact of treatment based on the presence of an actionable alteration are needed. This study is a first step into rigorous clinical investigation of large scale tumor profiling. The results, whether positive or negative, will inform the design of future clinical investigation of personalized cancer medicine in many types of cancer.

2.3  **POTENTIAL BENEFITS TO SUBJECTS AND/OR SOCIETY**

While technological advances are resulting in ever increasing possibilities for tumor profiling, research paradigms for studying the clinical utility of large scale tumor profiling and a personalized approach to cancer therapy in cancers lacking a previously validated actionable alteration are lacking. This will be the first attempt at rigorous academic study of a personalized cancer therapy approach for this category of cancer. If a reasonable proportion of participants can receive an iCat recommendation within this study we will demonstrate that, using the profiling technologies currently available, a personalized approach to treatment is feasible in recurrent / refractory / high risk solid tumors in pediatric participants. This result would have implications for other, more prevalent cancers in that it would support the conduct of similar studies in these diseases. In addition, if iCat is found to be feasible, future studies could then be designed to more rigorously evaluate the efficacy of a personalized approach to cancer therapy. It is possible that a personalized approach to therapy will not be feasible in this participant population using currently available profiling technologies. For this reason, clinical tumor profiling with next generation sequencing will be evaluated in this study as this technology may prove superior for identifying actionable alterations.

This will be the first attempt to broadly characterize the range of actionable alterations present in recurrent / refractory / high risk pediatric solid tumors. The actionable alterations identified in this study and the follow-up laboratory investigation promoted by those results has the potential to add greatly to our understanding of the oncogenic mechanisms in recurrent / refractory / high risk pediatric solid tumors.
in which a wide variety of tumor types are eligible, pediatric phase I trials rarely indicate which solid tumors are sensitive to the therapy under study. Therefore, one of the biggest challenges in pediatric oncology is the design of pediatric phase II studies. It is often difficult to determine which solid tumors should be included in which phase II trials of targeted agents. If, in this study, certain actionable alterations are found to be common in particular histologies, the results of this study may facilitate the design of these phase II trials. Alternatively, if this tumor profiling approach identified actionable alterations in a reasonable proportion of participants, it would support the incorporation similar tumor profiling into pediatric phase II trials.

This study has the potential to help individual children enrolled on the trial who will receive therapy on a more rational basis than is typical for relapsed / refractory solid tumors. Because we plan to follow the outcome of participants who receive treatment based on an iCat recommendation, we will have a preliminary understanding of whether the type of personalized cancer therapy studied here has the potential to impact the outcome of pediatric participants with recurrent / refractory solid tumors.

Finally, given that this study is the first of its kind, it will be important to analyze the impact of this unique data on patients and families. Previous research has shown that patients and families often conflate the goals of clinical care and research and have unrealistic expectations of early phase clinical trials. Genomic data and the inherent uncertainty associated with it only further complicates this issue. We will collect data on the perspectives of patients and families to characterize their hopes and expectations for genomic data and personalized medicine as well as their responses to the return of these results.

3.0 OBJECTIVES/STUDY AIMS

3.1 HYPOTHESIS
It will be feasible to identify an actionable alteration and make an iCat recommendation for pediatric participants with recurrent / refractory / high risk solid tumors.

3.2 PRIMARY OBJECTIVE
To determine whether it is feasible to identify actionable alterations and make an iCat recommendation for pediatric participants with recurrent / refractory / high risk solid tumors.

3.3 SECONDARY OBJECTIVES

3.3.1 To determine the response rate in participants with recurrent / refractory solid tumors receiving therapy based on an iCat recommendation.

3.3.2 To evaluate whether pediatric solid tumors acquire additional actionable alterations during progression.

3.3.3 To determine the spectrum of potentially actionable alterations present in relapsed / refractory solid tumors.

3.3.4 To explore the utility of novel technologies for the identification of actionable alterations.

3.3.5 To explore physicians’ opinions about personalize cancer medicine and determine whether there is a relationship between physician demographic variables (age, gender, race, ethnicity and practice setting) and physicians’ opinions regarding personalized cancer medicine.
3.3.6
To analyze the hopes and expectations of the families of children with recurrent / refractory / high risk solid tumors regarding genomic testing of these tumors and then evaluate if these hopes and expectations were met following the return of results.

3.3.7
To ascertain if there is an association between these hopes and expectations and characteristics such as personal knowledge or experience with genetics, prognosis, or clinical status.
4.0 STUDY DESIGN AND SCHEMA

This study is a multi-center, non-therapeutic trial of the feasibility of making a personalized cancer medicine recommendation using Simon’s two-stage design.

SCHEMA

Eligibility screening and consent

Study entry: Samples submitted to DFCI

Tumor profiling performed:
1) OncoMap
2) Copy number evaluation
3) Immunohistochemistry

Sufficient profiling data for an iCat recommendation? No

Case considered a technical failure

Yes

iCat Recommendation formed by Study Investigator and approved by Expert Panel

Patient agreed to communication of tumor profiling results and iCat Recommendation? No

Survey of parent (assessment tool 4) or subject (assessment tool 5) following return of Tumor Profiling results and iCat recommendation (if a recommendation was made)

Yes

Tumor Profiling results and iCat recommendation released to patient and treating oncologist

Tumor Profiling results and iCat recommendation recorded; no further contact with patient or treating oncologist

Tumor Profiling results and iCat recommendation released to patient and treating oncologist

Treating oncologists surveyed 1 week after iCat recommendation communicated (assessment tool 1) then every 3 months (assessment tool 2)

Assessment tool 2 response

Treatment according to the iCat Recommendation initiated

Treatment according to iCat recommendation never appropriate

Patient death

Other

Treating oncologists surveyed every 3 months (assessment tool 3) until termination of treatment according to iCat recommendation or patient progression, or death

No further contact with treating oncologist; study participation completed

Continue to survey treating oncologists every 3 months (assessment tool 2)
5.0 **ELIGIBILITY**

5.1 **INCLUSION CRITERIA**

5.1.1 **Age**
Age ≤30 years

5.1.2 **Diagnosis**
Diagnosis of recurrent, refractory or high risk solid tumor (excluding brain tumors):
- Refractory defined as tumor progression on standard first line chemotherapy
- High risk defined as overall survival for patient group with same histology, grade and stage estimated to be <25%

5.1.3 **Pathologic Criteria**
Histologic proof of malignancy at the time of diagnosis or recurrence

5.1.4 **Specimen Samples**
Sufficient tumor specimen available for profiling from diagnosis or recurrence; or surgery / biopsy planned for clinical care (See Section 8.1.1)

5.2 **EXCLUSION CRITERIA**

5.2.1 Insufficient tumor specimen available for profiling (See Section 8.1.1) from diagnosis or recurrence; or surgery / biopsy planned for clinical care NOT planned

6.0 **SUBJECT ENROLLMENT**

6.1 **SUBJECT IDENTIFICATION**
Potential subjects will be identified by the participant’s treating physician during routine clinical care.

6.2 **SUBJECT RECRUITMENT**

The protocol will be presented at scientific and protocol conferences at the participating institutions in order to educate potential referring physicians of the protocol’s existence. The protocol may be presented at scientific conferences and at grand rounds at regional institutions in order to educate potential referring physicians of the protocol’s existence. The study will be described on the DFCI, BCH, Columbia University, University of California San Francisco and Children’s National Medical Center websites, providing opportunities for patient self-referral. The study will be registered on clinicaltrials.gov. The protocol will not be advertised directly to patients and recruitment materials will not be provided to patients.

6.3 **ELIGIBILITY SCREENING**

Eligibility screening will be conducted by qualified clinical research personnel. Every potentially eligible participant will be seen at one of the participating sites prior to enrollment. A complete assessment will be performed by qualified clinical research personnel to determine eligibility.
Screening will involve the following:

- Review of the participant’s medical record
- If necessary, review of existing scans documenting recurrent / refractory / high risk disease
- If necessary, contact with a Pathologist at the institution where diagnostic or recurrent biopsy performed to confirm sufficient tumor material available
- History and physical examination
- If the participant was not diagnosed at one of the participating sites, a pathology review may be conducted to confirm the diagnosis.

6.4 SUBJECT CONSENT

Study-associated staff will offer eligible participants the opportunity to participate. Before issuing an invitation to participate, study-associated personnel will provide a full explanation of this protocol to the potential subject and a parent or legal guardian (if subject less than 18), review the consent form with the potential subject and a parent or legal guardian (if subject less than 18), and answer any and all associated questions. Those subjects who elect to participate in the study must sign the informed consent form. For participants who are at an appropriate developmental age to provide assent, a parent or legal guardian must sign the consent form and the participant must assent to participation and sign the consent form. For participants less than appropriate developmental age to provide assent, a parent or legal guardian must sign the consent form.

Subjects who consent will be either given or mailed a signed copy of the form for their records. Subjects who request additional time to consider participation will be provided with a copy of the consent form. A participant’s decision to participate or to not participate in this study will not affect the quality of care he or she receives.

Study participants who agree to further contact will be offered the opportunity to complete a questionnaire about their experiences with the iCat research study. This questionnaire is optional, and each subject's decision to participate or decline participation will not impact their inclusion in the remainder of the research study, nor will it impact the clinical care they receive. No separate written consent will be obtained for this questionnaire.

Physician consent: Signed informed consent will not be required for the primary treating oncologists who is asked to complete the iCat assessment tools. We request a waiver of the requirement to document informed consent, as this minimal risk survey study involves no procedures for which written consent is normally required outside of the research context. The treating oncologists will provide implied consent for the study via completion of the iCat Assessment Tools. iCat assessment tool 1 will be accompanied by a cover letter (appendix 6) explaining the study and the role of the oncologist in the study, if they choose to take part. The letter will also include an explanation of the exploratory objective to collect age, race, gender, training and background information for an analysis of physician bias for the study.

6.4.1 Informed Consent Form

The consent forms will ensure that each participant/donor signatory understands and agrees to the following:

- The procurement of participant biospecimens through: (i) obtaining already collected paraffin embedded (FFPE) specimens (ii) procedures that are called for by routine clinical care, after adequate material is collected for clinical diagnostic and treatment purposes; (iii) and an additional blood draw.

- The use of biospecimens for tumor profiling with OncoMap, comparative genomic hybridization array (CGH) or other method of copy number determination and IHC. The use of the tumor profiling to create
an individualized cancer therapy recommendation. The possibility that the iCat recommendation may indicate a clinical course of action, or eligibility for a particular clinical trial. Participants may consent to have these profiling results and the iCat recommendation conveyed to them and their treating oncologist, who may not be a study investigator.

- The collection, storage and use of participant health information and linkage of participant health information with tumor profiling data for the purposes of creating the iCat recommendation by study staff at DFCI and BCH.

- The use of materials and clinical data for additional investigational tests and experiments some of which have not yet been designed. The clinical utility of such tests are unknown and the results of these investigational tests will not automatically be made available to participants or their physician. A description of some of the specific tests to be performed including whole genome sequencing and derivation of cell lines and in vivo models. These additional investigations may be performed by researchers other than study investigators after approval of the study investigators. In this case, all specimens and data will be removed of identifying information.

- In some cases, specimens may be shared with for-profit companies that are working with researchers on a specific research project. Specimens will not be sold to any person or company for profit. Specimens shared with external companies will not contain identifying information. Subjects will not benefit from any financial gain to the institutions or their investigators based on these projects.

- Sharing or publication of de-identified genomic information. Subjects will be informed of the safeguards provided by de-identification but will also be informed that no one can predict how genomic information might be used in the future.

- There will be no costs to subjects for specimen contribution and no reimbursement to subjects.

- The optional activities for which consent is sought will be bundled into three individual requests for consent on the Consent Form: 1) iCat recommendation conveyed to participant and treating oncologist and follow-up data obtained from the treating oncologist; 2) investigational use of specimens (whole genome sequencing); 3) banking specimens for future use. Participants may provide consent for any of the three components or for all of them.

- Withdrawal of consent, as well as partial withdrawal from selected components, is possible at any time at participant discretion. Upon request by a participant, his or her specimens and derivative material will be removed from research specimen repositories. (Material collected for clinical purposes will not be removed from clinically relevant archives e.g., Departments of Pathology.)

6.5 REGISTRATION AND WITHDRAWAL

All subjects including those enrolled at collaborating sites will be registered in the protocol registration database and assigned a study ID number by the DFCI Quality Assurance Office for Clinical Trials (QACT).

6.5.1 General Guidelines for DF/HCC Institutions
Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system.
A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

6.5.2 Registration Process for DF/HCC Institutions
The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant’s medical/research record. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study.

5. The QACT Registrar will send an email confirmation to the person initiating the registration immediately following the registration.

6.5.3 Registration Process for Participating Institutions
Please refer to Appendix 4, Section 4.7 for guidelines and registration details.

6.5.4 Study Withdrawals
Participants may withdraw consent to participate in this study at any time. If a participant chooses to withdraw from the study, any remaining samples he/she contributed to research biorepositories will be discarded. However, data obtained prior to the participant’s withdrawal from the study will be kept. Samples essential for routine clinical care e.g., archived tissues in Departments of Pathology, will not be affected by study withdrawal. The subject’s privacy will be preserved. An indication will be made in the database regarding this individual’s desire to withdraw from the study to ensure that this individual is not contacted regarding this study in the future. Clinical data collected as part of other research studies in which a participant is participating and from which the participant does not withdraw consent will not be deleted or affected by withdrawal from this study. Additionally, a participant may withdraw selectively from particular components of the study.

7.0 CLINICAL DATA COLLECTION

7.1 PURPOSE OF CLINICAL DATA COLLECTION
Clinical data will be collected at the following time points: at study enrollment; following iCat recommendation (every 3 months until iCat initiation, progression or death); and after iCat initiation (every 3 months until progression or death).

The purpose of clinical data collection at these time points is:

1. At study enrollment: Obtain the information required for the iCat recommendation.
2. Following iCat recommendation: Determine whether treatment based on the iCat recommendation has been initiated; Collect data from patients/families regarding hopes and expectations regarding genomic data as well as impact of the data that has been returned to them.
3. Following iCat initiation: Determine response to treatment based on iCat recommendation.

In addition, participant identifiers will be collected by DFCI on participants from all study sites due to the need to perform testing on their tumors on CLIA certified laboratories at DFCI and, in some cases, by an outside vendor (see Sect. 9.1.4).

7.2 TYPE OF DATA COLLECTED

7.2.1 At Study Enrollment:
- Participant identifiers including name, medical record number and date of birth.
- Diagnosis
- Status (recurrent, progressive, high risk)
- Sites of disease
- Prior treatment and response to treatment
- Ability to take forms of oral medications
  - Pills
  - Liquid
- Treating oncologist name and contact information

7.2.2 Following iCat Recommendation:
- For all participants who agree to MD contact:
  - An iCat assessment tool (iCat assessment tool 1, Appendix 2) will assess the treating oncologist’s perceptions of the iCat recommendation letter. Examples of perceptions to be assessed are clinical utility of the iCat protocol and therapeutic benefit of the iCat protocol for the participant.
  - Tool to be administered to the treating oncologist 1 week after iCat recommendation letter sent.
- For participants who received an iCat recommendation and who agree to MD contact:
  - An iCat assessment tool (iCat assessment tool 2, Appendix 2) will, on an every three month basis, to determine whether the participant has received treatment according to the iCat recommendation and if treatment according to the iCat recommendation was not initiated, why not.
  - Tool to be administered to the treating oncologist 3 months after iCat recommendation letter sent and every 3 months until treatment according to iCat recommendation initiated, participant death or response from treating oncologist indicating treatment according to iCat recommendation will never be initiated.
- For participants age <18 years who agreed to MD contact:
  - An iCat assessment tool (iCat assessment tool 4, Appendix 2) to be administered to the parent or legal guardian of the participant (the individual who consented for the study) ≥1 month after...
return of results (if results were available) to collect information regarding his/her hopes and concerns about the iCat testing and the impact the testing has had on the respondent, patient, and his/her family

- For participants age ≥18 years who agreed to MD contact:
  - An iCat assessment tool (iCat assessment tool 5, Appendix 2) to be administered to the participant ≥1 month after return of results (if results were available) to collect information regarding the participant’s hopes and concerns about the iCat testing and the impact the testing has had on the participant and his/her family.

- For participants who receive treatment according to the iCat recommendation:
  - An iCat assessment tool (iCat assessment tool 3, Appendix 2) will obtain dates of treatment initiation, best response to treatment, date of best response and date of progression while receiving treatment based on the iCat recommendation.
  - Tool to be administered to the treating oncologist 3 months after treatment according to iCat recommendation initiated and every 3 months until progression, death or treatment termination.

- A review of the medical participants records at the participating institutions will be conducted with the goal of obtaining further information regarding therapy received (dose, duration), response to therapy received and outcome than it is possible to obtain from the iCat assessment tools.

7.3 DATA COLLECTION METHODS

At study enrollment every enrolled subject will have a baseline visit at one of the study sites with one of the study investigators. Baseline clinical data as outlined in Section 7.2.1 will be obtained both from the medical record and from history and physical examination. Study staff will input clinical data into a password protected, database constructed for the purposes of this study.

Clinical data following the iCat recommendation will be collected directly from the participant’s treating oncologist using iCat assessment tools. iCat assessment tools will be administered to the participant’s treating oncologist using a paper survey. Physicians will be provided a one time incentive to complete the iCat assessment tools. A $50.00 gift card will be included with iCat assessment tool 1. Treating oncologists who do not respond to an iCat assessment tool within 2 weeks of the initial mailing will have the relevant assessment tool mailed to them a second time. Treating oncologists who do not respond to the reminder (second) assessment tool within 2 weeks will receive a telephone call reminder by study staff.

Following the return of results and a treatment recommendation (if one was given), study staff will contact treating oncologists to request permission to contact participants who previously agreed to be contacted. Those participants (or parents/legal guardians for those <18 years) for whom permission is obtained will be contacted by phone or in person to ascertain their willingness to complete a survey about their experience with the iCat study. Study staff will at that time read from an informational letter (Appendix 9) that describes the survey objectives and includes information about confidentiality. Those who agree to complete a survey will be contacted in person in the oncology clinic or inpatient unit and/or mailed a paper questionnaire along with the aforementioned informational letter, a postage-paid return envelope, and an opt-out postcard if the study staff is unable to reach them by phone. The questionnaire will either be iCat Assessment tool 4 or 5, depending on whether the participant was at the time of iCat enrollment <18 years (Assessment tool 4) or ≥18 years (Assessment tool 5). Surveys will be offered to the individual who consented to take part in the iCat research study, either the patient with cancer (if ≥18 years at the time of enrollment) or his/her parent or legal guardian. All study participants who previously agreed to MD contact will be given the opportunity to take the survey, regardless of whether or not they received an iCat treatment recommendation. A $10.00 gift card will be included with iCat Assessment tool 4/5 for all invited participants. Participants who have not responded or
returned the opt-out postcard will be called within two weeks of initial contact. At that time, study staff will offer to answer any questions and provide a second questionnaire, either through the mail or by bringing it to the patient in the clinic or inpatient setting. A final attempt will be made approximately two weeks after the second attempt for participants who have not responded or returned the opt-out postcard. Participants who have not responded at that point will be mailed a paper copy of the questionnaire, informational letter, postage-paid return envelope, opt-out postcard, and a $10.00 gift card.

Assessment tools 4 and 5 will consist of a series of multiple-choice questions in various domains. These domains and a brief description of the topics addressed by the questions in each domain are as follows:

1) Experience with genetics and genetic testing – several yes/no questions addressing the respondent’s prior experiences with genetics and genetic testing
2) Genetic knowledge – several true/false questions addressing the respondent’s knowledge of genetics and genetic testing
3) Patient data – several multiple choice questions inquiring about the patient’s cancer, health status, treatment, and prognosis
4) Understanding of the iCat study and its purpose – several multiple-choice questions inquiring about the respondent’s understanding of the purpose of the iCat study, its purpose, and its potential impact on participants
5) Hopes for the iCat study – several multiple-choice questions addressing what hopes the respondent had for the iCat testing at the time that he/she enrolled in the study
6) Concerns about the iCat study -- several multiple-choice questions addressing what concerns the respondent had about the iCat testing at the time that he/she enrolled in the study
7) Return of results – several yes/no and multiple-choice questions inquiring as to what types of genetic/genomic information families would like to receive from future studies about cancer genomics
8) Research study requirements – several yes/no questions inquiring as to what requirements would be reasonable for enrollment in future studies about cancer genomics
9) Follow-up of results – several multiple-choice questions inquiring as to the patient’s current cancer treatment and how/if an iCat treatment recommendation played a role in this treatment choice
10) Impact of results – a series of multiple-choice or yes/no questions looking at the patient’s current medical status, how their treatment might have changed based on the iCat treatment recommendation, and what impact the iCat study and its results have had on the participant and his/her family
11) Participant demographics – several multiple-choice questions ascertaining the participant’s age, gender, education, race/ethnicity, and relationship to the patient with cancer.

Questionnaire items will be based on previously validated questions and indices, when available. When such is not available, questionnaire items will be created specifically for this assessment tool.

Because several new questions will be developed for this questionnaire, we will perform cognitive interviews with up to 10 of our first enrollees for the purpose of questionnaire validation. Research staff will meet in person in a private location with up to 10 participants (8 parents and 2 patients ≥18 years of age at the time of enrollment) who provide their verbal consent to take part in these interviews. Interviewers will take notes during the interviews to improve recall of salient issues. Subjects will be asked first to independently complete the appropriate assessment tool (4 or 5) about his/her experience with the iCat research study and to mark any questions that were not clear or were difficult to answer. The interviewer will then ask a series of questions focused on (1) understanding of questions, (2) clarity of questions, (3) the cognitive process of reflecting on their experience with iCat and choosing a response, including the time frame used, and (4) the extent to which questions reflect personal experiences, including any missing domains. Probing questions will be utilized to understand verbal responses and nonverbal cues. Cognitive interview sessions are expected to last ~30 minutes.
We will use results of these cognitive interviews to refine Assessment Tools 4 and 5 and to establish face and content validity. Cognitive interviewers will review their notes with other members on the research team to determine if findings from individual interviews can be grouped into themes (such as difficulties with comprehension of a particular question or set of questions). Once the cognitive interviews are completed, an action plan will be generated for each theme that was discovered (to revise or eliminate questions if indicated, to retain questions as previously expressed, or to defer specific changes pending further study). Once these action plans are enacted, a protocol revision will be submitted to the Institutional Review Board with the revised assessment tools (if necessary), and the revised questionnaires will be administered to the remaining iCat participants once approved by the IRB.

Timely quality data management will be performed in conjunction with the DFCI Quality Assurance Office for Clinical Trials (QACT) via the web-based electronic data capture InForm system for clinical trials. All participating institutions will be able to report data over the internet via the InForm screens.

The infrastructure for the conduct of the trial, data collection, and data analysis will be provided by the Clinical Translational Investigation Program (CTIP) and the Biostatistics Program of the Division of Pediatric Hematology/Oncology of BCH and DFCI. CTIP and Biostatistics faculty and staff will contribute expertise for study design and protocol development, assist with obtaining IRB approval, design and implement electronic data collection forms, monitor for adherence with regulatory requirements, facilitate specimen collection and data audit, perform statistical data analysis and interpretation, and participate in manuscript generation. The CTIP Biostatistics Program has dedicated computer servers, and SAS will be the primary analytic tool to address the study objectives.

7.4 RESEARCH DATABASE ARCHITECTURE

We will build the database using Phase Forward’s InForm™ ITM (Integrated Trial Management) software application. InForm is a Web-based electronic data capture (EDC) and clinical data management system used by research teams to facilitate study data collection, monitoring and analysis. InForm™ is based on open data standards (CDISC ODM, XML, etc.), is designed to facilitate the integration of disparate clinical or bioinformatics services and supports enhanced reporting and integration capabilities. The application software employs Microsoft and Oracle technologies to deliver secure Web services and data storage. Our DBAdb will be an Oracle (relational) database that is 21 CFR Part 11 compliant. Sites will have the ability to submit data over the internet via a secure network connection, and data will be stored on the servers of the Dana-Farber / Harvard Cancer Center’s (DF/HCC) Quality Assurance Clinical Trials Program behind the firewall maintained by the Partners Healthcare Information Systems.

8.0 BIOSPECIMEN COLLECTION AND PROCESSING

8.1 BIOSPECIMEN TYPES TO BE COLLECTED

8.1.1 Minimal Biospecimen Requirement
In order to be enrolled on the protocol participants must have adequate FFPE or frozen tumor tissue, from either diagnosis or recurrence for conduct of OncoMap already available or have a procedure scheduled for clinical purposes which is expected to provide sufficient material. Sufficient material for OncoMap is one paraffin block containing viable tumor or 15 unstained slides containing tumor or approximately 25 mg or 0.25 cm$^3$ flash frozen tumor specimen maintained at -80 degrees or 2 ml liquid bone marrow from participant with at least 25% bone marrow involvement with tumor or 10 ml of bodily fluid containing at least 5 atypical (tumor) cells per
mm³. To complete copy number analysis and IHC additional unstained slides will be required (up to 60 to complete all testing). Therefore, submission of the paraffin block and / or flash frozen tumor is strongly recommended.

8.1.2 Biospecimens to be Collected
- **Tissue** (one of the following is **required**, both can be submitted if available)
  - Paraffin embedded tumor block or 15 to 60 unstained slides from paraffin embedded tumor block from original tumor, recurrent tumor or, preferably, both (must contain viable tumor) **AND/OR**
  - 25 mg or 0.25 cm³ flash frozen tumor from original tumor, recurrent tumor or, preferably, both

- **Peripheral blood** (**required**)
  - 10 ml or 1 ml/kg, whichever is less

- **Other Liquid Specimens** (**requested**)
  - Bone marrow aspirate (2 ml) or biopsy containing tumor (minimum 25% tumor involvement) **AND/OR**
  - 10 ml of bodily fluid containing at least 5 atypical (cancer) cells per mm³ such as pleural fluid or ascites

*Of note, tumor specimens obtained following neo-adjuvant chemotherapy are permitted if viable tumor is present but tumor specimens obtained before neoadjuvant chemotherapy are preferred.

8.2 COLLECTION SITES

With the exception of blood, all biospecimens will have already been or will be collected as part of the participant’s routine clinical care at the participant’s treating institution. In participants less than 18 years old all attempts will be made to collect blood at the time of a clinically indicated anesthesia, phlebotomy, IV insertion or indwelling catheter access procedure. The quantity of blood to be collected will not exceed 10 ml or 1 ml/kg whichever is less.

For participants enrolled at participating sites other than Dana-Farber / Children’s Hospital Cancer Center biospecimens will be shipped to the Dana-Farber / Children’s Hospital Cancer Center as specified in Section 11.1.
8.3 SPECIMEN STORAGE/DISPOSAL

Frozen tissue and blood samples will be stored in secure -80º C freezers at BCH or the Boston Children’s Hospital Biorepository. Storage and retrieval of fixed and paraffin-embedded specimens will be handled using routine procedures of the Pathology Department of the hospital at which the specimen was collected. Additional detail regarding specimen tracking and storage is provided in Sections 11.1 and 11.3.

Disposal of biospecimens will be considered under certain circumstances including but not limited to reduced specimen integrity, exhausted capacity or insufficient funds for long-term maintenance or storage of low priority biospecimens. Determination of the integrity and priority of biospecimens is at the discretion of Principal Investigator.

8.4 BIOSPECIMEN COLLECTION RISKS TO PARTICIPANT

Participant tissues, bone marrow, and fluids used in this protocol will have been collected for clinical care purposes, so that additional adverse effects or toxicities will not be incurred. Thus, risks experienced by subjects would be the same as those consented to as part of their usual medical care.

One procedure which is not part of routine patient care will be performed and may result in physical side effects, described below.

- Blood draws may cause pain and erythema and/or ecchymosis at the needle insertion site. Efforts will be made to collect blood through preexisting intravenous access or at the time of a clinically indicated phlebotomy. The expected blood loss will be minimal.
  - In participants less than 18 years, every attempt will be made to perform blood draws at the time of a clinically indicated anesthesia, phlebotomy, IV insertion or indwelling catheter access procedure.

Occasionally, biological samples collected for research purposes will include excess tumor tissues and surrounding non-tumor tissue removed as part of a clinically indicated medical procedure that would have otherwise been discarded. Collection of these samples will not interfere with a participant’s diagnosis or clinical care.

9.0 TUMOR PROFILING AND iCAT RECOMMENDATION

9.1 TUMOR PROFILING

When available, both diagnostic and recurrent tumor specimens will be profiled in order to identify the actionable alterations present in the participants’ tumor.

9.1.1 OncoMap

Tumor will be profiled utilizing OncoMap to determine the presence of an oncogenic mutations at the Center for Advanced Molecular Diagnostics (CAMD) at the Brigham and Women’s Hospital. In preparation for OncoMap, a Boston Children’s Hospital pathologist will review H&E slides to confirm the diagnosis and to determine the region of the FFPE block with the greatest density of viable tumor cells. In the Brigham and Women’s Hospital CAMD FFPE blocks will be cored in the predetermined region of greatest viable tumor cell density, DNA will be extracted from the FFPE core and OncoMap will be performed. If the pathologist determines that there is insufficient viable tumor for DNA extraction, additional slides will be cut and stained. If
there is still insufficient viable tumor density, DNA extraction will not be performed and the participant will be considered a technical failure (see below, statistical methods).

The method mutation analysis performed by the CAMD may change over time in order to permit analysis of smaller tumor specimens or a larger number of genes. Potential CLIA certified methods of mutation analysis that may be performed by CAMD in the future may include exome or whole genome sequencing.

9.1.2 Candidate Gene Sequencing
When an enrolled participant has a tumor histology for which there is published evidence supporting the occurrence of an oncogenic mutation in a proportion of participants with that tumor type, for example ALK mutations in neuroblastoma, the participant’s tumor will be tested for the presence of that oncogenic mutation if candidate gene sequencing of the relevant gene is available in a CLIA certified laboratory.

9.1.3 Copy Number Analysis
Array CGH will be performed in a CLIA certified laboratory to allow for return of these results. Procedures for the extraction of germline and tumor-derived DNA will be determined by the facility conducting the testing. Using germline DNA and tumor-derived DNA, array CGH will be performed. The method of copy number analysis performed may change over time in order to permit analysis of smaller tumor specimens for copy number alterations.

9.1.4 Immunohistochemistry (IHC)
IHC will be performed in the Boston Children’s Hospital Department of Pathology or sent to an outside vendor CLIA certified laboratory if Boston Children’s Hospital Department of Pathology does not perform the specific IHC test desired. An immunohistochemistry (IHC) panel, designed to identify highly expressed tyrosine kinases for which targeted therapy is available will be performed on each tumor by the Boston Children’s Hospital Department of Pathology. Appropriate positive and negative controls will be performed whenever possible. The exact panel of proteins to be tested for by IHC may change during the protocol due to changes in antibody availability, basic research discoveries and targeted therapy trial results. The exact panel of proteins to be tested for by IHC for each participant will be tailored based on tumor specimen availability, diagnosis and results of OncoMap, candidate gene sequencing and copy number analysis. The panel to be performed at study initiation is listed in appendix 3.

9.2 GENOMIC AND HISTOLOGIC ANALYSES
OncoMap results will be interpreted and CGH data will be analyzed as previously described\(^7,14\) and in line with current protocols at BCH and BWH. IHC results will be scored by a pathologist in the Boston Children’s Hospital Department of Pathology.

9.3 iCAT RECOMMENDATION

9.3.1 Formulation of iCat Recommendation
The Principal Investigator or one of the Pediatric Oncology Co-Investigators will utilize clinical data and the interpreted profiling data to create and an iCat recommendation. As the basis for an iCat recommendation, actionable alterations will be ranked as follows (1=first choice): 1) oncogenic mutation identified by OncoMap or candidate gene sequencing; 2) expressed target with gene amplification; 3) expressed target without gene amplification. Considerations taken into account in determining the recommendation will include: IC\(_{50}\) of a particular drug against the particular mutation identified; available drug formulations; prior therapies received;
participant age and availability of data regarding a pediatric MTD; side effect profiles; availability of phase I/II trials.

9.3.2 Review and Approval of iCat Recommendation by Expert Panel
The iCat recommendation will be reviewed and approved by a panel composed of experts from pediatric oncology, developmental therapeutics, pharmacology, and cancer biology. The Expert Panel will meet bimonthly. Conference call-in information will be provided to the Expert Panel members to allow for travel and scheduling conflicts. Members of the panel will be available to the investigators for consultation during creation of the iCat recommendation as needed.

9.3.3 Communication of iCat Recommendation to Study Participants and Their Physician
In the consenting process, the participant will have the option to decline return of tumor profiling results and communication of the iCat recommendation. If the participant does not decline return of tumor profiling results and communication of iCat recommendation, this information will be released to the treating oncologist. Because of the complex nature of the tumor profiling and iCat information, this information will be released to participants via their treating oncologist.

For participants with high risk solid tumors, the tumor profiling results and iCat recommendation will only be released to the participant’s physician if the participant develops recurrent or refractory disease or if three years have elapsed from diagnosis, whichever occurs first. The delayed release of information is to ensure that decisions about upfront therapy are not influenced by the iCat recommendation. At the time of the release of the iCat recommendation to the high risk subset of participants only, the Expert Panel will re-review the recommendation before it is sent to the treating oncologist to ensure the information is still current.

The iCat recommendation will be provided to the participants’ treating oncologist in the form of a letter containing an assessment of the technical performance of the profiling, the interpreted IHC, CGH and OncoMap results, a list of the actionable alteration(s) identified and the iCat recommendation. The letter will clearly state that treatment based on the iCat recommendation is experimental and is not known to be better than standard therapy. The participant’s treating oncologist will also receive a phone call from the PI or one of the Pediatric Oncology Co-Investigators from the collaborating sites to inform them of the results and to ensure they received the letter.

10.0 EXPLORATORY TUMOR PROFILING
In those cases in which both diagnostic and recurrent tumor specimens were available for profiling, the tumor profiling results in the two specimens will be compared with the goal of determining whether additional actionable alterations are acquired during tumor progression and whether diagnostic tumor samples are adequate for tumor profiling at the time of progression.

Exploratory tumor profiling will be performed only after sufficient tumor material has been collected for the tumor profiling performed for the iCat recommendation.

In those cases in which sufficient tumor material is available, deep sequencing of targeted exomes known to be involved in cancer or whole exome sequencing may be performed. Whether these techniques identify potentially actionable alterations in addition to those identified with OncoMap will be determined.

Results from these exploratory studies will not be released to participants or physicians unless they are performed in CLIA certified laboratories or unless mutations with significant clinical implications are identified such as germline p53 mutation associated with the Li Fraumeni Syndrome. If such mutations are identified,
results will be released only after confirmation of result in a CLIA certified laboratory, the case has been discussed by the iCat expert panel and after consultation with the IRB. At the time of releasing germline mutation results, participants will be offered appropriate genetic counseling.

Additional research studies may be performed with de-identified tumor and fluid specimens acquired under this research protocol. These additional research studies may include derivation of cell lines and xenograft models.

11.0 SPECIMEN AND DATA MANAGEMENT, ACCESS AND OVERSIGHT

11.1 SPECIMEN TRACKING

Specimens will be obtained and delivered to the appropriate clinical research staff at DFCI as specified in the Specimen Handling Manual (Appendix 5).

For specimens submitted by collaborating sites, at the time of shipping a form will be completed by the site shipping specimens specifying study participant, case number, date of birth, number and type of specimens being shipped, date of collection of specimens and shipment tracking number. This form will be submitted to DFCI study personnel. When specimens are received by clinical research personnel from collaborating sites the contents of each shipment will be cross-checked with the information on the form received from the collaborating site. Clinical research personnel will hand deliver specimens to the respective DFCI, BCH and BWH Departments and labs for processing as specified in the Specimen Handling Manual (Appendix 5).

Once the specimens are delivered to the appropriate laboratories each specimen will be logged in the InForm study database as received. The following information will be logged: type, date of collection, number of tubes if multiple and laboratory to which delivered. Prior to using a returned result for the iCat recommendation, the returned result will be verified against the specimens received to ensure that each result has a corresponding specimen submitted.

FFPE blocks will be returned to the Pathology Department from which it came for clinical storage. All participant-derived materials not depleted by testing will be banked in the BCH Biorepository. If requested, participant-derived materials not depleted by testing will also be returned to the Pathology Department from which the FFPE block was submitted. The study database will contain detailed information regarding banked specimens and derivative material such as DNA and RNA, including amount banked, storage location, retrieval, and usage.

For all testing performed in CLIA certified laboratories, each specimen will be uniquely identified by at least 2 participants identifiers (such as the participant’s name, date of birth) and the study participant case number and a specimen ID number.

For research testing performed in non-CLIA certified laboratories results of which will not be used in formulating the iCat recommendation, specimens will be de-identified but will be uniquely identified with a study participant case number and a specimen ID number so that the resulting biologic data can be linked to clinical data for research purposes.
11.2 DATA CONFIDENTIALITY AND SECURITY

The confidentiality of each participant record will be rigorously maintained using existing DFCI standards. HIPAA and state/federal government regulations for protecting participant privacy and security will be strictly observed. Participant source documentation maintained by clinical research personnel will be kept in a locked file cabinet. The study data will be password protected, submitted over the internet via a secure network connection, and the database will be stored on the servers of the Dana-Farber / Harvard Cancer Center’s (DF/HCC) Quality Assurance Clinical Trials Program behind the firewall maintained by the Partners Healthcare Information Systems.

No participant or subject identifiable information will be given to third parties, including family members, unless that subject has given written or witnessed consent to do so. The results of research studies may be published but all data will be de-identified prior to publication and individual subjects will not be identified.

If a participant contacts the study’s project personnel, he or she will be informed of the status of the research without revealing specific findings.

11.3 ACCESS TO SPECIMENS AND DATA FOR RESEARCH PURPOSES

11.3.1 Access to Research Specimens
Access to research specimens or their derivative material by investigators other than those listed as Co-Investigators on the protocol will require, in all cases, approval by the Principal Investigator. The Principal Investigator will evaluate requests for access to these materials by balancing scientific merit and potential impact of the proposed study against the amount of remaining material. The specimens collected through this protocol may be shared with investigators other than those listed as Co-Investigators on the protocol through a Usage Agreement only if such investigators complete the following steps: i) obtain approval by the Principal Investigator; ii) Agree that samples will remain de-identified and that no attempt will be made to identify or contact study participants; iii) that any use of the material beyond that initially discussed with the Principal Investigator requires review and approval by the DFCI, and other applicable IRBs; and iv) that, when relevant, Material Transfer Agreements have been executed.

11.3.2 Data Safety Monitoring and Executive Committees
The activities governed by this protocol do not require oversight by a DSMC.

11.3.3 Data Access Oversight
In addition to the oversight provided by the DF/HCC IRB and DSMC, as described above, data access from the study database will be guided by institutional SOPs. All data access will occur through a secure access layer that authenticates the user. All access will be logged and periodically monitored following institutional SOPs. Investigators from collaborating sites will have the ability to access data containing identifiers from participants enrolled at their own site only.

In some cases data may be shared with investigators other than those listed as Co-investigators on the protocol. Access to data by investigators other than those listed as Co-Investigators on the protocol will require, in all cases, approval by the Principal Investigator. The Principal Investigator will evaluate requests for scientific merit and potential impact of the proposed study. The data collected through this protocol may be shared with investigators other than those listed as Co-Investigators on the protocol through a Usage Agreement only if such investigators complete the following steps: i) obtain approval by the Principal Investigator; ii) Agree that data will remain de-identified and that no attempt will be made to identify or contact study participants; iii) that any
use of the data beyond that initially discussed with the Principal Investigator requires review and approval by the DFCI, and other applicable IRBs; and iv) that, when relevant, Material Transfer Agreements have been executed.

11.4 SPECIMEN PROPERTY RIGHTS

Specimens collected from participants registered at DFCI, BWH, or BCH are the property of those hospitals and will remain at those hospitals even if the staff members who obtained those specimens leave. Specimens submitted by outside institutions continue to be the property of that institution. All FFPE blocks will be returned to the Pathology Department from which they came. Participant-derived materials not depleted by testing, including materials (except the FFPE blocks as noted above) from non-BCH/DFCI/BWH sites, will be banked in the BCH Department of Pathology until the BCH Biorepository opens. If requested, participant-derived materials not depleted by testing will also be returned to the Pathology Department from which the FFPE block was submitted.

12.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 ACCRUAL

The feasibility rule described below requires at most 100 eligible participants or 60 participants if we stop early due to lack of feasibility. Approximately 50 patients with recurrent / refractory solid tumors are evaluated per year the DF/CHCC. Approximately half of these patients receive ongoing care at the DF/CHCC and the other half are seen in consultation. Because additional procedures are not required for enrollment onto the study, we anticipate that the proportion of eligible subjects who consent to enrollment will be about 50% resulting in 25 eligible, enrolled subjects per year at DF/CHCC. The collaborating sites, Columbia, Children’s National Medical Center and the University of California, San Francisco anticipate a combined enrollment of 25 eligible participants per year. Overall, the accrual rate will be 50 participants per year, and enrollment of 100 eligible participants can be completed in about 2 years. Assuming a 5% drop-off to do unevaluable participants (e.g., insufficient pathologic samples) or losing participants to follow-up, it may be necessary to enroll up to 105 participants in order to achieve the 100 eligible participant accrual target.

12.2 DEFINITION OF FEASIBILITY

We anticipate that there will be a proportion of enrolled participants whose tumors can not be profiled because there was less tumor tissue available than was predicted at the time of enrollment or because the quality of the tumor tissue is such that the quality of DNA extracted is not adequate for OncoMap or array CGH. In order to be considered to have sufficient profiling data for an iCat recommendation, participants will need to have either a complete OncoMap result or a complete IHC AND CGH result. Based on prior experience with the assays, 20% of enrolled participants are expected to lack sufficient profiling data for an iCat recommendation. Participants who have insufficient profiling data for an iCat recommendation will be considered technical failures.

OncoMap in other tumor types has identified mutations in up to 20% of cases and when adult tumors are studied as many as 40% of tumors will have expressed alterations. Because large-scale assessment for oncogenic mutations such as is being performed in this study has not been performed in most pediatric solid tumors, it is difficult to estimate the proportion of tumors that will have actionable alterations. We predict that 40% of those tumors that are not technical failures will have an actionable alteration. We further predict that only 50% of the cases with an actionable alteration will have a drug to match the actionable alteration identified.
In summary, we define a participant to be “a candidate to receive iCat” as:

1. Those who have a tumor specimen of sufficient quantity and quality for a complete OncoMap or complete IHC and GCH result, i.e., not a technical failure (80% of eligible participants); AND
2. Those whose tumor has an identified targetable alteration for which it is possible to make an iCat recommendation (40% of participants who are not technical failures); AND
3. Those for whom the targetable alteration has a drug to match (50% of participants with a targetable alteration); AND,
4. Those for whom the iCat recommendation is made within 8 weeks of receipt of results of the last resulted profiling test (without regard for the participant’s life status) (90% of participants with targetable alteration and drug to match).

Thus the predicted proportion of enrolled participants who would be a candidate to receive an iCat recommendation is 14%. We will conclude that iCat is feasible if 14% or more of participants can receive an iCat recommendation.

To estimate the proportion of participants who are “a candidate to receive iCat”, we will use a Simon’s two-stage design.

**Stage 1**: Enroll 60 eligible participants. If less than 6 of the first 60 participants are “candidates to receive iCat” then accrual will be halted and the protocol would be considered to be not feasible. If ≥ 6 out of the first 60 are “candidates to receive iCat”, then accrual will continue in Stage 2.

**Stage 2**: Enroll 40 more eligible participants, for a total of 100. If less than 14 of the 100 participants are “candidates to receive iCat” then the protocol would be considered to be not feasible. If ≥14 out of 100 participants are “candidates to receive iCat”, then the protocol would be considered feasible. This rule has a type 1 error of 6.3% and 92% power to test the null hypothesis that the proportion of “candidates to receive iCat” is ≤9% versus the alternative that it is ≥19%, with a 54% probability of early termination.

**12.3 EFFICACY**

Response will be assessed only in those participants receiving treatment according to the iCat recommendation. Imaging studies to assess response will be performed at the discretion of the treating oncologist. Response will be determined by report from the participants’ treating oncologists via the iCat assessment tool 3 (Section 7.2.2 and Appendix 2). The proportion of participants receiving therapy according to the iCat recommendation with a partial or complete response while receiving therapy based on the iCat recommendation will be determined. The proportion of responders will be compared to the 10% reported response rate in all pediatric phase I trials because the participant population is similar to that enrolled on phase I trials.

**12.4 PATIENT/PARENT PERSPECTIVES**

The perspectives of patients and families regarding tumor genomic testing will be gathered using responses gathered via iCat assessment tools 4 and 5 (Section 7.2.2 and Appendix 2). Due to the small number of subjects enrolled in this study, data collected is expected to be primarily descriptive in nature. When feasible, tests for association will be performed in attempt to ascertain if differences are associated with patient/family hopes and expectations and characteristics such as knowledge of genetics, prognosis, and/or clinical status. Assuming a response rate of 80%, the questionnaire will have 80% power to detect a 15% difference between study subgroups with a confidence interval of 95%.
12.5 ASSESSMENT OF STUDY OBJECTIVES

12.5.1 Primary Objective
Feasibility of making an iCat recommendation will be addressed by the two-stage rule above. In addition, we will place a 95% confidence interval around the proportion of participants who were a candidate to receive iCat.

12.5.2 Secondary Objectives

12.5.2.1 Secondary Objective 1 will be addressed by placing a 95% confidence interval around the proportion of responders on this study. This study’s response rate will be descriptively compared to the historical 10% response rate.

12.5.2.2 Secondary Objective 2 will be addressed by a descriptive comparison of the number and sites of targetable alterations in the diagnostic tumor specimen to those identified in the specimen obtained at the time of relapse/progression.

12.5.2.3 Secondary Objective 3 to determine the spectrum of potentially actionable alterations present in relapsed / refractory solid tumors will be addressed by describing the actionable alterations found in all of the profiled tumors according to histology.

12.5.2.4 Secondary Objective 4, exploration of novel technologies for the identification of targetable alterations will be addressed by performing high-throughput next-generation sequencing of targeted cancer-associated exomes in a subset of tumors as described in Exploratory Tumor Profiling (section 10.0). A descriptive comparison of the difference of actionable mutations identified with OncoMap and sequencing will be reported.

12.5.2.5 Secondary objective 5, will be addressed by a descriptive summary of responses to questions 4 and 5 of iCat assessment tool 1 and by a test of association between each response and demographic, training and practice variables.

12.5.2.6 Secondary Objective 6, assessment of families’ hopes and expectations regarding tumor genomic testing, will be addressed by a descriptive summary of the responses by patients and families to the questions contained in iCat assessment tools 4 and 5. Respondents’ answers about their hopes and expectations for the testing will be compared to those addressing how they felt following the return of results. Frequencies will be analyzed for both, and descriptive comparisons will be reported.

12.5.2.7 Secondary Objective 7, assessment of various associations with these hopes and expectations, will be assessed by tests of association between each response to assessment tools 4 and 5 with characteristics such as demographics, experience with or knowledge of genetics/genomics, patient prognosis, and other clinical factors. Fisher’s exact test will be utilized to analyze the impact of each of these aforementioned characteristics on differences uncovered in respondents’ hopes and expectations regarding tumor genomic testing.
For example, we will use Fisher’s exact test to analyze whether a poor understanding of genetics (defined as incorrect answers to any of the four “Genetic Information” questions on page 3 of assessment tool 4/5)\textsuperscript{25} is associated with unrealistic hopes for tumor genomic testing (defined as those who chose “extremely true” or “very true” to the question “I hoped [the testing] would increase my child’s chance of being cured” on page 8 of assessment tool 4/5).

Similarly, we will also use a similar analysis with Fisher’s exact test to determine whether respondents with less education (defined as those who answered “8\textsuperscript{th} grade or less” as their highest completed level of schooling in question 31 on page 18 of assessment tool 4/5) is associated with unrealistic hopes for tumor genomic testing (defined as above).
REFERENCES


## APPENDIX 1

<table>
<thead>
<tr>
<th>Tyrosine Kinase Inhibitor</th>
<th>Drug</th>
<th>Targets</th>
<th>Pediatric dose</th>
<th>Source of pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imatinib</td>
<td>KIT, BCR-ABL, PDGFR</td>
<td>260 mg/m^2/day (max 600 mg)</td>
<td>Generally accepted dose</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>KIT, PDGFR, VEGF, RET, CSF-1R, FLT-3</td>
<td>15 mg/m^2/dose once daily</td>
<td>Unpublished results Children’s Oncology Group (COG) phase I</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>EGFR</td>
<td>400 mg/m^2/day^22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>EGFR, ERBB2, JAK2V617F (JAK2)</td>
<td>85 mg/m^2/day^18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>BCR-ABL, Src, Lyn, FAK</td>
<td>85 mg/m^2/dose twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
<td>EGFR, ERBB2</td>
<td>900 mg/m^2/dose twice daily</td>
<td></td>
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<tr>
<td></td>
<td>Sorafenib</td>
<td>Raf, PDGFR, VEGFR, Flt-3, KIT</td>
<td>200 mg/m^2/dose Q12 hrs</td>
<td>Unpublished results COG phase I</td>
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<tr>
<td></td>
<td>Pazopanib</td>
<td>VEGFR-1, -2, -3 PDGFR-α, -β, c-Kit</td>
<td>450mg/m2 Daily</td>
<td>Unpublished results COG phase I</td>
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</table>

### Antibodies

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Drug</th>
<th>Pediatric dose</th>
<th>Source of pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>ERBB2</td>
<td>4 mg/kg loading then 2mg/kg weekly</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>EGFR</td>
<td>250 mg/m^2 weekly</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>15 mg/kg Q 3 weeks</td>
</tr>
</tbody>
</table>
iCAT Assessment Tools

iCat assessment tool 1 - Instructions

• Administered to treating oncologists of all patient who agree to MD contact
• Administered once, 1 week after iCat recommendation letter sent

To be put in accompanying letter:

Your responses are an important component of our study. They will help us determine how treating oncologists perceive personalized cancer medicine and an iCat recommendation such as the one your patient, _____, received. Depending on your response you may receive another questionnaire in 3 months.
iCat Assessment Tool 1

Your patient, _____________, is enrolled in the iCat protocol. For this patient:

1. **Who initiated referral for the iCat protocol?**
   - [ ] Patient
   - [ ] Me
   - [ ] Other physician

2. **Did you receive the iCat treatment recommendation letter regarding this patient?**
   - [ ] Yes
   - [ ] No

3. **Did you receive a phone call from an iCat study physician regarding the iCat treatment recommendation for this patient?**
   - [ ] Yes
   - [ ] No

Personalized cancer medicine (PCM) is defined as *treatment based on molecular and other tumor profiling*. PCM is now being considered for use in the treatment of pediatric patients with relapsed / recurrent solid tumors.

4. **Prior to having your patient enrolled in the iCat protocol did you think there was a role for PCM in the treatment of this patient population?**
   - [ ] Yes
   - [ ] No

5. **Now that you have had a patient enroll in the iCat protocol do you think there is a role for PCM in the treatment of this patient population?**
   - [ ] Yes
   - [ ] No

Please turn over to complete remaining questions.
6. To date, has participating in the iCat protocol been helpful for your patient?
   ☐ Yes
   ☐ No

You have almost completed the survey. We would now appreciate if you would tell us a little bit about yourself.

7. Please select your gender:
   ☐ Female
   ☐ Male

8. Please select your race:
   ☐ American Indian or Alaska Native
   ☐ Asian
   ☐ Black or African American
   ☐ Native Hawaiian or Other Pacific Islander
   ☐ White
   ☐ Two or more races

9. Please identify your ethnicity:
   ☐ Hispanic or Latino
   ☐ Not Hispanic or Latino

10. How old are you (please answer in years): _____________________

11. In what year did you graduate from medical school: _____________

12. Please select your degree:
   ☐ MD
   ☐ MD/PhD
   ☐ Other (please identify): _____________

13. Please select your practice setting:
   ☐ located within, or on the campus of an academic medical center
   ☐ affiliated with an academic medical center, but located off-campus
   ☐ not affiliated with an academic center

Thank you for completing our survey.
iCat Assessment Tool 2 - Instructions

- Administered to treating oncologists of patients who receive an iCat recommendation AND agreed to MD contact
- Administered 3 months after iCat recommendation letter sent and every 3 months until treatment according to iCat recommendation initiated or patient death

To be put in accompanying letter:

Thank you for your responses. Your responses are an important component of our study. They will help us determine whether treatment according to an iCat recommendation such as the one your patient, _____, received is practical to implement by treating oncologists. Depending on your response you may receive another questionnaire in 3 months.
iCat Assessment Tool 2

Please answer the questions below about your patient, ______________, enrolled in the iCat protocol.

1. What is the current vital status of your patient:
   □ Dead ➤ Date of Death (mm/dd/yy): _______________
   □ Alive

2. Have you elected to initiate treatment based on the iCat recommendation in the letter dated ______________ during the past 3 months?
   □ Yes ➤ Date of iCat initiation (mm/dd/yy): _______________
   □ No

If no, please tell us why not: (Please check all that apply)
   □ Clinical status of patient makes iCat inappropriate at this time
   □ Disease well controlled on more standard therapy
   □ Disease too advanced
   □ Organ function not adequate
   □ Other: _____________________________________________
   □ I do not feel treatment according to iCat recommendation is appropriate at any point in this patient. Please explain:__________________________________________

Thank you for completing our survey.
iCat Assessment Tool 3 - Instructions

- Administered to treating oncologists of patients who receive treatment based on the iCat recommendation AND agreed to MD contact
- Administered 3 months after treatment according to iCat recommendation initiated and every 3 months until progression, death or treatment termination for another reason

To be put in accompanying letter:

Thank you for your responses. Your responses are an important component of our study. They will help us determine whether treatment according to an iCat recommendation such as the one your patient, _____, received has the potential to impact disease progression. Depending on your response you may receive another questionnaire in 3 months.
iCat Assessment Tool 3

Please answer the questions below about your patient, _____________, enrolled in the iCat protocol.

1. Is this patient still receiving treatment based on the iCat recommendation provided in the iCat recommendation letter dated ____________?
   - □ No
   - □ Yes

   If No, why not: (Please check all that apply)
   - □ Unable to tolerate drug due to toxicities
   - □ Tumor progression → Date of tumor progression: __________
   - □ Patient death → Date of patient death: __________
   - □ Patient choice to terminate drug
   - □ Physician choice to terminate drug
   - □ Other: __________________________

   If No, date treatment according to iCat terminated (mm/dd/yy): ________________

2. During the past 3 months of treatment according to the iCAT recommendation, what was the tumor’s BEST response to treatment?

   Please grade response according to RECIST criteria (provided on reverse)
   - □ Unknown (no staging studies performed)
   - □ Complete response
   - □ Partial response
   - □ Stable disease
   - □ Mixed response
   - □ Progressive disease →

   If progressive disease, please complete the following:
   - Date of progression (mm/dd/yy): ______________
   - Date treatment terminated (mm/dd/yy): ______________

Thank you for completing our survey.
RECIST guidelines for evaluation of Target Lesions

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

**Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

**Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
APPENDIX 3

Initial IHC panel to be performed
- Kit
- PDGFR
- HER-2
- FLT-3
- Ret
- CSF1R
- EGFR
- VEGFR

IHC panel may change depending on antibody availability and performance, basic research discovery, drug and clinical trial availability.
APPENDIX 4: Data and Safety Monitoring Plan (DSMP)

DSMP Table of Contents

1.0 Introduction
   1.1 Purpose
   1.2 Data and Safety Monitoring Plan Components

2.0 General Roles and Responsibilities
   2.1 Protocol Chair
   2.2 Coordinating Center
   2.3 Participating Institution

3.0 Protocol Development
   3.1 Activation of a Protocol
   3.2 Coordinating Center Support Function

4.0 Protocol Management
   4.1 Protocol Distribution
   4.2 Protocol Revisions and Closures
   4.3 Informed Consent Requirements
   4.4 IRB Documentation
   4.5 IRB Re – Approvals
   4.6 Participant Confidentiality and Authorization
   4.7 Participant Registration
   4.8 DF/HCC Multi-center Protocol Case Number
   4.9 DF/HCC Multi-center Protocol Registration Policy
   4.10 Schedule of Data Submission
   4.11 Data Form Review
   4.12 Missing and Deficient Memorandum

5.0 Protocol Violations and Deviations
   5.1 Definitions
   5.2 Reporting Procedures

6.0 Monitoring: Quality Control
   6.1 Ongoing Monitoring of Protocol Compliance
   6.2 Evaluation of Participating Institution Performance

7.0 Auditing: Quality Assurance
   7.1 DF/HCC Sponsored Trials
   7.2 Participating Institution
   7.3 Coordinating Center
   7.4 Substandard Performance
1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 PURPOSE

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations; Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 MULTI-CENTER DATA AND SAFETY MONITORING PLAN COMPONENTS

The Multi-Center Data and Safety Monitoring Plan includes the following components:

**DF/HCC Multi-center Protocol:** One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CHB, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines. The Lead Institution is the home of the Overall PI.

**DF/HCC Contract Principal Investigator:** Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

**Protocol Chair:** The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies.

**Participating Institution:** A Participating Institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The Participating Institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

**Coordinating Center:** In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

**Clinical Trials Office:** The clinical trials offices of the DF/HCC consortium members support investigators and their study teams with the coordination, submission and ongoing conduct of research protocols involving human subjects. Specifically, these offices support four core service areas including; pre-review of PI initiated protocols; assistance in the preparation and management of Investigational New Drug (IND)
applications and subsequent required reporting to the FDA; regulatory consultation and guidance in the interpretation of local, federal, and ICH/GCP guidelines and policies; and the orientation and ongoing training support of clinical research personnel.

**DF/HCC Quality Assurance Office for Clinical Trials:** The DF/HCC QACT is a unit that has been developed to computerize, manage, and QC & QA data and DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to audit DF/HCC trials.

### 2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair, Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

#### 2.1 PROTOCOL CHAIR (DF/HCC PRINCIPAL INVESTIGATOR)

The Protocol Chair, Katherine Janeway, MD, will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling subjects.
- For international trials, assure that the protocol is provided to Participating Institutions in the primary language spoken at the site.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
2.2 COORDINATING CENTER (LEAD INSTITUTION)

The Coordinating Center is the DF/HCC Lead Institution’s study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution, Dana-Farber Cancer Institute, will ensure that all Participating Institutions within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution’s study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of FWA and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Monitor at Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Verify that eligibility has been confirmed by the investigator and that appropriate consent has been obtained.
- Provide auditing services (funding and QACT approval required).

2.3 PARTICIPATING INSTITUTION

Each Participating Institution will provide to the Coordinating Center a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards. The general responsibilities for each Participating Institution are as follows:

- Commit to accrual to the Lead Institution’s (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit deviations and violations to local IRB and the Coordinating Center.
- Secure investigational agents per federal guidelines and protocol requirements.
3.0 PROTOCOL DEVELOPMENT

3.1 ACTIVATION OF PROTOCOL

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting violations and deviations per DFCI IRB guidelines.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify, qualify and initiate Participating Institutions and obtain accrual commitments.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

3.2 COORDINATING CENTER SUPPORT FUNCTION

The DF/HCC Lead Institution’s study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution’s study staff or designee include:

- Maintain Regulatory documents for all Participating Institutions.
- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all Participating Institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all Participating Institutions (conference call, emails, etc)
- Maintain documentation of all communications.
4.0 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Coordinating Center must maintain copies of all IRB approvals, for each Participating Institution.

4.1 PROTOCOL DISTRIBUTION

The Coordinating Center will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

4.2 PROTOCOL REVISIONS AND CLOSURES

The Participating Institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual Participating Institution’s responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating Institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

Protocol Closures and Temporary Holds: Participating Institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

4.3 INFORMED CONSENT REQUIREMENTS

The DF/HCC approved informed consent document will serve as a template for the informed consent from participating institutions. As best a possible, the template should be followed with the specifications outlined in the DF/HCC guidance document on Model Consent Language.

Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Lead Site for their revision prior to submission to the participating site's IRB.
4.4 IRB DOCUMENTATION

The following must be on file with the DF/HCC Lead Institution or designee and must be submitted and approved by the DFCI IRB prior to participant registration:

- Approval Letter of the institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution’s IRB
- IRB approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the DF/HCC Lead Institution their IRB approval for Amendments to a protocol.

4.5 IRB RE-APPROVAL

Annual IRB re-approval from the Participating Institution is required in order to continue research and register participants onto a protocol. There is no grace period for continuing approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution from the Participating Institutions on or before the anniversary of the previous approval date.

4.6 PARTICIPANT CONFIDENTIALITY AND AUTHORIZATION STATEMENT

The HIPPA of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol, the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol Participating Institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.
4.7 PARTICIPANT REGISTRATION

4.7.1 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator, Ian Dumont, via the DF/HCC Quality Assurance for Clinical Trials (QACT) office. Registration must occur prior to shipping any samples to the DF/HCC Lead Institution.

Registration with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday.

**DFCI Study Coordinator Contact Information:**
- Name: Ian Dumont
- Phone: 617-632-5222
- Email: Ian_Dumont@dfci.harvard.edu
- Backup Email: dfcipo_solidtumorreg@dfci.harvard.edu
- Fax: 617-394-2957

4.7.2 Registration Process for Other Participating Institutions

To register a participant at any non DF/HCC site, the subsequent procedure is to be followed.

To register a participant, the following documents should be completed by the research nurse or data manager at the Participating Institution and sent to the DFCI Study Coordinator via one of the two methods listed below.

4.7.2.1 The Participating Institutions’ research nurse or data manager should contact the DFCI Study Coordinator via telephone or email (see section 4.7.1 for contact information) to complete the following:
- Notify the DF/HCC Lead Institution of the pending registration;
- Verify the study’s status;
- Confirm the method (i.e., email vs. fax) of sending documents for the registration;
- Communicate the desired timeline of the registration

4.7.2.2 The Participating Institutions’ research nurse or data manager should then send the following documents via **email (preferred)** or fax to the DFCI Study Coordinator (see section 4.7.1 for contact information):
- Signed study consent form
- HIPAA authorization form (if separate from the informed consent document at your site)
- Eligibility checklist

4.7.2.3 The DFCI Study Coordinator will review the received documents to verify eligibility and will notify the Participating Institution of receipt via email.

4.7.2.4 The DFCI Study Coordinator will register the participant with QACT and will notify the Participating Institution of the successful registration via email which will include the following:
- Participant study number;
- Sample shipment deadline (10 business days after registration, see below);
Following registration, participating sites should submit samples within 10 business days if at all possible (see Appendix 5 for details). Issues that would cause a delay should be discussed with the DFCI Study Coordinator. If a participant does not have enough tissue to satisfy the study’s requirements, the participant’s protocol status must be changed. The DFCI Study Coordinator should be notified of participant status changes as soon as possible.

4.8 DF/HCC MULTI-CENTER PROTOCOL CASE NUMBER

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

4.9 DF/HCC MULTI-CENTER PROTOCOL REGISTRATION POLICY

4.9.1 Biospecimen collection:
Participants must be registered with the DF/HCC QACT before biospecimens are submitted. Specimens may not be submitted until the Participating Institution receives a faxed or e-mailed copy of the participant’s Registration Confirmation memo from the DF/HCC QACT. Specimens must be submitted per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy.

4.9.2 Eligibility Exceptions:
The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. In addition, the Cancer Therapy Evaluation Program (CTEP) specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. The DF/HCC QACT requires each institution to fully comply with this requirement.

4.9.3 Verification of Registration:
A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Specimens may not be submitted until the site receives a faxed or e-mailed copy of the registration confirmation memo.

4.9.4 Confidentiality:
All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant’s full name & social security number “blacked out” and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

4.10 SCHEDULE OF DATA SUBMISSION

The DF/HCC QACT develops a set of electronic case report forms, (eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study.
4.10.1 Eligibility Checklist:

**Purpose** - Outlines protocol-specific eligibility criteria and includes the following:
- Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)
- Parameters for eligibility
- Parameters for exclusion
- Parameters for stratifications

4.10.2 On-study Form(s):

**Purpose** – Documents the following items:
- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant’s physical status at protocol registration
- Disease site specific data

4.10.3 Baseline Assessment Form(s):

**Purpose** – Documents objective and subjective disease status as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.11 DATA FORM REVIEW

When data forms arrive at the DF/HCC QACT, they are reviewed for:

**Completeness**: Is all the information provided as required per protocol?

4.12 MISSING AND DEFICIENT MEMORANDUM

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

**Incomplete or Questionable Data**

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

**Missing Forms**

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.
5.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms “protocol violation” or “protocol deviation.” All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all Institutions Participating in the DF/HCC Multi-center Protocol.

5.1 DEFINITIONS

**Protocol Deviation:** Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

**Protocol Exception:** Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a subject who does not meet all inclusion/exclusion criteria.

**Protocol Violation:** Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

5.2 REPORTING PROCEDURES

**The Protocol Chair:** is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

**Participating Institutions:** Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the Participating Institution’s own IRB, per its institutional policy.

A copy of the Participating Institution’s IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

**Coordinating Center:** Upon receipt of the violation/deviation report from the Participating Institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the Participating Institution’s IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.
6.0 MONITORING: QUALITY CONTROL

Although the activities governed by this protocol do not constitute a therapeutic clinical trial, the complexity of this effort merits a quality control process providing verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality control oversight for the DF/HCC Multi-center Protocol.

6.1 ONGOING MONITORING OF PROTOCOL COMPLIANCE

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

The DF/HCC Lead Institution will implement monitoring activities ongoing to ensure that Participating Institutions are complying with regulatory and protocol requirements and data quality. DF/HCC will perform virtual monitoring of each Participating Institution on an on-going basis. Monitoring will include but not be limited to: eligibility requirements (including source documents verifying eligibility), timely and accurate data submission, timely specimen submission, and regulatory records for the study.

Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, regulatory records and site trial master files, and data management. There will be regular and ongoing communication with the Participating Institutions about study related information that may include: Participation in regular Lead Institution initiated teleconferences, distribution of communications highlighting overall protocol progress and important announcements, and collecting source documents from Participating Institutions, at specific data points, that support the primary and or secondary endpoints.

For all study-wide teleconferences, attendance will be taken; minutes will be kept and distributed by the Lead Institution.

Monitoring will occur before the protocol begins and will continue during protocol performance through study completion.

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution’s Coordinators, the Principal Investigators, and the Protocol Chair.

6.2 EVALUATION OF PARTICIPATING INSTITUTION PERFORMANCE

6.2.1 Eligibility Checklist:

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.
6.2.2 Accrual of Eligible Participants:

Annual accrual rates for eligible participants enrolled onto the study will be calculated for each institution and will be compared to the anticipated accrual rate.

7.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. The main focus in auditing is to measure if the standards and procedures set are being followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the Code of Federal Regulations.

7.1 DF/HCC SPONSORED TRIALS

Each participating site that accrues at least 3 subjects will be audited once (virtually) by the QACT. Additional audits may be required if there are concerns or findings of significant non-compliance and/or at the discretion of the DF/HCC Lead Institution.

7.2 PARTICIPATING INSTITUTION

It is the Participating Institution’s responsibility to notify the DF/HCC Lead Institution of all scheduled audit dates and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

7.3 LEAD INSTITUTION

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

7.4 SUB-STANDARD PERFORMANCE

The Protocol Chair, DFCI IRB, is charged with considering the totality of an institution’s performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

7.4.1 Corrective Actions:

Participating Institutions that fail to meet the performance goals of submission of timely accurate data, adherence to protocol requirements, and compliance with state, federal, and Good Clinical Practice guidelines, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures.
Participating Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.
APPENDIX 5: Specimen Handling Manual

Specimens will obtained and delivered to the appropriate clinical research staff at DFCI as specified below:

Table 1. Specimen delivery

<table>
<thead>
<tr>
<th>Sample</th>
<th>Collection</th>
<th>DFCI</th>
<th>Collaborating sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE tumor specimen</td>
<td>N/A</td>
<td>Notify clinical research staff who will communicate with Boston Children’s Hospital Department of Pathology.</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>10 ml or 1 ml/kg whichever is less in EDTA/purple top tube</td>
<td>Send to Boston Children’s Hospital Department of Laboratory Medicine</td>
<td>Send via FedEx <strong>Priority</strong> Overnight* to: Erin Parker (617) 632-5222 Dana-Farber Cancer Institute 1 Jimmy Fund Way, DA 155F** Boston, MA 02115 FedEx Account #: 1281-7790-6 Billing Reference #: 9617433</td>
</tr>
<tr>
<td>Bone Marrow (requested)</td>
<td>2 x 2 ml in EDTA/purple top tube</td>
<td>Send to Boston Children’s Hospital Department of Laboratory Medicine</td>
<td></td>
</tr>
<tr>
<td>Fluid (requested)</td>
<td>2 x 10 ml in sterile collection tube</td>
<td>Send to Boston Children’s Hospital Department of Laboratory Medicine</td>
<td></td>
</tr>
</tbody>
</table>

*All packages must be sent **Priority** Overnight. If First Overnight is selected, shipping charges may be reversed to the submitting institution.
**Room number (DA 155F) must be included on the FedEx airbill to ensure timely receipt of samples.
Clinical research personnel will hand deliver specimens to the respective DFCI, BCH and BWH Departments and labs for processing as specified in Table 2 below. In the event samples are sent to outside institutions for testing, they will be processed and shipped according to the policies and procedures of the facility conducting the testing:

Table 2. Specimen distribution

<table>
<thead>
<tr>
<th>Sample</th>
<th>Lab delivery</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE tumor specimen (block or unstained slides)</td>
<td>BCH Pathology</td>
<td>Mark slides for mutation detection and copy number analysis then transfer to BWH CAMD for mutation detection and laboratory conducting copy number analysis</td>
</tr>
<tr>
<td>Blood</td>
<td>Claritas Genomics, or Other CLIA certified lab</td>
<td>DNA for copy number analysis</td>
</tr>
<tr>
<td>Bone Marrow specimen 1</td>
<td>BWH CAMD</td>
<td>DNA for mutation detection</td>
</tr>
<tr>
<td>Bone marrow specimen 2</td>
<td>Claritas Genomics, or Other CLIA certified lab</td>
<td>DNA for copy number analysis</td>
</tr>
<tr>
<td>Fluid specimen 1</td>
<td>BWH CAMD</td>
<td>DNA for mutation detection</td>
</tr>
<tr>
<td>Fluid specimen 2</td>
<td>Claritas Genomics, or Other CLIA certified lab</td>
<td>DNA for copy number analysis</td>
</tr>
</tbody>
</table>
Appendix 6
Letter To Treating Oncologist (Assessment Tool 1):

Dear Dr. ________:

As you may know, your patient [ ] is enrolled in a research study, “Individualized Cancer Therapy (iCat) Recommendation for Patients with Recurrent, Refractory, or High Risk Solid Tumors.” This study is being conducted at Dana Farber / Children’s Hospital Cancer Center, Children’s National Medical Center, Columbia University Medical Center, and the UCSF Benioff Children’s Hospital.

This research study is evaluating the feasibility of using tumor profiling to identify actionable alterations and make an individualized cancer therapy (iCat) recommendation in patients with recurrent, refractory, or high risk solid tumors. In this study, tumor profiling consists of mutation testing with a test called OncoMap\(^1\), copy number analysis with array CGH (aCGH), and, in some cases, determination of protein expression with immunohistochemistry (IHC).

When consented, your patient gave their permission for us to communicate with their primary oncologist about the tumor profiling results, the iCat recommendation and, their clinical status. You are receiving this letter because the patient identified you as the primary oncologist. You are invited to participate in this research study as well. In order to better understand physician and patient perceptions of this type of research, we would like to ask you to complete the attached brief one-page survey. Responses to this survey will help us with a secondary study objective in which we will evaluate whether age, race, gender, training and background information impact perceptions of individualized cancer therapy. A secondary objective of this study is to determine the response rate in participants with recurrent / refractory solid tumors receiving therapy based on an iCat recommendation. In order to do this, we will ask treating oncologists of those patients who received an iCat recommendation to complete surveys approximately every 3 months. We understand that your time is valuable and so we plan to include a gift card with the first of these surveys as a token of appreciation for your participation.

Participation in this study is voluntary. You do not have to take part. You may choose not to answer part or all of this questionnaire or any additional questionnaires you receive related to this study. We will not share any of your answers to questions with this child’s parent, and all of your answers will be confidential. They will not go in this child’s medical record. All information will be kept in locked cabinets and computer files. Only the investigators in this study will have access to patients’, parents’, and providers’ names. Your name will not appear in any reports or publications about this study. This study has been approved by the Institutional Review Board, a committee at Dana-Farber/Harvard Cancer Center that is responsible for overseeing research with patients. The Institutional Review Board may be reached at 617-632-3029.

We have enclosed a copy of the questionnaire. If you decide to participate in this study, you may complete this questionnaire and return it to us. If you decide not to participate in this study you may simply not respond to this questionnaire, future reminders and future questionnaires. If you wish to avoid receiving reminders and questionnaires about this patient in the future, please write a brief note indicating your desire to not participate in the survey portion of this study on the enclosed questionnaire and return it to us in the enclosed envelope. You may contact me (617-632-4994) with any questions about participating in this study. Thank you for your help.
Sincerely,
Katherine A. Janewsay, MD, MMSc
Appendix 7:
Letter To Treating Oncologist (Assessment Tool 2):

Dear Dr. __________,

You patient, __________, is participating in a non-therapeutic research study based at Dana Farber/Harvard Cancer Center in Boston, MA. This study works to identify actionable alterations in your patient’s tumor via state-of-the-art tumor profiling techniques. Your patient has consented to our contacting you, the treating oncologist. We have already sent you a formal individualized cancer therapy (iCat) recommendation, and a previous survey or surveys. Thank you for your response to the previous survey(s).

You are receiving this additional survey because we would like to understand whether treatment according to an iCat recommendation such as the one your patient received is practical to implement by treating oncologists. This survey will take approximately 10 minutes to complete. Thank you for your responses, they are an important component of our study. Depending on your response you may receive another questionnaire in 3 months.

Participation in this study is voluntary. You do not have to take part. You may choose not to answer part or all of this questionnaire or any additional questionnaires you receive related to this study.

Sincerely,

Katherine A. Janeway, MD
Principal Investigator
Appendix 8:
Letter To Treating Oncologist (Assessment Tool 3):

Dear Dr. __________,

You patient, __________, is participating in a non-therapeutic research study based at Dana Farber/Harvard Cancer Center in Boston, MA. This study works to identify actionable alterations in your patient’s tumor via state-of-the-art tumor profiling techniques. Your patient has consented to our contacting you, the treating oncologist. We have already sent you a formal individualized cancer therapy (iCat) recommendation, and a previous survey or surveys. Thank you for your response to the previous survey(s).

You are receiving this additional survey because we would like to understand whether treatment according to an iCat recommendation such as the one your patient received has the potential to impact disease progression. This survey will take approximately 10 minutes to complete. Thank you for your responses, they are an important component of our study. Depending on your response you may receive another questionnaire in 3 months.

Participation in this study is voluntary. You do not have to take part. You may choose not to answer part or all of this questionnaire or any additional questionnaires you receive related to this study.

Sincerely,

Katherine A. Janeway, MD
Principal Investigator
Dear Dr. [Blank],

As you may know, your patient [Blank], is enrolled in a research study, “Individualized Cancer Therapy (iCat) Recommendation for Patients with Recurrent, Refractory, or High Risk Solid Tumors.” This study is being coordinated by the Dana-Farber / Children’s Hospital Cancer Center. In addition to Dana-Farber / Children’s Hospital Cancer Center, this study is being conducted at Children’s National Medical Center, Columbia University Medical Center, and the UCSF Benioff Children’s Hospital.

This research study is evaluating the feasibility of using tumor profiling to identify actionable alterations and make an individualized cancer therapy (iCat) recommendation in patients with recurrent, refractory, or high risk solid tumors. In this study, tumor profiling consists of mutation testing with a test called OncoMap®, copy number analysis with array CGH (aCGH), and, in some cases, determination of protein expression with immunohistochemistry (IHC).

When consented, your patient gave their permission for the tumor profiling results and iCat recommendation to be communicated with their primary oncologist. You are receiving this letter because the patient identified you as the primary oncologist. The purpose of this letter is to communicate the results of the tumor profiling as well as the iCat recommendation and to inform you about future study-related activities. If you believe you are identified as the primary oncologist in error, please let us know (contact information is at the end of this letter).

Newly diagnosed: At the time of enrollment, your patient had a newly diagnosed, high-risk solid tumor. Consequently, by study protocol, tumor profiling results and iCat recommendation will NOT be released at this time. This is because we believe that the tumor profiling results and iCat recommendation would not affect your patient’s initial treatment. The tumor profiling results will be shared with you if the patient’s cancer recurs, is refractory to standard treatment, or when 3 years have passed.

Inadequate tissue: Tumor profiling requires a substantial amount of viable tumor material. In this research study we are only able to utilize tumor material obtained for diagnostic or therapeutic purposes (i.e., we are not able to perform a biopsy for research purposes). For your patient, it was not possible to perform tumor profiling due to inadequate tumor tissue. The tumor specimens evaluated were: [Blank] and [Blank].

If you believe the patient has viable tumor tissue available from a different biopsy or surgery performed for clinical purposes, please let us know (contact information is at the end of this letter).

Adequate tissue: Tumor profiling requires a substantial amount of viable tumor material. In this research study we are only able to utilize tumor material obtained for diagnostic or therapeutic purposes (i.e., we are not able to perform a biopsy for research purposes). For your patient, we were able to identify sufficient viable tumor material to attempt tumor profiling. The tumor specimens utilized for tumor profiling were: [Blank] and [Blank].

Technical performance: In some cases even when there is adequate viable tumor tissue, tumor profiling tests fail to produce results for technical reasons such as poor quality DNA.

The technical performance of the profiling tests for your patient’s tumor specimens are in the table below:

| Specimen | OncoMap | aCGH | IHC | Other:
<table>
<thead>
<tr>
<th></th>
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</tbody>
</table>

Key: S = Successful || F = Failed || ND = not done

Process for Making an iCat Recommendation
In this study, an expert panel consisting of pediatric oncologists, pathologists, molecular biologists, developmental therapeutics experts and cancer biologists review the tumor profiling results and determine whether there is a cancer-causing or actionable alteration present in your patient’s tumor. If there is an actionable alteration identified, the panel determines whether there is a targeted drug available that could potentially be active against that alteration. This assessment of alterations and drug availability forms the basis of the iCat recommendation. In making an iCat recommendation the expert panel also takes into consideration the type of alteration present (mutation vs. copy number alteration), the activity of the drug against the particular target identified, available drug formulations, prior therapies received, patient age and availability of data regarding pediatric dosing and availability of pediatric clinical trials of novel agents.

No actionable alteration: No actionable alterations were identified in your patient’s tumor. This result does not guarantee that your patient’s tumor lacks actionable alterations. The tumor profiling performed as part of this study does not assess the tumor for every possible actionable alteration. In addition, false negative results are possible.

Actionable alteration: The following actionable alterations were identified:

<table>
<thead>
<tr>
<th>Specimen</th>
<th>OncoMap</th>
<th>aCGH</th>
<th>IHC</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Previously known alteration: The expert panel recognizes that this alteration was known prior to the tumor profiling performed for this study. The tumor profiling performed for this study did confirm the presence of this alteration by an additional method (______).

No iCat recommendation: The expert panel was unable to make an iCat recommendation for your patient. This occurred either because there was no actionable alteration identified in your patient’s tumor or because there was no targeted therapy available that the expert panel felt would be appropriate to use to try to counteract the actionable alteration identified in your patient’s tumor.

iCat recommendation: The following iCat recommendation can be made for your patient based on the results of the tumor profiling performed in this study.

This iCat recommendation was designated as a Tier ____ recommendation.

Whether to administer treatment based on this iCat recommendation is a clinical decision and is outside the scope of the current research study. As research investigators, we believe clinical decisions are best made by clinicians most familiar with the patient. Consequently, we are communicating the tumor profiling results and iCat results with you rather than directly to your patient. If, after speaking with your patient about the profiling results and iCat recommendation, you have questions we would be happy to speak with you to answer those questions.

Before electing to proceed with treatment according to the iCat recommendation it is important that you understand some limitations of the tumor profiling tests and the iCat recommendation. OncoMap, aCGH and IHC were performed in CLIA or CAP certified laboratories but these tests are not yet validated to be predictive of response to therapy targeting an identified actionable alteration. As the treating oncologist you may elect to perform validated tests to confirm the tumor profiling results contained in this letter. The tumor profiling was performed on a small portion of tumor from your patient. There is known to be heterogeneity between tumors in an individual patient and even within a single tumor mass. Therefore, the tumor profiling results provided in this letter may not be reflective of the genome of the entire tumor burden in your patient. Using tumor profiling as a
basis for a treatment recommendation is unproven. In particular, it is not known whether this approach is superior to standard care. The understandings of cancer biology, of drug activity, and of drug toxicities change over time as do the patient factors taken into consideration in making the iCat recommendation. Consequently, the expert panel is not able to predict whether an iCat recommendation made now will still be reasonable at a future time.

**Future study-related activities:**
In order to better understand physician and patient perceptions of this type of research, you will receive a brief one-page survey in approximately 2 weeks. A secondary objective of this study is to determine the response rate in participants with recurrent/refractory solid tumors receiving therapy based on an iCat recommendation. In order to do this, we will ask treating oncologists of those patients who received an iCat recommendation to complete surveys approximately every 3 months. We understand that your time is valuable and so we plan to include a gift card with the first of these surveys.

Please contact a member of the iCat team if you would like to provide additional feedback about this experience.

On behalf of the iCat Expert Panel (listed in full on the following page),

**Dr. XYZ**  
*Primary Reviewer*

Brian Crompton, MD,  
*Instructor in Pediatrics, Harvard Medical School*  
*Associate Physician, Pediatric Oncology, Dana-Farber/Children’s Hospital Cancer Center*  
*Principal Investigator, iCat Protocol (DFCI #11-406)*

**Please contact the Study Coordinator with Questions/Comments:**  
Erin P. Parker  
*Phone: 617-632-5222*  
*Email: erinp_parker@dfci.harvard.edu*
Expert Panel Members:

Lisa Diller, MD  
Professor of Pediatrics, Harvard Medical School  
Director of Clinical Services, Dana-Farber Children’s Hospital Cancer Center

Steven Dubois, MD, MS  
Associate Professor of Pediatrics, UCSF  
Site Principal Investigator, UCSF Benioff Children’s Hospital

Julia Glade-Bender, MD  
Associate Professor of Clinical Pediatrics, Columbia University  
Site Principal Investigator, Columbia University Medical Center

Todd Golub, MD  
Professor of Pediatrics, Harvard Medical School  
Chief Scientific Officer and Cancer Program Director, Broad Institute

Marian Harris, MD, PhD  
Instructor in Pathology, Harvard Medical School  
Boston Children’s Hospital

Katherine A. Janeway, MD, MMSc  
Assistant Professor of Pediatrics, Harvard Medical School  
Associate Physician, Pediatric Oncology, Dana-Farber / Children’s Hospital Cancer Center  
Principal Investigator

AeRang Kim, MD, PhD  
Assistant Professor of Pediatrics, The George Washington School of Medicine  
Site Principal Investigator, Children’s National Medical Center

Neal Lindeman, MD  
Associate Professor of Pathology, Harvard Medical School  
Director, Center for Advanced Molecular Diagnostics, Brigham and Women’s Hospital

Laura MacConaill, PhD  
Senior Scientist, Harvard Medical School  
Scientific Director, Center for Cancer Genome Discovery, Dana-Farber Cancer Institute

Carlos Rodriguez-Galindo, MD  
Associate Professor of Pediatrics, Harvard Medical School  
Director, Solid Tumor Program, Dana-Farber / Children’s Hospital Cancer Center

Barrett Rollins, MD, PhD  
Linde Family Professor of Medicine, Harvard Medical School  
Chief Scientific Officer, Dana-Farber Cancer Institute

Suzanne Shusterman, MD  
Assistant Professor of Pediatrics, Harvard Medical School  
Associate Physician, Pediatric Oncology, Dana-Farber / Children’s Hospital Cancer Center

Kimberly Stegmaier, MD  
Assistant Professor of Pediatrics, Harvard Medical School  
Associate Physician, Pediatric Oncology, Dana-Farber / Children’s Hospital Cancer Center
iCat recommendation tiers:

Tier 1: Alteration in a tumor type for which there is clinical trial data demonstrating a benefit for targeted therapy in patients with the same tumor and an alteration in the same gene.

- Tier 1 A: The observed alteration has previously been reported in the same tumor.
- Tier 1 B: The observed alteration has not previously been reported in the same tumor but can be expected to produce the same biologic effect as the alterations seen in those patients with clinical benefit.

Examples:
1) Recommendation for vemurafenib in patient with melanoma with V600E mutation (Tier 1A)
2) Recommendation for imatinib in GIST patient with mutation in kinase domain of KIT gene (even if exact mutation has not previously been demonstrated to confer oncogenesis / sensitivity to imatinib) (Tier 1B)
3) Recommendation for crizotinib in patient with IMT and ALK translocation. (Tier 1A)

Tier 2: Alteration in a tumor type for which there is clinical trial data demonstrating a benefit for targeted therapy in patients with a different tumor and an alteration in the same gene.

- Tier 2A: The observed alteration has previously been reported in the tumor type in which clinical benefit has been seen.
- Tier 2B: The observed alteration has not previously been reported but can be expected to produce the same biologic effect as the alterations seen in those patients with clinical benefit.

Examples:
1) Recommendation for vemurafenib in patient with embryonal rhabdomyosarcoma with V600E mutation (Tier 2A)
2) Recommendation for imatinib in osteosarcoma patient with mutation in kinase domain of KIT gene (even if exact mutation has not previously been demonstrated to confer oncogenesis / sensitivity to imatinib) (Tier 2B)
3) Recommendation for crizotinib in a patient with metastatic paraganglioma and ALK translocation. (Tier 2A)
4) Recommendation for Trastuzumab in a patient with osteosarcoma and ERBB2 gene amplification (Tier 2A)

Tier 3: Alteration in a tumor type for which there is published, presented or in press pre-clinical data demonstrating a benefit for targeted therapy in models of the same tumor and an alteration in the same gene. The observed alteration in the iCat enrolled patient should be expected to produce the same biologic effect as the alterations seen in those models with clinical benefit.

Examples:
1) Recommendation for bromodomain inhibitor in a patient with neuroblastoma with MYCN amplification
2) Recommendation for Met inhibitor in patient with MITF family tumor and high c-Met expression by IHC

Tier 4: Alteration in a tumor type for which there is published, presented or in press pre-clinical data demonstrating a benefit for targeted therapy in models of a different tumor and an alteration in the same gene. Gene expression alone is not sufficient to declare alteration in this Tier. The observed alteration in the iCat enrolled patient should be expected to produce the same biologic effect as the alterations seen in those models with clinical benefit.

Examples:
1) Recommendation for bromodomain inhibitor in a patient with EWS with MYCN amplification
2) Recommendation for beta-catenin inhibitor in patient with adrenal cortical carcinoma.

Tier 5: Anything else the Expert panel thinks is sufficient to qualify for iCat recommendation
iCat Assessment Tool 4

Parents’ Perspectives on Genomic Data and Individualized Cancer Therapy

Jonathan Marron, MD
Pediatric Hematology/Oncology
Dana-Farber/Boston Children’s Cancer and Blood Disorders Center
This questionnaire includes many questions about your child, his/her cancer diagnosis, and your experiences so far with the iCat research study, a study looking at specialized genetic testing of pediatric tumors. Some of these questions may seem more important to you than other questions, but please do your best to answer as many of the questions as possible. All of your responses will be kept confidential. Your child’s oncologist will NOT be given any information about your answers to this questionnaire.

The purpose of this questionnaire is to help doctors and scientists learn about families’ experiences with genetic testing of their child’s tumor as well as how families respond to hearing the test results. The information from this study will help oncologists understand more about families’ perspectives on testing like this and to better care for children like yours in the future.
Experience with Genetics and Genetic Testing

Please answer the following questions about your personal experience with genetics and genetic testing.

1. Other than the testing that was done for this research study, have you or anyone in your immediate family ever undergone genetic or genomic testing?
   - Yes
   - No
   - I am not sure

2. Do you have regular exposure to genetics or experience with genetics and/or genetic information (such as a job in genetics or a similar field)?
   - Yes
   - No

3. Have you ever taken any classes (such as in high school or college) on genes or genetics, or have you been to any talks or lectures on genes or genetics?
   - Yes
   - No

Genetic Information

We are hoping to learn more about what families understand about genetics and genetic information. For each of the following statements about genetics, please indicate whether you feel the statement is true or false by circling the appropriate response.

<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once a genetic marker for a disorder is identified in a person, the disorder can be prevented or cured.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a person has a genetic marker for a disorder, the person will always get the disorder.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only mothers can pass on genetic disorders.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People who have a genetic marker for a disease are unhealthy.</td>
<td></td>
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</tr>
</tbody>
</table>
Patient Cancer Information

Please answer the following questions about your child’s cancer and your child’s cancer treatment.

4. Is your child currently receiving treatment for his/her cancer?
   - Yes
   - No

5. How would you rate your child’s current state of overall health?
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor

6. How likely do you feel that your child is to be cured of his/her cancer?
   - Very likely to be cured (Greater than 80%)
   - Likely to be cured (60-80%)
   - Possible to be cured (40-59%)
   - Unlikely to be cured (20-39%)
   - Very unlikely to be cured but still possible (Less than 20%)
   - No chance of cure

7. What do you think your child’s chance of being cured of his/her cancer is, compared to other children with the same cancer diagnosis?
   - My child’s chance of being cured is much greater than other children with the same diagnosis.
   - My child’s chance of being cured is somewhat greater than other children with the same diagnosis.
   - My child’s chance of being cured is about the same as other children with the same diagnosis.
   - My child’s chance of being cured is somewhat less than other children with the same diagnosis.
   - My child’s chance of being cured is much less than other children with the same diagnosis.
Understanding of Testing and Purpose of Testing

We are trying to understand how well families understand the purpose of testing tumors for genetic changes ("mutations"). Please think back to when you enrolled on the iCat research study, and answer the following questions about your thoughts about the study and what you expected from it.

8. Do you remember signing up to participate in the iCat research study to test your child’s tumor for changes in its genes ("mutations")?
   - Yes
   - No

9. How well do you remember the conversation(s) you had with your child’s doctor about the iCat research study and the genetic testing involved in it?
   - Extremely well
   - Well
   - Moderately
   - Poorly
   - Extremely poorly

10. How well did you understand the information you were told about this research study and the genetic testing involved in it?
    - Extremely well
    - Well
    - Moderately
    - Poorly
    - Extremely poorly
Understanding of Testing and Purpose of Testing (continued)

11. When you first agreed to participate in this research study, how likely did you think it was that the genetic testing of your child’s tumor would show that there was a change in the genes ("mutation")?

☐ Very likely to find a mutation
☐ Likely to find a mutation
☐ Somewhat likely to find a mutation
☐ Unlikely to find a mutation
☐ Very unlikely to find a mutation

12. When you first agreed to participate in this research study, how likely did you think it was that the genetic testing of your child’s tumor would find a change in the genes ("mutation") that would suggest a new treatment option for your child?

☐ Very likely to suggest a new treatment or medicine
☐ Likely to suggest a new treatment or medicine
☐ Somewhat likely to suggest a new treatment or medicine
☐ Unlikely to suggest a new treatment or medicine
☐ Very unlikely to suggest a new treatment or medicine

13. If the results from the genetic testing of your child’s tumor showed that there WAS a change in the genes ("mutation") that suggested a new treatment option, how did you think this would change your child’s chances of being cured?

☐ Much more likely to be cured
☐ Slightly more likely to be cured
☐ No change
☐ Slightly less likely to be cured
☐ Much less likely to be cured

14. If the results from the genetic testing of your child’s tumor showed that there WAS NOT a change in the genes ("mutation") that suggested a new treatment option, how did you think this would change your child’s chances of being cured?

☐ Much more likely to be cured
☐ Slightly more likely to be cured
☐ No change
☐ Slightly less likely to be cured
☐ Much less likely to be cured
Understanding of Testing and Purpose of Testing (continued)

Please think back to when you enrolled on the iCat research study and what you understood about the research study at that time. For each of the following, please indicate whether you agree with the statement, disagree with the statement, or are unsure about the statement by circling the appropriate response.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Disagree</th>
<th>Unsure</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>By participating in this study, I was helping doctors and scientists learn information that may benefit my child.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>By participating in this study, I was helping doctors and scientists learn information that may benefit future cancer patients.</td>
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<tr>
<td>The main reason this study was done was to improve the treatment of my child.</td>
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<tr>
<td>The main reason this study was done was to improve the treatment of future cancer patients.</td>
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<tr>
<td>There may not have been direct medical benefit to my child from participating in this study.</td>
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<tr>
<td>I can be sure that participating in this study provided my child the best chance of cure.</td>
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<tr>
<td>Participating in this study means that new treatments may be suggested that could be helpful in treating my child’s cancer.</td>
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<tr>
<td>Treatment recommendations from this study are certain to be effective for children that receive them.</td>
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<tr>
<td>Any treatment recommendations from this study are standard for my child’s type of cancer.</td>
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<tr>
<td>All children participating in this research study received a treatment recommendation.</td>
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</tbody>
</table>
Hopes for Testing

*Please indicate how much you agree with the following statements about why you chose to participate in this research study. Choose how true each statement was for you at the time you signed up to take part in the iCat research study.*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>I hoped it would increase my child’s chance of being cured.</td>
<td></td>
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<tr>
<td>I hoped that doing this testing would provide me with peace of mind.</td>
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<tr>
<td>I hoped it would help find cures for future patients.</td>
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<tr>
<td>I hoped it would help provide information to me and my child’s doctor about my child’s cancer.</td>
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<tr>
<td>I hoped it would teach me about my child’s genes.</td>
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<tr>
<td>I hoped it would teach me about my family’s genes.</td>
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<tr>
<td>I hoped it would give my child a greater number of treatment options.</td>
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<tr>
<td>I hoped to help doctors and scientists learn more about the genes involved in cancer.</td>
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<tr>
<td>My doctor recommended the study.</td>
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<tr>
<td>Participating in this research study gave me hope for my child.</td>
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<tr>
<td>I did not expect any benefit to my child or my family from this research.</td>
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</tbody>
</table>
Hopes for Testing (continued)

Please answer the following questions about the hopes and expectations you had at the time you enrolled in this research study.

15. Who did you expect to benefit most from the genetic testing of your child’s tumor? Please choose one.
   - My child
   - Me and my family members
   - Future patients
   - Doctors and scientists
   - Other (please specify: ________________________________)

16. Which of the following did you MOST HOPE WOULD HAPPEN because of your participation in this research study? Please choose only one.
   - My child would have a better chance of being cured.
   - Doing this testing would give me peace of mind.
   - Doctors would be better able to find cures for future patients.
   - My doctors would be able to learn more about my child’s cancer.
   - I would learn about my child’s genes.
   - I would learn about my family’s genes.
   - My child would have a greater number of treatment options.
   - I did not hope anything would happen as a result of this research.
   - Other (please specify: ________________________________)

17. Which of the following did you think was MOST LIKELY TO HAPPEN because of your participation in this research study? Please choose only one.
   - My child would have a better chance of being cured.
   - Doing this testing would give me peace of mind.
   - Doctors would be better able to find cures for future patients.
   - My doctors would be able to learn more about my child’s cancer.
   - I would learn about my child’s genes.
   - I would learn about my family’s genes.
   - My child would have a greater number of treatment options.
   - I did not think anything was likely to happen as a result of this research.
   - Other (please specify: ________________________________)


### Concerns about Testing

Please indicate how much you agree with each of the following statements about concerns you had about participating in this research study. Choose how true each statement was for you at the time you signed up to take part in the iCat research study.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>I worried that I would learn information about my child’s cancer that would be stressful or cause anxiety.</td>
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<tr>
<td>I worried that I would learn information about my child’s genes that would be stressful or cause anxiety.</td>
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</tr>
<tr>
<td>I worried that I would learn information about myself or my family that would be stressful or cause anxiety.</td>
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<tr>
<td>I worried that I would learn that my child’s cancer was less treatable or more aggressive than previously thought.</td>
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<tr>
<td>I worried that the information learned in this research study would not be kept private.</td>
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<tr>
<td>I worried that the information learned could have hurt my family’s ability to get insurance.</td>
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<tr>
<td>I worried that the information learned could have hurt my family’s ability to get or keep a job.</td>
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<tr>
<td>I worried that the results would take a long time to come back.</td>
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<tr>
<td>I worried that no new information would be found to help my child, causing me and my family to be disappointed.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I did not have any worries or concerns about this research.</td>
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</tbody>
</table>
Concerns about Testing (continued)

Please answer the following questions about the concerns you had at the time you enrolled in this research study.

18. Which of these statements best describes which you MOST WORRIED WOULD HAPPEN because of your participation in this research study? Please choose only one.

☐ I worried that I would learn information about my child’s cancer that would cause me anxiety.
☐ I worried that I would learn information about my child’s genes that would cause me anxiety.
☐ I worried that I would learn information about myself or my family that would cause me anxiety.
☐ I could have learned that my child’s cancer was less treatable or more aggressive.
☐ I worried that the information learned in this research study would not be kept private.
☐ I worried that the information learned could have hurt my family’s ability to get insurance.
☐ I worried that the information learned could have hurt my family’s ability to get or keep a job.
☐ I worried that the results would take a long time to come back.
☐ I worried that no new information would be found, causing me and my family to be disappointed.
☐ I did not have any worries or concerns about this research.
☐ Other (please specify: ________________________________)

19. Which of these statements best describes which you thought was MOST LIKELY TO HAPPEN because of your participation in this research study? Please choose only one.

☐ I could have learned information about my child’s cancer that would cause me anxiety.
☐ I could have learned information about my child’s genes that would cause me anxiety.
☐ I could have learned information about myself or my family that would cause me anxiety.
☐ I could have learned that my child’s cancer was less treatable or more aggressive.
☐ The information learned in this research study might not be kept private.
☐ The information learned could have hurt my family’s ability to get insurance.
☐ The information learned could have hurt my family’s ability to get or keep a job.
☐ The results would take a long time to come back.
☐ No new information would be found, causing me and my family to be disappointed.
☐ I did not have any concerns or worries that were likely to result from this research.
☐ Other (please specify: ________________________________)

11
### Reporting of Cancer and Medication Results

We are looking to learn about what types of information families want to receive from studies such as this. Please again think back to when you enrolled on the iCat research study. For each of the following, please choose if you would have wanted or would not have wanted each type of information reported back to you.

<table>
<thead>
<tr>
<th>Would have wanted</th>
<th>Would not have wanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information that told doctors that your child was MORE likely to be cured of his/her cancer</td>
<td></td>
</tr>
<tr>
<td>Information that told doctors that your child was LESS likely to be cured of his/her cancer</td>
<td></td>
</tr>
<tr>
<td>Information that directed doctors toward a new treatment option that might be beneficial to your child based on the genetic changes (“mutations”) found in his/her tumor</td>
<td></td>
</tr>
<tr>
<td>Information that told doctors about genetic changes (“mutations”) in your child’s tumor but these changes did not suggest a new treatment</td>
<td></td>
</tr>
</tbody>
</table>

### Reporting of Other Results

We are looking to learn about what types of information families want to receive from studies such as this. Please again think back to when you enrolled on the iCat research study. For each of the following, please choose if you would have wanted or would not have wanted each type of information reported back to you.

<table>
<thead>
<tr>
<th>Would have wanted</th>
<th>Would not have wanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information that told doctors that you and others in your family might be at an increased risk of developing certain types of cancers</td>
<td></td>
</tr>
<tr>
<td>Information that told doctors about a change in your child’s genes that could be passed onto his/her own children and cause an illness or condition other than cancer (even if your child does not have that condition)</td>
<td></td>
</tr>
<tr>
<td>Information about your child’s or family’s genes or health that could allow doctors to screen for or prevent certain illnesses or conditions</td>
<td></td>
</tr>
<tr>
<td>Information about your child’s or family’s genes or health, but there was nothing that doctors could do to screen for or prevent these illnesses or conditions</td>
<td></td>
</tr>
</tbody>
</table>
Information about your child’s or family’s genes or health, but doctors did not know if this would cause any illnesses or conditions

Research Study Requirements

We are also trying to better understand what requirements are reasonable for research studies involving cancer and genetics. Please answer the following questions about requirements for research studies.

20. If a research study such as iCat required your child to have another tumor biopsy that he/she would not get otherwise, do you think that you would choose to enroll in the research study and have the biopsy?
   - [ ] Yes
   - [ ] No

21. If a research study such as iCat required your child to have another tumor biopsy that he/she would not get otherwise but your doctor recommended it, do you think that you would choose to enroll?
   - [ ] Yes
   - [ ] No

22. If a research study such as iCat required your child to have another tumor biopsy that he/she would not get otherwise and this biopsy had a moderate-high (>50%) chance of injury, infection, or other negative effect, do you think that you would choose to enroll in the research study and have the biopsy?
   - [ ] Yes
   - [ ] No
Follow-up of Results

*Please answer the following questions about the results and information you received as part of this research study.*

23. Did the genetic testing of your child’s tumor find any changes in the genes ("mutations") that were reported back to you and your doctors?

☐ Yes
☐ No
☐ I do not know

24. As part of this research study, was a treatment recommendation reported back to you and your child’s doctors?

☐ Yes → Go to Question 25
☐ No → Go to Question 25
☐ I do not know → Go to Question 25

24a. Why did you not receive a treatment recommendation reported back to you? *Please check all that apply.*

☐ No changes in the genes ("mutations") were found that suggested a new treatment for my child.

☐ There was not enough tumor sample to do the necessary testing.

☐ My family did not want to have the results of the testing reported back to us and our doctors.

☐ We did not receive a treatment recommendation but I do not know why.

24b. Please consider how the fact that your child did not receive a treatment recommendation impacted you and your family. *Please check all that apply.*

☐ I was disappointed to have not received a treatment recommendation.

☐ I was surprised to have not received a treatment recommendation.
Follow-up of Results (continued)

25. Has your child ever received a treatment that was recommended as part of this research study, either now or in the past?
- [ ] Does not apply; no treatment recommendation was made → Go to Question 26
- [ ] Yes → Go to Question 26
- [ ] No → Go to Question 26
- [ ] I do not know → Go to Question 26

25a. Why has your child not received a treatment recommended as part of this research study? Please check all that apply.
- [ ] No treatment recommendation was made.
- [ ] My child is doing well on standard treatment so we are continuing to use that treatment.
- [ ] My doctor did not want to use the recommended treatment.
- [ ] My family and I did not want to use the recommended treatment.
- [ ] We were unable to get the recommended treatment.
- [ ] My child has been too sick to receive the recommended treatment.
- [ ] My child is doing well off of treatment so we have never started the recommended treatment.

26. If you could make the decision again of choosing to participate in this research study, would you choose to participate?
- [ ] Yes
- [ ] No

27. Do you feel that participating in this research study has been helpful for you and your child?
- [ ] Yes
- [ ] No
**Impact of Results**

*Please consider how strongly you agree with the following statements about the impact that participating in this research study has had on you and your family. Choose one response for each statement to describe how true it is for you.*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating in this study gave me more hope that my child would be cured.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Participating in this study taught me about my child’s cancer.</td>
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<tr>
<td>Participating in this study taught me about my child’s genes and genetics.</td>
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<tr>
<td>Participating in this study gave me hope that we will be able to cure future children with cancer.</td>
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<tr>
<td>Participating in this study gave me false hope.</td>
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<tr>
<td>My child experienced direct medical benefit from participating in this study.</td>
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<tr>
<td>My family and I benefited from participating in this study.</td>
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<tr>
<td>I am glad I chose to participate in this study.</td>
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</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety.</td>
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<tr>
<td>Waiting for results from this study caused me added stress and anxiety.</td>
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<tr>
<td>Participating in this study caused me added stress and anxiety about my child’s cancer.</td>
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</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety about my child’s genes.</td>
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</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety about myself and/or my family.</td>
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</tr>
</tbody>
</table>
28. Which of the following do you feel was the **MOST POSITIVE IMPACT** on you and your family about your participation in the iCat research study? *Please choose only one.*

- [ ] It gave me more hope that my child would be cured.
- [ ] It gave me hope that we will be able to cure future children with cancer.
- [ ] It taught me about my child’s genes and cancer.
- [ ] It provided me with peace of mind that I have done everything I could for my child.
- [ ] It directed my child’s doctors to new treatment options for my child.
- [ ] My child experienced direct medical benefit by participating in this study.
- [ ] Participating in this research study had no positive impact on me and my family.
- [ ] Other (please specify: ________________________________ )

29. Which of the following do you feel was the **MOST NEGATIVE IMPACT** on you and your family about your participation in the iCat research study? *Please choose only one.*

- [ ] It gave me false hope.
- [ ] It caused me added stress and anxiety about my child’s cancer.
- [ ] It caused me added stress and anxiety about my child’s genes.
- [ ] It caused me added stress and anxiety about myself and/or my family.
- [ ] It hurt my family’s ability to get or keep insurance.
- [ ] It hurt my family’s ability to get or keep a job.
Waiting for results from the study caused me added stress and anxiety.
Participating in this research study had no negative impact on me and my family.
Other (please specify: ________________________________________________________________)

Demographic Information

Please answer the following questions about yourself to help us understand more about who is participating in this research study.

30. How old are you?
☐ Less than 20 years old
☐ 20-29 years old
☐ 30-39 years old
☐ 40-49 years old
☐ 50 years old or older

31. What is the highest level of school you have completed?
☐ 8th grade or less
☐ Some high school
☐ High school graduate or equivalent
☐ Some college or technical school
☐ College graduate (either associate or bachelor’s degree)
☐ Graduate or professional school (e.g., MD, PhD, JD, MA, MS)

32. What is your gender?
☐ Male
☐ Female

33. Which group best describes your racial/ethnic background?
☐ White
☐ Black/African-American
☐ Hispanic/Latino
☐ Asian/Pacific Islander
☐ Native American
☐ Other

34. What is your relationship to the child who had genomic testing?
☐ Mother
☐ Father
☐ Grandparent
☐ Other relative
☐ Foster parent
☐ Step-parent
☐ Other (please specify ______________________)

You have reached the end of our questions. Thank you very much for participating. If you have other comments about your family's experiences with the iCat research study that you would like to share, please feel free to write them in below.

_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________


Dear «Parent Name»:

You previously agreed to take part in the iCat research study, a project looking at the use of genetic and genomic testing of tumor samples to find new treatment options for children and young adults with cancer. As part of this research study, we would also like to learn about parents’ and young adults’ experiences with this type of testing, and we would like to invite you to complete a survey about your thoughts on the iCat project.

Genomic testing is a new and very exciting area of pediatric cancer research, but it can also be very confusing. We believe it is very important for patients and families to have a say in how we get genetic information and what genetic information they want to know about. This is why we are asking for your help. We would like for you to consider completing a questionnaire about your experiences with the iCat research study from the time you enrolled on the study until now.

We will be asking you many questions about you, your child, and your experiences with the iCat study. For example, we will be asking you about your child's treatment and prognosis, about what hopes or concerns you had about taking part in the study, and how you feel now, after you have received a treatment recommendation (if one was made). We know that some of these questions may be hard, and you can skip any questions that you find stressful or that you prefer not to answer.

We are very grateful to you for considering completing this questionnaire. Included with this letter and questionnaire is a gift card as a token of our appreciation. We recognize the challenges you are facing at this time, but we also hope that your contributions can help other families of children with cancer at difficult times in the future.

Sincerely,

Jonathan Marron, MD
Study Co-Investigator
617-632-3453

Brian Crompton, MD
Study Principal Investigator

Carlos Rodriguez-Galindo, MD
Director, Solid Tumor Program
We are contacting parents of children with cancer who previously have agreed to take part in the iCat research study. We obtained your name and address from the iCat project database as someone who agreed to be contacted about studies such as this survey. If you agree to do so, we will ask you to complete a questionnaire about your experiences with the iCat study: what hopes and concerns you had, what you did or did not understand about the study, and how you feel about the research study now that you have received a treatment recommendation (if a recommendation was made). The questionnaire takes about 45 minutes to complete.

Participation in this study is voluntary. About 100 individuals taking part in the iCat research study will be asked to participate. You do not have to take part, and your decision about participation will not affect the care your child receives. We will keep your answers to this survey confidential. We will not share them with anyone involved in your child's care. They will not go in his or her medical record. We will not list your name or other identifying information together with your answers. Instead, we will keep a separate list of your name together with a number that identifies your questionnaire. All information will be kept in locked cabinets and computer files. Only the investigators in this study will have access to patients’ and parents’ names. Your name will not appear in any reports or publications about this study.

You may skip any items that you prefer not to answer. Some of the items in the survey may raise questions or concerns in your mind about your child's cancer and his or her treatment. If you do have any questions or concerns about your child's treatment, please feel free to discuss them with his or her provider. In addition, if you find the questions distressing, please feel free to discuss this with your child’s psychosocial worker, or call me so that I can ensure that a psychosocial worker contacts you. We have enclosed a gift card as a token of our appreciation of the time you have taken to complete this survey. There is no direct benefit to you (i.e., you will not receive monetary payment or alteration in your child’s cancer care), but the information we learn will be very helpful as we try to improve genetic testing like the iCat program for others with cancer in the future.

We have enclosed a copy of the questionnaire. If you decide to participate in this study, you may complete this questionnaire and hand it back to us or mail it back in the enclosed envelope. If you prefer not to participate and do not wish to be contacted in the future, simply return the postcard enclosed. If we do not receive your completed questionnaire or postcard in two to three weeks, we will send you another copy. We may also call you to find out if you have any questions about the questionnaire.

This study has been approved by the Institutional Review Board, a committee at Dana-Farber/Harvard Cancer Care that is responsible for overseeing research with patients. The Institutional Review Board may be reached at 617-632-3029.
You may contact Jonathan Marron, MD, at any time (617-632-3453) with questions about participating in this study.
Appendix 11

Individualized Interview for Pilot-testing of Parent Questionnaire (Assessment Tool 4)

Thank you for agreeing to help us with this study. Let me explain a little about it. This is a questionnaire for parents of children who enrolled in the iCat research study. Right now, we are working on a questionnaire to study patients’ and families’ hopes and expectations for genomic testing, like the testing that your child had on his/her tumor as part of the iCat study. We are also looking to learn about the impact that the study had on you and your family, now that you might have received results from it. One important step in this process is getting the opinions of parents about our questionnaire. I would like to show you a questionnaire and talk with you about the questions in it.

If any part of this interview makes you uncomfortable, we can stop at any time. We won’t tell anyone about the answers you give.

I’d like to ask you to look at this questionnaire. We will go through it together, one section at a time. At the end of each page, we will talk about the questions and how well they apply to you. I would like for you to think about which questions are unclear or hard to understand, and whether this questionnaire asks about the things that are most important to you.

Please go ahead and complete the first page of questions (page 3) now.

Now let’s talk about your answers. On this page we ask several questions about genetics and genetic testing. Did you understand these questions? Were there any that were unclear or that you did not know how to answer?

Please turn to page 4 and complete those questions. These questions are asking about your child’s health and cancer. Were these questions difficult to answer?

Let’s move on to the next page. Please turn to page 5 and complete the questions here and on the next page. These questions ask you to think back to when you signed up to participate in the iCat study. Do you remember when you agreed to participate in iCat? About how long ago was that for you? What is hard to remember what you were thinking at that time? Can you remember if you understand things now about the genetic testing of your child’s tumor that you did not understand then? Do you understand what the questions are asking when they mention “genetic testing” and “mutations”?

Please now turn to page 7 and complete those questions. Was it hard to pick one answer for any of these questions? Were there any that you weren’t sure how to answer? Are you able to remember how you felt when you signed up for the iCat study compared to how you feel now?

Now turn to page 8 and complete those questions. These questions are about what you hoped the genetic testing would do for you. Did you have any hopes when you signed up for the study that weren’t one of the options in the questions? Was it hard or easy to say how true the different
statements were for you? Do you remember how you felt when you signed up for the iCat study?

Now please turn to page 10 and complete those questions. This section is similar to the last one but instead of hopes, these questions ask about what you were worried would happen as a result of the iCat testing. Were you worried about anything related to the genetic testing that wasn’t one of the options? Was it hard or easy to say how true the different statements were for you? Were you surprised that people might be worried about any of these things?

Now turn to page 11 and complete those questions. Was it easy to pick a single choice for each of these questions? Were there any answer choices you wish were there for you to pick that were not? Was it hard to separate the difference between what you most worried would happen in question 18 and what you thought was most likely to happen in question 19?

Please now turn to the next page, page 12, and complete those questions. These questions are asking about what kinds of genetic information about themselves and their families that people want from testing like iCat. Was that clear? Were any of the types of information that were being discussed confusing? Were you able to easily answer whether you wanted each of the different types of information?

Now turn to page 13 and answer those questions. These questions are asking about whether you would want your child to have another biopsy of his/her tumor if that was needed to get the genetic information about the tumor. Was that confusing? Did you understand the difference between the different questions that were asked on this page?

Turn to page 14 now and complete the questions on this page and the next page. Did you understand what the questions were asking when they talked about a “treatment recommendation”? Was it hard to understand which questions to answer and which questions to skip? Were there any of these questions that were hard for you to answer?

Now turn to page 16 and answer those questions as well as the questions on the next page. These questions are trying to understand how participating in the iCat study has made you feel, now that you’re done. Did taking part in the study have any effects on you and your family that weren’t discussed in these questions? Was it hard to say how true some of these statements were for you? For question 28, was it hard to pick one choice for the thing that had the most positive impact on you? Is there anything you would have chosen instead if it was an answer choice? For question 29, was it hard to pick one choice for the thing that had the most negative impact on you? Is there anything you would have chosen instead if it was an answer choice?

Now please turn to page 18 and complete those questions. These questions ask a little information about you. Were any of these hard to answer? Did any of them make you feel uncomfortable? Were any of the answer choices hard to understand?

Finally, what do you think about the questionnaire overall? Do you think that it misses anything that is very important when thinking about your experiences? Did you find it upsetting to fill it
out? Was it difficult to think about these questions? What do you think about the amount of time it would take to fill this out? Is this too much time for you? Can you think of any ways we could make it easier for you to fill it out?

Would you like to speak with a psychosocial worker about anything related to the questionnaire or our conversation? We can help set that up if you found this especially upsetting and want to talk with someone about it.

Thank you for your help with this study. I hope that your input will help us to learn more from parents about their experiences with the iCat study and genetic testing of their children’s tumors.
iCat Assessment Tool 5

Patients’ Perspectives on Genomic Data and Individualized Cancer Therapy

Jonathan Marron, MD
Pediatric Hematology/Oncology
Dana-Farber/Boston Children’s Cancer and Blood Disorders Center
This questionnaire includes many questions about you, your cancer diagnosis, and your experiences so far with the iCat research study, a study looking at specialized genetic testing of pediatric tumors. Some of these questions may seem more important to you than other questions, but please do your best to answer as many of the questions as possible. All of your responses will be kept confidential. Your oncologist will NOT be given any information about your answers to this questionnaire.

The purpose of this questionnaire is to help doctors and scientists learn about patients’ and families’ experiences with genetic testing of tumors as well as how patients and families respond to hearing the test results. The information from this study will help oncologists understand more about patients’ and families’ perspectives on testing like this and to better care for adolescents like you in the future.
Experience with Genetics and Genetic Testing

Please answer the following questions about your personal experience with genetics and genetic testing.

1. Other than the testing that was done for this research study, have you or anyone in your immediate family ever undergone genetic or genomic testing?
   - [ ] Yes
   - [ ] No
   - [ ] I am not sure

2. Do you have regular exposure to genetics or experience with genetics and/or genetic information (such as a job in genetics or a similar field)?
   - [ ] Yes
   - [ ] No

3. Have you ever taken any classes (such as in high school or college) on genes or genetics, or have you been to any talks or lectures on genes or genetics?
   - [ ] Yes
   - [ ] No

Genetic Information

We are hoping to learn more about what patients understand about genetics and genetic information. For each of the following statements about genetics, please indicate whether you feel the statement is true or false by circling the appropriate response.

<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once a genetic marker for a disorder is identified in a person, the disorder can be prevented or cured.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a person has a genetic marker for a disorder, the person will always get the disorder.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only mothers can pass on genetic disorders.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People who have a genetic marker for a disease are unhealthy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient Cancer Information

Please answer the following questions about your cancer and your cancer treatment.

4. Are you currently receiving treatment for your cancer?
   □ Yes
   □ No

5. How would you rate your current state of overall health?
   □ Excellent
   □ Very good
   □ Good
   □ Fair
   □ Poor

6. How likely do you feel that you are to be cured of your cancer?
   □ Very likely to be cured (Greater than 80%)
   □ Likely to be cured (60-80%)
   □ Possible to be cured (40-59%)
   □ Unlikely to be cured (20-39%)
   □ Very unlikely to be cured but still possible (Less than 20%)
   □ No chance of cure

7. What do you think your chance of being cured of your cancer is, compared to other young adults with the same cancer diagnosis?
   □ My chance of being cured is much greater than others with the same diagnosis.
   □ My chance of being cured is somewhat greater than others with the same diagnosis.
   □ My chance of being cured is about the same as others with the same diagnosis.
   □ My chance of being cured is somewhat less than others with the same diagnosis.
   □ My chance of being cured is much less than others with the same diagnosis.
Understanding of Testing and Purpose of Testing

We are trying to understand how well patients understand the purpose of testing tumors for genetic changes ("mutations"). Please think back to when you enrolled on the iCat research study, and answer the following questions about your thoughts about the study and what you expected from it.

8. Do you remember signing up to participate in the iCat research study to test your tumor for changes in its genes ("mutations")?
   - Yes
   - No

9. How well do you remember the conversation(s) you had with your doctor about the iCat research study and the genetic testing involved in it?
   - Extremely well
   - Well
   - Moderately
   - Poorly
   - Extremely poorly

10. How well did you understand the information you were told about this research study and the genetic testing involved in it?
    - Extremely well
    - Well
    - Moderately
    - Poorly
    - Extremely poorly
Understanding of Testing and Purpose of Testing (continued)

11. When you first agreed to participate in this research study, how likely did you think it was that the genetic testing of your tumor would show that there was a change in the genes ("mutation")?
   - Very likely to find a mutation
   - Likely to find a mutation
   - Somewhat likely to find a mutation
   - Unlikely to find a mutation
   - Very unlikely to find a mutation

12. When you first agreed to participate in this research study, how likely did you think it was that the genetic testing of your tumor would find a change in the genes ("mutation") that would suggest a new treatment option for you?
   - Very likely to suggest a new treatment or medicine
   - Likely to suggest a new treatment or medicine
   - Somewhat likely to suggest a new treatment or medicine
   - Unlikely to suggest a new treatment or medicine
   - Very unlikely to suggest a new treatment or medicine

13. If the results from the genetic testing of your tumor showed that there WAS a change in the genes ("mutation") that suggested a new treatment option, how did you think this would change your chances of being cured?
   - Much more likely to be cured
   - Slightly more likely to be cured
   - No change
   - Slightly less likely to be cured
   - Much less likely to be cured

14. If the results from the genetic testing of your tumor showed that there WAS NOT a change in the genes ("mutation") that suggested a new treatment option, how did you think this would change your chances of being cured?
   - Much more likely to be cured
   - Slightly more likely to be cured
   - No change
   - Slightly less likely to be cured
   - Much less likely to be cured
### Understanding of Testing and Purpose of Testing (continued)

Please think back to when you enrolled on the iCat research study and what you understood about the research study at that time. For each of the following, please indicate whether you agree with the statement, disagree with the statement, or are unsure about the statement by circling the appropriate response.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Disagree</th>
<th>Unsure</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>By participating in this study, I was helping the doctors and scientists learn information that may benefit me.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By participating in this study, I was helping doctors and scientists learn information that may benefit future cancer patients.</td>
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<tr>
<td>The main reason this study was done was to improve my treatment.</td>
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<tr>
<td>The main reason this study was done was to improve the treatment of future cancer patients.</td>
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<tr>
<td>There may not have been direct medical benefit to me from participating in this study.</td>
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<tr>
<td>I can be sure that participating in this study provided me the best chance of cure.</td>
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<tr>
<td>Participating in this study means that new treatments may be suggested that could be helpful in treating my cancer.</td>
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<tr>
<td>Treatment recommendations from this study are certain to be effective for patients that receive them.</td>
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<tr>
<td>Any treatment recommendations from this study are standard for my type of cancer.</td>
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<tr>
<td>All patients participating in this research study received a treatment recommendation.</td>
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</table>
Hopes for Testing

Please indicate how much you agree with the following statements about why you chose to participate in this research study. Choose how true each statement was for you at the time you signed up to take part in the iCat research study.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>I hoped it would increase my chance of being cured.</td>
<td></td>
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<tr>
<td>I hoped that doing this testing would provide me with peace of mind.</td>
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<tr>
<td>I hoped it would help find cures for future patients.</td>
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<tr>
<td>I hoped it would help provide information to me and my doctor about my cancer.</td>
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<tr>
<td>I hoped it would teach me about my genes.</td>
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<tr>
<td>I hoped it would teach me about my family’s genes.</td>
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<tr>
<td>I hoped it would give me a greater number of treatment options.</td>
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<tr>
<td>I hoped to help doctors and scientists learn more about the genes involved in cancer.</td>
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<tr>
<td>My doctor recommended the study.</td>
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<tr>
<td>Participating in this research study gave me hope.</td>
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<tr>
<td>I did not expect any benefit to me or my family from this research.</td>
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</tbody>
</table>
Hopes for Testing (continued)

Please answer the following questions about the hopes and expectations you had at the time you enrolled in this research study.

15. Who did you expect to benefit most from the genetic testing of your tumor? Please choose one.
   - Me
   - My family members
   - Future patients
   - Doctors and scientists
   - Other (please specify: ________________________________)

16. Which of the following did you MOST HOPE WOULD HAPPEN because of your participation in this research study? Please choose only one.
   - I would have a better chance of being cured.
   - Doing this testing would give me peace of mind.
   - Doctors would be better able to find cures for future patients.
   - My doctors would be able to learn more about my cancer.
   - I would learn about my genes.
   - I would learn about my family’s genes.
   - I would have a greater number of treatment options.
   - I did not hope anything would happen as a result of this research.
   - Other (please specify: ________________________________)

17. Which of the following did you think was MOST LIKELY TO HAPPEN because of your participation in this research study? Please choose only one.
   - I would have a better chance of being cured.
   - Doing this testing would give me peace of mind.
   - Doctors would be better able to find cures for future patients.
   - My doctors would be able to learn more about my cancer.
   - I would learn about my genes.
   - I would learn about my family’s genes.
   - I would have a greater number of treatment options.
   - I did not think anything was likely to happen as a result of this research.
   - Other (please specify: ________________________________)

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## Concerns about Testing

*Please indicate how much you agree with each of the following statements about concerns you had about participating in this research study. Choose how true each statement was for you at the time you signed up to take part in the iCat research study.*

<table>
<thead>
<tr>
<th>Concern</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>I worried that I would learn information about my cancer that would be stressful or cause anxiety.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I worried that I would learn information about my genes that would be stressful or cause anxiety.</td>
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</tr>
<tr>
<td>I worried that I would learn information about my family that would be stressful or cause anxiety.</td>
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<tr>
<td>I worried that I would learn that my cancer was less treatable or more aggressive than previously thought.</td>
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<tr>
<td>I worried that the information learned in this research study would not be kept private.</td>
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<tr>
<td>I worried that the information learned could have hurt my family’s ability to get insurance.</td>
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<tr>
<td>I worried that the information learned could have hurt my family’s ability to get or keep a job.</td>
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</tr>
<tr>
<td>I worried that the results would take a long time to come back.</td>
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<td></td>
</tr>
<tr>
<td>I worried that no new information would be found to help me, causing me and my family to be disappointed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I did not have any worries or concerns about this research.</td>
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<td></td>
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</tbody>
</table>
Concerns about Testing (continued)

Please answer the following questions about the concerns you had at the time you enrolled in this research study.

18. Which of these statements best describes which you MOST WORRIED WOULD HAPPEN because of your participation in this research study? Please choose only one.
   - □ I worried that I would learn information about my cancer that would cause me anxiety.
   - □ I worried that I would learn information about my genes that would cause me anxiety.
   - □ I worried that I would learn information about my family that would cause me anxiety.
   - □ I could have learned that my cancer was less treatable or more dangerous-aggressive than previously thought.
   - □ I worried that the information learned in this research study would not be kept private.
   - □ I worried that the information learned could have hurt my family’s ability to get insurance.
   - □ I worried that the information learned could have hurt my family’s ability to get or keep a job.
   - □ I worried that the results would take a long time to come back.
   - □ I worried that no new information would be found, causing me and my family to be disappointed.
   - □ Other (please specify: _____________________________________________________ )

19. Which of these statements best describes which you thought was MOST LIKELY TO HAPPEN because of your participation in this research study? Please choose only one.
   - □ I could have learned information about my cancer that would cause me anxiety.
   - □ I could have learned information about my genes that would cause me anxiety.
   - □ I could have learned information about my family that would cause me anxiety.
   - □ I could have learned that my cancer was less treatable or more dangerous-aggressive than previously thought.
   - □ The information learned in this research study might not be kept private.
   - □ The information learned could have hurt my family’s ability to get insurance.
   - □ The information learned could have hurt my family’s ability to get or keep a job.
   - □ The results would take a long time to come back.
   - □ No new information would be found, causing me and my family to be disappointed.
   - □ I did not have any concerns or worries that were likely to result from this research.
   - □ Other (please specify: _____________________________________________________ )
### Reporting of Cancer and Medication Results

We are looking to learn about what types of information patients want to receive from studies such as this. Please again think back to when you enrolled on the iCat research study. For each of the following, please choose if you would have wanted or would not have wanted each type of information reported back to you.

<table>
<thead>
<tr>
<th>Information</th>
<th>Would have wanted</th>
<th>Would not have wanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information that told doctors that you were <strong>MORE</strong> likely to be cured of your cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information that told doctors that you were <strong>LESS</strong> likely to be cured of your cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information that directed doctors toward a treatment option that might be beneficial to you based on the genetic changes (“mutations”) found in your tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information that told doctors about genetic changes (“mutations”) in your tumor but these changes did not suggest a new treatment</td>
<td></td>
<td></td>
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</tbody>
</table>

### Reporting of Other Results

We are looking to learn about what types of information patients want to receive from studies such as this. Please again think back to when you enrolled on the iCat research study. For each of the following, please choose if you would have wanted or would not have wanted each type of information reported back to you.

<table>
<thead>
<tr>
<th>Information</th>
<th>Would have wanted</th>
<th>Would not have wanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information that told doctors that you and others in your family might be at an increased risk of developing certain types of cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information that told doctors about a change in your genes that could be passed onto your own children and cause an illness or condition other than cancer (even if you do not have that condition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information about your or your family’s genes or health that could allow doctors to screen for or prevent certain illnesses or conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information about your or your family’s genes or health, but there was nothing that doctors could do to screen for or prevent these illnesses or conditions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Information about your or your family’s genes or health, but doctors did not know if this would cause any illnesses or conditions

Research Study Requirements

We are also trying to better understand what requirements are reasonable for research studies involving cancer and genetics. Please answer the following questions about requirements for research studies.

20. If a research study such as iCat required you to have another tumor biopsy that you would not get otherwise, do you think that you would choose to enroll in the research study and have the biopsy?
   - Yes
   - No

21. If a research study such as iCat required you to have another tumor biopsy that you would not get otherwise but your doctor recommended it, do you think that you would choose to enroll?
   - Yes
   - No

22. If a research study such as iCat required you to have another tumor biopsy that you would not get otherwise and this biopsy had a moderate-high (>50%) chance of injury, infection, or other negative effect, do you think that you would choose to enroll in the research study and have the biopsy?
   - Yes
   - No
Follow-up of Results

Please answer the following questions about the results and information you received as part of this research study.

23. Did the genetic testing of your tumor find any changes in the genes (“mutations”) that were reported back to you and your doctors?
   □ Yes  □ No  □ I do not know

24. As part of this research study, was a treatment recommendation reported back to you and your doctors?
   □ Yes  □ No  □ I do not know

24a. Why did you not receive a treatment recommendation reported back to you? Please check all that apply.
   □ Changes in the genes ("mutations") were found that suggested a new treatment for me.
   □ There was not enough tumor sample to do the necessary testing.
   □ I did not want to have the results of the testing reported back to me and my doctors.
   □ I did not receive a treatment recommendation but I do not know why.

24b. Please consider how the fact that you did not receive a treatment recommendation impacted you. Please check all that apply.
   □ I was disappointed to have not received a treatment recommendation.
   □ I was surprised to have not received a treatment recommendation.
   □ Not receiving a treatment recommendation has significantly...
25. Have you ever received a treatment that was recommended as part of this research study, either now or in the past?

- [ ] Does not apply; no treatment recommendation was made → Go to Question 26
- [ ] Yes → Go to Question 26
- [ ] No → Go to Question 26
- [ ] I do not know → Go to Question 26

25a. Why have you not received a treatment that was recommended as part of this research study? *Please check all that apply.*

- [ ] Treatment recommendation was made.
- [ ] I am doing well on standard treatment so we are continuing to use that treatment.
- [ ] My doctor did not want to use the recommended treatment.
- [ ] My family and I did not want to use the recommended treatment.
- [ ] We were unable to get the recommended treatment.
- [ ] I have been too sick to receive the recommended treatment.

26. If you could make the decision again of choosing to participate in this research study, would you choose to participate?

- [ ] Yes
- [ ] No

27. Do you feel that participating in this research study has been helpful for you?

- [ ] Yes
- [ ] No
Impact of Results

Please consider how strongly you agree with the following statements about the impact that participating in this research study has had on you and your family. Choose one response for each statement to describe how true it is for you.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Extremely true</th>
<th>Very true</th>
<th>Somewhat true</th>
<th>A little true</th>
<th>Not at all true</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating in this study gave me more hope that I would be cured.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Participating in this study taught me about my cancer.</td>
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<td></td>
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</tr>
<tr>
<td>Participating in this study taught me about my genes and genetics.</td>
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<tr>
<td>Participating in this study gave me hope that we will be able to cure future patients with cancer.</td>
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<tr>
<td>Participating in this study gave me false hope.</td>
<td></td>
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<tr>
<td>I experienced direct medical benefit from participating in this study.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>My family and I benefited from participating in this study.</td>
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<tr>
<td>I am glad I chose to participate in this study.</td>
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<tr>
<td>Participating in this study caused me added stress and anxiety.</td>
<td></td>
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</tr>
<tr>
<td>Waiting for results from this study caused me added stress and anxiety.</td>
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<td></td>
</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety about my cancer.</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety about my genes.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participating in this study caused me added stress and anxiety about myself and/or my family.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Participating in this study hurt my family’s ability to get or keep insurance. ☐ ☐ ☐ ☐ ☐ ☐
Participating in this study hurt my family’s ability to get or keep a job. ☐ ☐ ☐ ☐ ☐ ☐
I was disappointed with the results that I received as part of this study. ☐ ☐ ☐ ☐ ☐ ☐
Participating in this study provided me with peace of mind. ☐ ☐ ☐ ☐ ☐ ☐
Participating in this study gave me the feeling that I had done everything I could for my health. ☐ ☐ ☐ ☐ ☐ ☐
I feel that I helped myself by participating in this study. ☐ ☐ ☐ ☐ ☐ ☐
I feel that I helped others by participating in this study. ☐ ☐ ☐ ☐ ☐ ☐
I feel that I was hurt by participating in this study. ☐ ☐ ☐ ☐ ☐ ☐
I regret having participated in this study. ☐ ☐ ☐ ☐ ☐ ☐

28. Which of the following do you feel was the **MOST POSITIVE IMPACT** on you and your family about your participation in the iCat research study? *Please choose only one.*

☐ It gave me more hope that I would be cured.
☐ It gave me hope that we will be able to cure future patients with cancer.
☐ It taught me about my genes and cancer.
☐ It provided me with peace of mind that I have done everything I could for my health.
☐ It directed my doctors to new treatment options for me.
☐ I experienced direct medical benefit by participating in this study.
☐ Participating in this research study had no positive impact on me and my family.
☐ Other (please specify: ________________________________ )

29. Which of the following do you feel was the **MOST NEGATIVE IMPACT** on you and your family about your participation in the iCat research study? *Please choose only one.*

☐ It gave me false hope.
☐ It caused me added stress and anxiety about my cancer.
☐ It caused me added stress and anxiety about my genes.
☐ It caused me added stress and anxiety about myself and/or my family.
☐ It hurt my family’s ability to get or keep insurance.
It hurt my family’s ability to get or keep a job.
Waiting for results from the study caused me added stress and anxiety.
Participating in this research study had no negative impact on me and my family.
Other (please specify: _______________________________________________________________ )

Demographic Information

Please answer the following questions about yourself to help us understand more about who is participating in this research study.

30. How old are you?
   □ Less than 20 years old
   □ 20-29 years old
   □ 30-39 years old
   □ 40-49 years old
   □ 50 years old or older

31. What is the highest level of school you have completed?
   □ 8th grade or less
   □ Some high school
   □ High school graduate or equivalent
   □ Some college or technical school
   □ College graduate (either associate or bachelor’s degree)
   □ Graduate or professional school (e.g., MD, PhD, JD, MA, MS)

32. What is your gender?
   □ Male
   □ Female

33. Which group best describes your racial/ethnic background?
   □ White
   □ Black/African-American
   □ Hispanic/Latino
   □ Asian/Pacific Islander
   □ Native American
   □ Other
You have reached the end of our questions. Thank you very much for participating. If you have other comments about your experiences with the iCat research study that you would like to share, please feel free to write them in below.

_____________________________________________________________________________________
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_____________________________________________________________________________________
Participant letter

7/17/2014

«Participant Name»
«Address1»
«Address2»
«City», «State» «ZIP»

Dear «Participant Name»:

You previously agreed to take part in the iCat research study, a project looking at the use of genetic and genomic testing of tumor samples to find new treatment options for children and young adults with cancer. As part of this research study, we would also like to learn about parents’ and young adults’ experiences with this type of testing, and we would like to invite you to complete a survey about your thoughts on the iCat project.

Genomic testing is a new and very exciting area of pediatric cancer research, but it can also be very confusing. We believe it is very important for patients and families to have a say in how we get genetic information and what genetic information they want to know about. This is why we are asking for your help. We would like for you to consider completing a questionnaire about your experiences with the iCat research study from the time you enrolled on the study until now.

We will be asking you many questions about you and your experiences with the iCat study. For example, we will be asking you about your treatment and prognosis, about what hopes or concerns you had about taking part in the study, and how you feel now, after you have received a treatment recommendation (if one was made). We know that some of these questions may be hard, and you can skip any questions that you find stressful or that you prefer not to answer.

We are very grateful to you for considering completing this questionnaire. Included with this letter and questionnaire is a gift card as a token of our appreciation. We recognize the challenges you are facing at this time, but we also hope that your contributions can help other families of children with cancer at difficult times in the future.

Sincerely,

Jonathan Marron, MD
Study Co-Investigator
617-632-3453

Brian Crompton, MD
Study Principal Investigator

Carlos Rodriguez-Galindo, MD
Director, Solid Tumor Program
We are contacting young adults with cancer who previously have agreed to take part in the iCat research study. We obtained your name and address from the iCat project database as someone who agreed to be contacted about studies such as this survey. If you agree to do so, we will ask you to complete a questionnaire about your experiences with the iCat study: what hopes and concerns you had, what you did or did not understand about the study, and how you feel about the research study now that you have received a treatment recommendation (if a recommendation was made). The questionnaire takes about 45 minutes to complete.

Participation in this study is voluntary. About 100 individuals taking part in the iCat research study will be asked to participate. You do not have to take part, and your decision about participation will not affect the care you receive. We will keep your answers to this survey confidential. We will not share them with anyone involved in your care. They will not go in your medical record. We will not list your name or other identifying information together with your answers. Instead, we will keep a separate list of your name together with a number that identifies your questionnaire. All information will be kept in locked cabinets and computer files. Only the investigators in this study will have access to patients’ and parents’ names. Your name will not appear in any reports or publications about this study.

You may skip any items that you prefer not to answer. Some of the items in the survey may raise questions or concerns in your mind about your cancer and your treatment. If you do have any questions or concerns about your treatment, please feel free to discuss them with your provider. In addition, if you find the questions distressing, please feel free to discuss this with your psychosocial worker, or call me so that I can ensure that a psychosocial worker contacts you. We have enclosed a gift card as a token of our appreciation of the time you have taken to complete this survey. There is no direct benefit to you (i.e., you will not receive monetary payment or alteration in your cancer care), but the information we learn will be very helpful as we try to improve genetic testing like the iCat program for others with cancer in the future.

We have enclosed a copy of the questionnaire. If you decide to participate in this study, you may complete this questionnaire and hand it back to us or mail it back in the enclosed envelope. If you prefer not to participate and do not wish to be contacted in the future, simply return the postcard enclosed. If we do not receive your completed questionnaire or postcard in two to three weeks, we will send you another copy. We may also call you to find out if you have any questions about the questionnaire.

This study has been approved by the Institutional Review Board, a committee at Dana-Farber/Harvard Cancer Care that is responsible for overseeing research with patients. The Institutional Review Board may be reached at 617-632-3029.

You may contact Jonathan Marron, MD, at any time (617-632-3453) with questions about participating in this study.
Thank you for agreeing to help us with this study. Let me explain a little about it. This is a questionnaire for young adults who enrolled in the iCat research study. Right now, we are working on a questionnaire to study patients’ and families’ hopes and expectations for genomic testing, like the testing that you had on your tumor as part of the iCat study. We are also looking to learn about the impact that the study had on you and your family, now that you might have received results from it. One important step in this process is getting the opinions of young adults about our questionnaire. I would like to show you a questionnaire and talk with you about the questions in it.

If any part of this interview makes you uncomfortable, we can stop at any time. We won’t tell anyone about the answers you give.

I’d like to ask you to look at this questionnaire. We will go through it together, one section at a time. At the end of each page, we will talk about the questions and how well they apply to you. I would like for you to think about which questions are unclear or hard to understand, and whether this questionnaire asks about the things that are most important to you.

Please go ahead and complete the first page of questions (page 3) now.

Now let’s talk about your answers. On this page we ask several questions about genetics and genetic testing. Did you understand these questions? Were there any that were unclear or that you did not know how to answer?

Please turn to page 4 and complete those questions. These questions are asking about your health and cancer. Were these questions difficult to answer?

Let’s move on to the next page. Please turn to page 5 and complete the questions here and on the next page. These questions ask you to think back to when you signed up to participate in the iCat study. Do you remember when you agreed to participate in iCat? About how long ago was that for you? What is hard to remember what you were thinking at that time? Can you remember if you understand things now about the genetic testing of your tumor that you did not understand then? Do you understand what the questions are asking when they mention “genetic testing” and “mutations”?

Please now turn to page 7 and complete those questions. Was it hard to pick one answer for any of these questions? Were there any that you weren’t sure how to answer? Are you able to remember how you felt when you signed up for the iCat study compared to how you feel now?

Now turn to page 8 and complete those questions. These questions are about what you hoped the genetic testing would do for you. Did you have any hopes when you signed up for the study that weren’t one of the options in the questions? Was it hard or easy to say how true the different
statements were for you? Do you remember how you felt when you signed up for the iCat study?

Now please turn to page 10 and complete those questions. This section is similar to the last one but instead of hopes, these questions ask about what you were worried would happen as a result of the iCat testing. Were you worried about anything related to the genetic testing that wasn’t one of the options? Was it hard or easy to say how true the different statements were for you? Were you surprised that people might be worried about any of these things?

Now turn to page 11 and complete those questions. Was it easy to pick a single choice for each of these questions? Were there any answer choices you wish were there for you to pick that were not? Was it hard to separate the difference between what you most worried would happen in question 18 and what you thought was most likely to happen in question 19?

Please now turn to the next page, page 12, and complete those questions. These questions are asking about what kinds of genetic information about themselves and their families that people want from testing like iCat. Was that clear? Were any of the types of information that were being discussed confusing? Were you able to easily answer whether you wanted each of the different types of information?

Now turn to page 13 and answer those questions. These questions are asking about whether you would want to have another biopsy of your tumor if that was needed to get the genetic information about the tumor. Was that confusing? Did you understand the difference between the different questions that were asked on this page?

Turn to page 14 now and complete the questions on this page and the next page. Did you understand what the questions were asking when they talked about a “treatment recommendation”? Was it hard to understand which questions to answer and which questions to skip? Were there any of these questions that were hard for you to answer?

Now turn to page 16 and answer those questions as well as the questions on the next page. These questions are trying to understand how participating in the iCat study has made you feel, now that you’re done. Did taking part in the study have any effects on you and your family that weren’t discussed in these questions? Was it hard to say how true some of these statements were for you? For question 28, was it hard to pick one choice for the thing that had the most positive impact on you? Is there anything you would have chosen instead if it was an answer choice? For question 29, was it hard to pick one choice for the thing that had the most negative impact on you? Is there anything you would have chosen instead if it was an answer choice?

Now please turn to page 18 and complete those questions. These questions ask a little information about you. Were any of these hard to answer? Did any of them make you feel uncomfortable? Were any of the answer choices hard to understand?

Finally, what do you think about the questionnaire overall? Do you think that it misses anything that is very important when thinking about your experiences? Did you find it upsetting to fill it
out? Was it difficult to think about these questions? What do you think about the amount of time it would take to fill this out? Is this too much time for you? Can you think of any ways we could we make it easier for you to fill it out?

Would you like to speak with a psychosocial worker about anything related to the questionnaire or our conversation? We can help set that up if you found this especially upsetting and want to talk with someone about it.

Thank you for your help with this study. I hope that your input will help us to learn more from young adults about their experiences with the iCat study and genetic testing of their tumors.