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

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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%. 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 of 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) and trastuzumab in ERBB2-positive breast cancer 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 heterogeneity.
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 *ALK* gene in approximately 8% of neuroblastomas and *FGFR4* gene mutations in rhabdomyosarcomas. 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. 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, large B cell lymphoma, neuroblastoma and other cancers, targeting this type of alteration has resulted in improved outcomes. Although there is some data to suggest that tumors acquire genetic, epigenetic and proteomic changes during progression, 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. 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. Several groups have demonstrated the ability to perform high quality array CGH from FFPE clinical specimens. 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. By the nature of their design
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 cacer 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?

Yes

iCat Recommendation formed by Study Investigator and approved by Expert Panel

Patient agreed to communication of tumor profiling results and iCat Recommendation?

No

Case considered a technical failure

Yes

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

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)

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

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

Treatment according to the iCat Recommendation initiated

Treatment according to iCat recommendation never appropriate

Patient death

Other

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

Assessment tool 2 response

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 <18years) 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 cm³ 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.
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\textsuperscript{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\textsubscript{50} of a particular drug against the particular mutation identified; available drug formulations; prior therapies received;
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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 bi-monthly. 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 \(^7\) and when adult tumors are
studied as many as 40% of tumors will have expressed alterations \(^24\). 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) 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 “8th 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).
13.0 REFERENCES


