

The State of Solid Tumor Biopsies : Innovative approaches to address and understand limited pediatric solid tumor samples and data

May 14, 2021

Blurred Lines:
Therapeutic vs
Research-only Biopsies



Background:

The annual CureSearch Summit serves as a unique platform for driving critical stakeholder collaborations to accelerate the pace of pediatric oncology drug development. The 2021 CureSearch Summit is hosted as a series of four virtual sessions focused on addressing the relative paucity of available pediatric cancer tissue and data.

To develop this topic, CureSearch convened a diverse set of stakeholders (Appendix 1) to identify a challenge to efficient pediatric drug development that could be addressed at the 2021 CureSearch Summit. The working group recommended solid tumor biopsies as a timely, relevant, and important topic for discussion.

More tumor tissue samples would accelerate the development of new therapies and diagnostics for pediatric solid tumors. Pediatric cancers are as collection of rare diseases; a limited patient pool requires concerted efforts towards efficient, effective, and open resource collection and sharing. It is imperative that innovative approaches to sample collection and sharing be identified and implemented with careful construction of pediatric clinical trial protocols.

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The Summit Working Group identified four primary topics of discussion to address the issue of limited and/or inaccessible patient samples to advance pediatric cancer research. Wide ranging experts in the field are convening to contribute to session discussions and presentations, including thought leaders from academia, the pharmaceutical industry, patient advocacy groups, patient families, and regulatory entities.

Session 1: March 19, 2021 - New Technologies for Maximizing Analysis of Solid Tumors: A set of panelists from academia and industry will discuss the promise and challenges associated with incorporating liquid biopsies into widespread clinical practice.

Session 2: May 14, 2021 - Blurred Lines: Therapeutic vs Research-only Biopsies This panel discussion will explore the factors that differentiate therapeutic biopsies from research-only biopsies and examine how new technologies and biomarkers are increasing the potential for therapeutic benefit.

Session 3: July 13, 2021 - The Journey of a Post-Mortem Tissue Donation Panelists will discuss approaching families about tissue donation, the collection process, and the applications for post-mortem tissue in research.

Session 4: September 14, 2021 - Biorepository Form and Function This session will provide insight into biorepositories, specifically how tissue is acquired, the types of samples and data that biorepositories house, and their accessibility.

This outcome-driven meeting will provide resources to the pediatric cancer community aimed at increasing biopsy use and data sharing to support and accelerate research in the field. A white paper will follow each of the four CureSearch Summit sessions. These white papers will review the topic, highlight benefits and challenges to implementation of increased biopsy acquisition and data sharing in the pediatric cancer space, and identify future actions to address the challenges and increase pediatric-specific therapy development.

Session 2- Blurred Lines: Therapeutic vs Research-Only Biopsies

Session 2 of the 2021 CureSearch Summit addressed additional biopsies outside of standard diagnostic collection as a potential source of tissue for research purposes. Recognizing the regulations and parental concerns associated with tissue collection from pediatric patients, this meeting explored the concepts of direct benefit and minimal risk as applied to pediatric biopsies. Panelists representing regulatory agencies and academia (Appendix 2) were selected based on their expertise with ethical, regulatory and technical aspects relating to pediatric biopsies.

The session was designed around the individual experiences of each panelist to provide a balanced, inclusive, and informative discussion. This white paper provides an overview of the panel discussion as well as case studies pertaining to the concepts of direct benefit and minimal risk as they apply to pediatric biopsies.

Introduction

Over the past fifty years, pediatric cancer survival has improved drastically for many tumor types. Clinical trials offering new therapies that are more targeted to children's tumors as opposed to those of adults continue to offer safer and more effective treatment options. Despite these improvements, there is still work to be done in defining the targets and appropriate drugs for pediatric cancers. Tissue samples from patient tumors are one of the most direct ways to collect information on the breadth of molecular subtypes that exist in pediatric cancers. Thus, the potential impact of solid tumor biopsies in children cannot be overstated. Of note, this importance continues to increase with the development of molecularly targeted therapies and immunotherapies that are revolutionizing cancer treatment.

There are several points in time at which tumor tissue collection could benefit the understanding of the biology of a tumor. At the time of diagnosis, tissue collection and analysis enables identification of molecular targets and possibly biomarkers that can point the care team to clinical trials testing targeted therapies or to targeted drugs that are already approved for a given disease. Following treatment, biopsies allow examination of biomarkers that may reveal whether the therapy hit its target. At the time of recurrence or relapse, tumor tissue collection and molecular analysis enables doctors to determine what changes have occurred in the tumor to enable its return and how these new changes might be targeted with a different therapy. Post-mortem biopsies, the topic of the third Summit session in this series, also offer the opportunity to understand the biology of the tumor and, potentially, metastases.

In the case of post-mortem biopsies, tumor samples benefit pediatric oncology knowledge in general. In instances where biopsies are not standard of care, an additional biopsy might serve to provide information that allows physicians to make decisions regarding a patient's treatment. In this case, the additional biopsy has the potential to provide a direct therapeutic benefit if treatment is tailored based upon the biopsy result. This, as well as risk of the procedure itself, are important concepts when considering an additional biopsy, especially in the case of pediatric patients where regulations have been put in place to protect this vulnerable population from excess risk.

In order for researchers to treat pediatric cancers more effectively in the future, the study of patient tumors is incredibly important today, and tissue samples are a valuable source of information. How do researchers obtain that tissue and how do they ensure clear and transparent communication with patients and families when discussing biopsy requests? Questions considered during this panel presentation and subsequent Q&A included:

- How do we respect and respond to patients and family perspectives on benefit and risk?
- How do we design clinical trials that incorporate biopsies?
- How can we leverage the information obtained from those biopsies to influence treatment, providing the potential for direct benefit to the patient?
- How do we utilize new therapies and biomarkers to promote clinical benefit in the present and the future?

Regulations Regarding Additional Biopsy in Pediatric Patients

Children comprise a vulnerable population when it comes to human studies. For this reason, specific regulatory protections have been put in place for the pediatric population. The Belmont Report was published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission was created as a result of the National Research Act of 1974 and was charged with identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects. In addition, they developed guidelines to assure that such research is conducted in accordance with those principles. This report has informed federal regulations, both for the National Institutes of Health (NIH) and for the US Food and Drug Administration (FDA), on the issues of "minimal risk" and "greater than minimal risk". Of note, the guideline pertaining to "greater than minimal risk" states that research where an intervention presents greater than minimal risk is only appropriate where the risk is justified by the anticipated direct benefit to the enrolled subject and the relation of the anticipated benefit to such risk is at least as favorable as that presented by available alternative approaches (21 CFR 50.52).

When an ethics board considers a proposed clinical trial with the aim to determine whether the procedure(s) proposed comprise greater than minimal risk or provide the potential for direct benefit, they perform a component analysis. This is the process whereby each intervention or procedure within a clinical protocol must be evaluated separately to determine whether it represents more than a minor increase in risk and if it has any potential to offer direct benefit to the enrolled child. For example, if a clinical trial is assessing a new therapeutic in a given pediatric population and there's potential for benefit from receiving the drug of interest, institutional review boards (IRBs) have to separate out any biopsy that might also be included in the protocol and determine whether that also provides the potential for clinical benefit to the patient.

Regulations noted above have been developed to protect a vulnerable population. As such, it is important, when trials are designed for children, that the concepts of direct benefit and risk are taken into account. Clinicians cannot put children through procedures that pose greater than minimal risk but do not have a direct impact on their healthcare, even if the knowledge created has the potential to benefit other patients. Where the lines blur is in defining therapeutic benefit and risk. Panelists with extensive experience on the regulatory, ethics, and clinical levels weigh in on how the regulations apply in the real world.

An Alternate Regulatory Pathway

The 407 Review Process is a regulatory pathway that can be pursued when the proposed research is not otherwise approvable because it contains a research intervention which offers no prospect of direct benefit yet entails more than a minor increase over minimal risk, but presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting pediatric patient health. If all of these conditions are met, the IRB or other appropriate institutional official may submit the protocol and supporting materials for consideration for approval at the federal level. A panel of experts in pertinent disciplines - for example, science, medicine, education, ethics, and relevant pediatric advocates- are asked to review the protocol and provide recommendations on whether the benefits of the protocol outweigh the risks. In addition, this process allows for review and comment by the local community where the research is to be conducted before a decision is made on whether to proceed with the research. This process serves as an extended peer review through which the protocol may be approved if it does, in fact, provide an opportunity to decrease the burden of a serious problem affecting the health of children. For more information on 407 review process, see guidance provided by the US Department of Health and Human Services (HHS).

Benefit and Risk

According to the Belmont Report, the assessment of risks and benefits requires presentation and review of relevant data that, in some cases, also includes the provision of alternative, lower-risk methods for obtaining the benefit that is sought in the research. Review of the risk-benefit ratio enables the investigator to determine whether the study has been properly designed (see section below on this topic) and the review committee to determine whether the risks are justified by the presumed benefit. According to federal regulations (§46.102(i)), minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. When risk exceeds this definition, it is considered an increase over minimal risk. While this concept can be considered subjective, it is generally understood that a solid tumor biopsy presents an increase over minimal risk as the risks of the procedure can include bleeding, infection, and the potential morbidity or mortality associated with the specific biopsy type. Consideration must also be made regarding a patient's comorbidities that may increase risks above baseline for an individual patient. In addition, solid tumor biopsies often require the use of anesthesia which carries its own set of risks, especially in children. The Pediatric Ethics Subcommittee of Pediatric Advisory Committee (PAC) of the FDA held a meeting on March 23, 2015 to determine the risk of anesthesia. Approximately half of the Subcommittee members said that anesthesia could never be considered only a minor increase over minimal risk, and half said it might be in some circumstances. There are also instances where biopsy technology at a given institution is minimally invasive enough to reduce risk to an acceptable level. These cases must be considered carefully when assessing risk. With the advent of new technologies that are becoming standard of care for different tumor types- including one of the most deadly brain tumors, diffuse intrinsic pontine glioma (DIPG) - there may be a need for recalibration of the understanding of risk in the context of perceived benefit.

Regulations note that an intervention that presents greater than minimal risk is only appropriate where the risk is justified by the anticipated direct benefit to the enrolled children. In order to perform a risk-benefit assessment, the benefit of a given protocol must also be assessed. Clinical benefit is defined as a favorable effect on a meaningful aspect of how a patient feels, functions, or survives as a result of a treatment or procedure. In the simplest terms, if a clinician is going to use information obtained from a biopsy to modify therapy – change therapy if it is not working, for example – then there is a direct benefit to the patient and a biopsy may be warranted. The understanding in this example is that an actual change will be made if there is a demonstrable reason to alter the course of therapy. If a brainstem tumor biopsy reveals that a drug is not getting to the tumor, then the treatment should be stopped and an alternative treatment should be pursued. Even proving benefit includes some subjectivity. In addition, the advent of new targeted therapies and biomarkers may increase the likelihood that a biopsy will provide direct clinical benefit to the patient by identifying targetable mutations within the tumor. In fact, the argument could be made that enrolling a patient on a trial for a drug with a specific target and not determining whether the target exists in the patient's tumor is doing a disservice to the patient by allowing them to enroll in a trial in which there is not a reasonable expectation that he/she will benefit.

The complexity of determining the accurate risk-benefit ratio could be reduced with proper preparation and clinical trial design.

Optimizing Clinical Trial Design for Biopsy Collection

Clinical trials are, by definition, research. Clinicians do not know how a patient will respond when given a particular therapy, though there is reasonable anticipation of benefit due to the significant preliminary research conducted before a therapy moves into human testing. The goal of a clinical trial is to determine if a particular approach to diagnosis or therapy will benefit patients. Clinical trial protocols should always be designed with the ultimate goal of patient benefit and minimization of risk. Data should also be collected to ensure that generalizable information is learned that can benefit future patients. Some of the most important generalizable evidence that also directly benefits the patient revolves around learning why a drug did not work. If it does not enter the tumor tissue or affect the anticipated target, understanding why is essential to reducing further exposure of patients to an ineffective therapy. There are considerations that can be made early in the protocol design phase that promote these goals as they pertain to biopsy collection, and it is important to consider them early and thoroughly.

Clinicians should create studies that, if a drug is unsuccessful, should inform future therapeutic approach. That may mean going past a single biopsy to perform multiple biopsies for children with difficult to treat tumors such as DIPG. In these cases, doctors can use the first biopsy to confirm the target exists, give the drug, and then do a second biopsy to determine if the drug reached the tumor and produced some pharmacologic benefit in order to rationalize continued exposure of the child to the drug. In this case, the design of a trial to include a biopsy at the time of another medical procedure may reduce risk by, for example, decreasing the number of times that a patient is put under anesthesia.

Consideration of alternate, lower-risk paths to reach a given research goal is also an important aspect of clinical trial design. Promotion of the movement of techniques such as liquid biopsy into regular clinical practice can greatly benefit patients by providing data on the status of the tumor with minimal risk to the patient (see CureSearch white paper on New Technologies for Maximizing Analysis of Solid Tumors). Alternatively, the number or size of additional biopsies may be reduced by carefully considering the data to be collected from the biopsy as well as the specific need of the biopsy in terms of determining patient care.

Clinical trial design should also involve a thorough review of novel trial designs that might enable a reduction in the number of patients needed for a given trial or improve the data obtained. For studies that incorporate biopsies, clinicians should carefully consider the sample size required to obtain clear information regarding the utility of the biomarker for predicting drug effectiveness. Other aspects of the trial design, such as end points, technology to be used for molecular analysis and tumor/symptom monitoring should be carefully considered in the context of the biopsy and its utility within the study.

Finally, trial design is most successful when it incorporates the needs and preferences of the patient community. Patients and patient families should be consulted throughout the clinical trial development process to ensure that the demands of the research are considered commensurate with the perceived benefit.

Considering the Parental and Patient Perspective

Parents and patients, upon receiving a diagnosis of pediatric cancer, face psychological, emotional, and physical turmoil. Making a decision about clinical trial participation, while it may seem academically easy, is incredibly difficult for families, and that challenge can be exacerbated by extensive consenting processes, multiple trial options, and lack of clarity on the details of the trial. Dr. Donald Very provided the parent's perspective for this panel and his story is informative to the discussion of risk-benefit assessment from the perspective of a parent or patient diagnosed with cancer.

Case Study: The Parental Perspective

Perspective provided by Dr. Donald Very, PhD; edited lightly for flow.

My name is Don Very. I'm an immunologist. I've spent over 30 years in the diagnostic medical device industry. During that time, much of my research has been devoted to developing new diagnostic tests to detect the presence of cancer, predict a patient's response to treatment or likely outcome of that treatment, and try to identify which patients might benefit from a particular treatment. For that work, clinical samples derived from the patient were absolutely critical. Yet, I also bring another perspective, that of the parent of a pediatric cancer survivor, someone who sat across from an oncologist and heard those words that really change your life forever: "your son has cancer."

So, you might think that with my training and my background, when my son's clinical team approached me with the opportunity for him to participate in a clinical study that wasn't going to directly influence his treatment—strictly a research study - it would be an easy decision for me to allow his participation. However, I said no.

Now let me be clear, Mike did participate in some experimental treatment studies testing new therapies that were added to what was considered the standard of care treatment that he received. The study in which we did not participate was clearly identified by the clinical team as a research study; it would have no direct benefit to his course of treatment. This protocol consisted of extensive blood work and extensive imaging analysis, a whole series of X rays, CT scans, MRIs, and a couple of PET scans. All of it relatively minimally invasive; still, I said no.

I am still convinced that was the right decision. But I want to put that decision in context, because that context can better inform our understanding of a parent's perspective and may ultimately lead to access to more clinical specimens for research in drug discovery and development, and for the development of novel diagnostic tests. At the time that the clinical team approached our family with the opportunity to participate in these clinical studies, we had just been given Mike's diagnosis and what were considered the standard of care treatment options for him at that time: 36 weeks of chemotherapy, six cycles of multiple, highly toxic chemotherapeutic drugs with all of the horrible side effects that we all know: nausea, weight loss, decreased blood counts. We also received his prognosis based on the stage and grade of his disease and it was not a good prognosis. Finally, added to the 36 weeks of treatment, he would have multiple surgeries. One to remove the tumor and one to reconstruct his knee and give him an artificial knee to replace the diseased bone in his leg. Then, lastly, multiple lung surgeries to remove the cancer that had left the primary site and metastasized to his lung. As so much was happening to him at this time that was beyond my control, I would have done anything to protect him that I could. Therefore, my response to this particular study that would not directly affect his treatment was in my control. So, I said no.

So, the question that I want answered is: Can we design clinical research studies in a way that ensures they provide information that can better inform the physician's treatment decisions for his or her patients, clearly communicate that message to the patient and parents, and deliver that message to the parents in a way and at a time that they are receptive to hearing it?

A significant aspect of Dr. Very's question relates to an important phase in the communication of the clinical trial to the patient and family, the consent process.

Improving the Consent Process

It can be difficult to explain pediatric oncology trials to families of children with cancer. There can be a disconnect in understanding how parents interpret the information presented to them, and physicians may assume that certain topics are covered in the informed consent document and therefore need not be discussed. Additionally, clinicians may not fully explain a topic before moving on to new concepts, which can be confusing to parents and patients who require more, detailed, and simplified information to understand the goals, risks, potential outcomes and options available. Based on the panel discussion on consent, some important approaches to consider include:

- Provide a realistic overview of the clinical trial and its potential outcomes. Language matters and it is important to be clear and transparent about the protocol.
- Parents find themselves overwhelmed when selecting therapies for their child. Ensure that the description of the trial does not seem coercive.
- Present the information in a manner that is easier for the parent or guardian to comprehend and digest. Describe complicated components in multiple ways to improve understanding.
- Present the information at a time at which the parent or guardian will not be overwhelmed. Provide parents with the time to digest treatment and prognostic information that is presented at initial diagnosis prior to sharing additional research study information.
- Limit consent forms to the most essential information. A simple 2-3 page consent is far more digestible than a 45-page consent.
- Describe the trial in lay terms, at the sixth-grade level, and avoid medical jargon.
- Utilize a two-step consenting process where the initial consent is for standard of care, and additional consents regarding research protocols are discussed separately.
- Provide plenty of time for parents and patients to ask questions.

Next Steps

By convening a community of stakeholders in the pediatric cancer ecosystem, CureSearch provides a platform to think strategically and work collaboratively. CureSearch is in a unique position to compile information across stakeholders and disseminate outcomes and lessons learned to the broader community. Scientific and drug discovery opportunities lie in providing platforms for discussion amongst academia, industry, patient families, advocacy groups, and regulatory bodies. After the annual Summit, CureSearch works collaboratively with meeting participants and contributors to identify action items and move the topic toward resolutions of the challenges discussed.

A topic that stands out as one that, with deeper consideration, could improve the success of obtaining solid tumor biopsies is the development of best practices for consenting patients. CureSearch will convene a working group comprised of ethicists, regulatory representatives, clinicians, and parents/patients to recommend best practices in consent design, communicating clinical research with patients and parents, and ensuring that the consent allows for utilization of tissue and data in a manner that will enable research advancements.

Updates on working group progress will be provided to 2021 Summit participants in 2022 in the form of a list of action items that are updated quarterly to demonstrate progress.

CureSearch would like to thank panelists and attendees for their contributions to this session of the 2021 virtual CureSearch Summit. The success of this meeting would not have been possible without the engagement of all participants.

Appendix 1. Summit topic working group members.

WORKING GROUP MEMBER	DESIGNATION	AFFILIATION
Richard Drachtman, MD	Clinical Section Chief, Pediatric Hematology/Oncology Sequencing	Rutgers Cancer Institute of New Jersey
	Professor of Pediatrics	Rutgers-Robert Wood Johnson Medical School
	Chair	Pediatric Central Institutional Review Board
Lia Gore, MD	Co-Director, Developmental Therapeutics Program	University of Colorado Cancer Center
	Ergen Family Chair in Pediatric Oncology - Section Head, Pediatric Hematology/Oncology/BMT	Children's Hospital Colorado
Amanda Jacobson, PhD	Associate Director, Clinician, Early Clinical Development Oncology	Pfizer
Su Young Kim, MD, PhD	Senior Medical Director	AbbVie
Donald Very, PhD	President and CEO	Naviter Bioanalytics, LLC
	Parent	Stage IV osteosarcoma survivor

Appendix 2. Panelist representation for the CureSearch Summit session Blurred Lines: Therapeutic vs Research-only Biopsies.

PANELIST	DESIGNATION	AFFILIATION
Richard Drachtman, MD	Clinical Section Chief, Pediatric Hematology/Oncology Sequencing	Rutgers Cancer Institute of New Jersey
	Professor of Pediatrics	Rutgers-Robert Wood Johnson Medical School
	Chair	Pediatric Central Institutional Review Board
Liza-Marie Johnson, MD, MPH, MSB	Associate Member, St. Jude Faculty. Program Director, Oncology Hospitalist Medicine Bioethics Consultant Therapeutics Program	St. Jude Children's Research Hospital
Roger J. Packer, MD	Senior Vice President, Center for Neuroscience and Behavioral Medicine Director, Gilbert Neurofibromatosis Institute Director, Brain Tumor Institute	Children's National
	Professor of Neurology and Pediatrics	George Washington University
Donald Very, PhD	President and CEO	Naviter Bioanalytics, LLC
	Father	Stage IV osteosarcoma survivor
Robert Wechsler-Reya, PhD	Director and Professor, Tumor Initiation and Maintenance Program	Sanford Burnham Prebys Medical Discovery Institute
	Director, Claves Research Center for Neuro-Oncology and Genomics	Rady Children's Institute for Genomic Medicine



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CureSearch Summit: Solution

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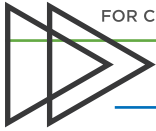
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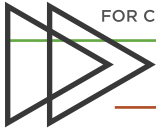
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ILLABO. OMNITIUS SIMENDIGENTO BLA

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Business Case Study

Case Study **TEMPLATE**

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Overview

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Actions

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