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CureSearch Summit: The State of Solid Tumor Biopsies

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

Written by: CureSearch for Children's Cancer in Collaboration with Thermo Fisher Scientific

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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.

PRESENTERS

Brian Crompton, MD[1]
Kelli Bramlett, PhD[2]
Sarah Leary, MD[3]
Matthew Hiemenz, MD[4]
Ryan Hartmaier, PhD[5]

CONTRIBUTING AUTHORS

Simone Sredni, MD, PhD[2]
Luca Quagliata, PhD[2]
Jose Luis Costa, PhD[2]
Jen Salstrom, MD, PhD[6]
Tony Pillari[7]
Caitlyn Barrett, PhD[8]

Author Affiliations: [1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, [2]Thermo Fisher Scientific, [3]Cancer and Blood Disorders Center, Seattle Children's Hospital, University of Washington School of Medicine, [4]Foundation Medicine, [5]AstraZeneca, [6]Parexel, [7]Excelis Consulting, [8]CureSearch for Children's Cancer

More tumor tissue samples would accelerate the development of new therapies and diagnostics for pediatric solid tumors, however, solid tumor biopsies are difficult to perform due to inconsistent tissue banking and difficulty acquiring samples and data from repositories. Pediatric cancer is a rare disease; fewer patients require 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.

The Summit Working Group identified four primary topics of discussion key focus areas to address the issue of limited and/or inaccessible patient samples for the advancement of 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: 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 concepts of "direct benefit" and "minimal risk" as they apply to biopsies and examine how new technologies and biomarkers are increasing the potential for therapeutic benefit with decreasing risk.

Session 3: July 13, 2021 - The Journey of a Post-Mortem Tissue Donation: This session will focus on post-mortem tissue donation and the research potential for this tissue. Panelists will discuss approaching families about tissue donation: the reasons these conversations are so important, the benefits donation confers to the entire community, and some suggested approaches to having these sensitive but critical conversations. We will discuss ethical guidelines for post-mortem donation as well as 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 each topic, highlight benefits and challenges to implementation of increased biopsy acquisition and data sharing in pediatric cancer space, and identify future actions to address the challenges and increase pediatric-specific therapy development.

Session 1: New Technologies for Maximizing Analysis of Solid Tumors

Session one of the 2021 CureSearch Summit addressed issues associated with incorporating liquid biopsies into widespread clinical practice. Sample collection and analysis of tumor cells and molecules within biofluids such as blood plasma and cerebral spinal fluid (CSF) has the potential to allow researchers to collect data while decreasing the need for more invasive solid tumor biopsies. Panelists representing industry and academia (Appendix 2) were selected based on their liquid biopsy expertise.

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 and critical next steps that aim to support more widespread adoption of liquid biopsy in pediatric patients.

Introduction to the State of Tumor Biopsies

At present, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, and small molecules obtained from solid tumor biopsies are generally used to define the genomic and proteomic changes within a tumor (the tumor's molecular landscape). The current procedures for tumor tissue biopsies are invasive and a risk to the patient. In children with cancer, minimizing risk is a high priority. In addition, since the tumor's molecular landscape can change over time, biopsies taken at diagnosis may not continue to represent the tumor after a few months of therapy. A mechanism for less-invasive sampling that can take place longitudinally and provide information on the tumor at diagnosis, during treatment, and at follow-up would greatly benefit the pediatric cancer community. The need for a ubiquitous mechanism is especially highlighted by the emergence of molecularly driven therapeutics (targeted therapy, precision medicine).

Liquid biopsy is a minimally invasive test performed on a sample of human biofluid (such as blood, plasma, saliva, urine, or CSF) to look for tumor cancer cells or pieces of molecular material originating from the tumor. While there is potential for the context-dependent identification of tumor material in a range of biofluids, liquid biopsies most frequently utilize blood. However, in the case of brain tumors, CSF seems to be the most efficient biofluid for liquid biopsy [1]. So far, research indicates the greatest potential for blood and CSF, but more research may expedite the use of other biofluid candidates in the future.

Sources of Cancer-Derived Materials

The most common components analyzed by liquid biopsy include circulating tumor cells (CTCs), cell-free circulating nucleic acids, primarily circulating tumor DNA (ctDNA) but also circulating tumor RNA and exosomes (Figure 1).

- CTCs are cancer cells that are shed from the primary or metastatic tumor mass. The advantage of CTCs in liquid biopsy is that DNA, RNA, and protein-based assays can be used to study whole tumor cells. CTCs are extremely rare, and concentration of these cells are incredibly low in comparison to other types of blood cells. The isolation of intact CTCs from the blood is constrained by the complexity of the isolation procedure.

- Circulating tumor DNA (ctDNA) is DNA that comes from cancer cells and is shed into the blood. Likely sources of ctDNA include: dying tumor cells, active secretion from live tumor cells and CTCs.

- Exosomes are a type of extracellular vesicle. Exosomes can contain a range of cellular molecules, including proteins, lipids and nucleic acids derived from the cells that secrete them. The molecules contained within tumor exosomes differentiate them from normal cells and analysis of tumor-secreted exosomes could be leveraged as novel cancer biomarkers.

This circulating tumor material holds information that can be studied through new liquid biopsy technologies. The ability to identify tumor-specific variants are key to the detection of circulating cancer material. Pediatric tumors harbor a range of molecular changes, many of which are different from those found in adult tumors [2-6]. For example, one class of somatic events that are frequently recurrent in pediatric cancer and less common in adult cancers are chromosomal translocations. A translocation is a genetic change resulting from a break in a chromosome that then attaches to another section of the chromosome or another chromosome altogether. In some cases, pieces from two different chromosomes can trade places with one another. Translocations can be identified in circulating DNA. It is also hypothesized that RNA (free in circulation or inside exosomes) may serve as a source for translocation identification.

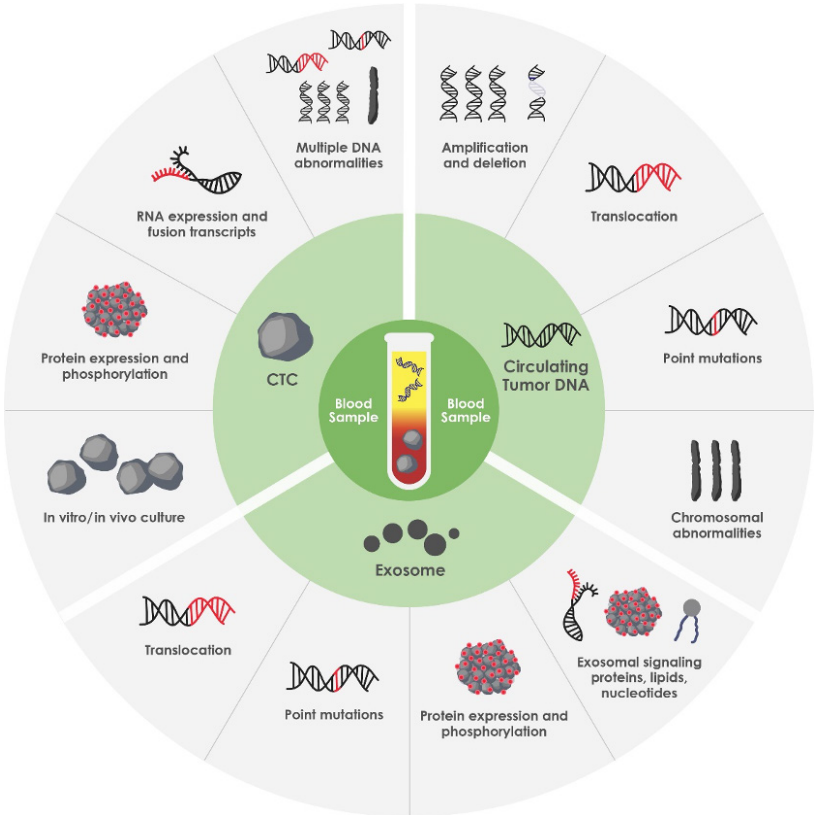

Figure 1: Sources of cancer-derived material and variants that can be identified from each source. Modified from [7].

Liquid Biopsy Applications

In comparison to solid tumor biopsies, liquid biopsies offer a less invasive opportunity for longitudinal sampling across the span of a patient's cancer timeline, from diagnosis to follow-up (Figure 2). As targeted therapy becomes more common in pediatric oncology treatment, effective therapeutic strategies will require genotyping of tumors, fast diagnostic assessment, and real-time treatment response measurements. Liquid biopsy could play a role in the following applications:

Screening

There is interest in studying whether liquid biopsies can help with early cancer detection. Given the rarity of pediatric cancer, it may be most practical to assess the potential for liquid biopsy in cancer screening in the context of children with a higher risk of cancer, including those with cancer predisposition syndromes. However, there remains a need to develop liquid biopsy assays that can detect the presence of cancer in patients who are frequently at risk for multiple types of malignancies, each with unique molecular features. Of note, efforts to coordinate the collection of longitudinal blood samples in children at risk for developing cancer would accelerate efforts to validate liquid biopsy assays for early cancer detection once promising tests become available.

Diagnosis

Tissue biopsies are currently required for the diagnosis of most solid tumor malignancies. However, surgical biopsies are invasive procedures that carry associated risks of anesthesia, infection, post-operative pain, high procedural costs, insufficient tissue collection, and a limited ability to capture the complete heterogeneity of a tumor. In contrast, liquid biopsies are minimally invasive and could provide an alternative or additive solution to surgical biopsies. The shedding of tumor material from of all the involved areas of the body could help provide a more complete assessment of a cancer's somatic landscape. However, liquid biopsies also have limitations, including a loss of information of tumor architecture, microenvironment, and potentially low levels of tumor shed into circulation. Additional work will be needed to determine whether liquid biopsies can enhance the current accepted practices used to make a definitive tissue-based diagnosis for a patient with a suspected pediatric solid tumor malignancy.

Staging and Prognosis

Staging is an analysis of physical characteristics of a tumor comprising of many factors such as how large the tumor is, where it is located, and how much it has spread. Staging is taken into account when treatment options are considered and it is an important factor in determining prognosis. While liquid biopsy will not be able to replace tissue imaging for staging purposes, current clinical risk stratification strategies are still not granular enough to differentiate patients who have similar clinical features but ultimately respond differently to a given therapy. Liquid biopsies may provide additional information to aid risk stratification since there is evidence that the level of cancer material shed into the blood correlates with prognosis [8]. In addition, liquid biopsy approaches can be used to identify genomic features associated with prognosis.

Therapy Selection

In patients where there is limited tissue available or surgical biopsies are contra-indicated, liquid biopsies may serve as an option for identification of targetable genomic features. Liquid biopsy may also be useful as a measure of treatment response as levels of detectable circulating tumor material appears to decrease most significantly in patients who are experiencing an effective response to therapy [9]. Furthermore, surviving cancer cells can develop drug resistance due to mutation and evolutionary selection. Identification of points at which tumor biomarkers for these surviving cells change during or after therapy may allow for a quick transition to an efficacious alternative therapy, often before imaging or clinical signs of tumor growth are observed [10]. However, more studies will need to be done to validate these concepts and to understand how to best implement these measures of treatment response into clinical care.

Monitoring

Post-treatment surveillance and in situ surveillance during clinical remission varies depending on the cancer type. Surveillance currently entails repeated physical, hematological, and radiological examinations which can happen as frequently as every 3-6 months. Performing these examinations is costly and burdensome to patients and their families. Studies have aimed to develop surveillance strategies based upon individualized risk [11], however simpler approaches could be implemented with the addition of liquid biopsy, minimizing the burdens patients and families face. A shift toward routine serial implementation of liquid biopsy stands to benefit patients by providing a minimally invasive strategy to detect the presence of residual disease, identify disease progression, and detect the acquisition of somatic events that promote treatment resistance. It is especially important that liquid biopsy be cost-effective for this application, as numerous longitudinal tests may be needed once patients complete therapy and are being monitored for possible relapse [12].

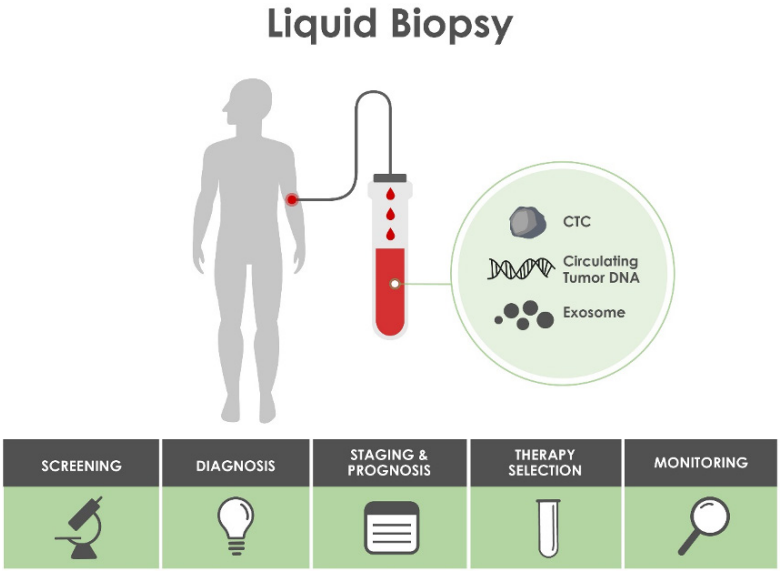

Figure 2: Liquid biopsy applications.

Challenges to Liquid Biopsy Implementation in Pediatric Cancer

There has been a recent uptick in the incorporation of liquid biopsies into clinical trials. In pediatrics, the utility of ctDNA in clinical trials is still being determined. In adult cancer care, liquid biopsies are being used in clinical decision making. For instance, ctDNA is now used within the clinical evaluation process in metastatic non-small cell lung cancer (NSCLC) patients. Widespread implementation of liquid biopsies in pediatric cancer clinical care is still challenging due to several factors:

- **Pediatric tumors have different patterns of genetic mutations than those observed in adults:** The most immediate analysis of circulating tumor nucleic acids focuses on specific alterations in commonly known altered genes. Many pediatric cancers are driven by structural variants such as translocations or changes in the number of copies of a gene, as opposed to point mutations that are commonly seen in adults. Technologies that are optimized to detect these variants are needed in a clinical laboratory environment.
- **More data correlated with tumor tissue is needed from children:** Though there are active prospective pediatric studies that are sampling for liquid biopsy, more are needed with open data sharing agreements. Pediatric cancer is a rare disease and within any given type of pediatric cancer there may only be 300 patients in the United States per year. Large pediatric cancer clinical studies, especially phase 3 studies should incorporate optimized longitudinal liquid biopsy sample collection.
- **Collection, storage, and analysis of liquid biopsy data requires dedicated funds:** The current funding structure for pediatric clinical trials is not well-suited to supporting sampling efforts. Funding of correlative studies in association with clinical trials needs to become a priority for successful implementation of liquid biopsies.
- **Liquid biopsy assays require a lot of blood**: Many liquid biopsy assays, including those that are commercially available, require multiple tubes of blood. This is a challenge that could prohibit the utility of these assays for our youngest patients. However, much of the pediatric-specific liquid biopsy research done thus far demonstrates that these assays are feasible with smaller volumes. Clinical implementation of liquid biopsy assays for pediatrics will need to account for lower volumes of input material
- **Consistent protocols and procedures must be developed for liquid biopsy**: Variation in testing protocols and procedures among different liquid biopsy methods can produce varying results. It is essential that strict standards and regulation of analytical validation are implemented for liquid biopsies to enter regular clinical use. Proper validation requires sufficient sample quantities for repeated testing of known targeted mutations, an especially challenging ask when considering pediatrics. Preanalytical variables should always be controlled as much as possible prior to performing a liquid biopsy test. Rigorous validation ensures confidence in the results of the tests. Validation is also a time and sample intensive process in an environment where these factors are of upmost importance when considering pediatric cancer.

Critical Factors to Promote Liquid Biopsy Adaptation in Pediatric Cancer

During this Summit session, panelists emphasized the activities that would progress successful implementation of liquid biopsies.

Understanding the Pediatric Cancer Landscape

Because liquid biopsy requires an understanding of the variants within a tumor, its implementation in children with cancer requires a thorough understanding of the molecular changes in over 12 major types and 100 subtypes of pediatric cancer. In the past several years, a wide array of sequencing projects have aimed to reveal the molecular changes seen in a range of pediatric cancers. From these, we have learned that:

- The burden of somatic point mutations in pediatric cancer is relatively low compared to adult cancers [5, 13]
- Copy number alterations and structural variants comprise the majority of molecular changes in pediatric cancers [3, 13]
- Pediatric cancers are infrequently driven by somatic mutations that are vulnerable to currently available targeted therapies [2]

Technology that Caters to Pediatric Cancer Alterations

While the current FDA approved assays are indicated for adult cancer, the extensive coverage includes many genes relevant to pediatric cancers, including detection of gene fusions. The widespread availability of these assays suggests they should be evaluated for their suitability for management of pediatric cancers. As strategies arise for adoption of liquid biopsy for pediatric cancer, it is important to tailor our efforts to the unique genomic features of these tumors. Of note, we all need to think creatively about how to move research assays optimized for pediatric cancers into the clinic. This could include new partnerships with industry, academic clinical labs, the FDA, and the NIH. This will not be an easy problem to solve and is probably the most important problem to fix if liquid biopsies are ever going to be a clinical tool for pediatric oncology.

Samples and Data

Serial sampling of patients in prospective pediatric clinical trials is the most efficient way to ensure that there is sufficient data from a limited patient pool to fully understand the feasibility of incorporating liquid biopsy into clinical practice. In practice, efforts to collect serial blood samples, particularly for the study of ctDNA, has gained signficiant support in the pediatric research community. Many of the largest prospective studies sponsored by collective groups and funded by the NIH have now begun to incorporate the collection of serial blood samples for ctDNA studies and other liquid biopsy assays.

It is imperative that these studies be performed on collaboration with providers and patients to ensure adequate clinical trial enrollment and increased emphasis on developing robust, clinically annotated biorepositories. Establishing or increasing capacity of an extant well-equipped infrastructure to handle sample processing, storage, and distribution is also necessary to support the comprehensive study of liquid biopsy in pediatric cancer.

Case Study 1: Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer – Lessons Learned from Adults

Efforts towards successful implementation of liquid biopsy in pediatric oncology can benefit from lessons learned in other disease spaces. Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is an early example of precision medicine in which liquid biopsy has been incorporated into regular practice. Three major themes have contributed to the success of liquid biopsy in this disease:

- Model cancer type: EGFR mutant lung cancer posed as a prime indication to spearhead liquid biopsy efforts because many variables were removed due to the unique biology of the disease. EGFR mutant NSCLC is defined by a few mutations that are clonal drivers and druggable targets. Clear specificity afforded more flexibility in terms of technology options and allowed researchers to collect more data points and perform deeper analyses.
- Early adoption: In 2016, there was an effort to incorporate ctDNA sampling into early-stage clinical trials, including but not limited to the pivotal AURA3 and FLAURA trials, at AstraZeneca. Consistent, early, and methodical liquid biopsy collection and analysis advanced Guardant Health – which led to the first ctDNA NGS CDx – and Biodesix Genestrat – a CLIA ddPCR assay for genotyping EGFR mutations in ctDNA – into regular practice in fewer than five years.
- Serial sampling: Data collected throughout the treatment process has enabled the development of a formalized process that will enable the use of ctDNA for treatment decision making as well as development of new drugs.

Case Study 2: The Blood Profiling Atlas in Cancer

A collaborative model revolving around liquid biopsy implementation has been developed and can serve as a model for developing a pediatric oncology-centered liquid biopsy collaborative. The Blood Profiling Atlas in Cancer (BloodPAC) Consortium was launched on October 17, 2016 as a commitment to the White House Cancer Moonshot to accelerate the development, validation and clinical use of liquid biopsy assays to better inform medical decisions and improve patient care and outcomes. BloodPAC relies on input from regulatory, industry and academic institution members to develop standards and best practices, organize and coordinate research studies through its members and operate the BloodPAC Data Commons (BPDC) to support the exchange of raw and processed data generated by the liquid biopsy research community. Data from retrospective basic, clinical and regulatory member studies, as well as BloodPAC sponsored projects are aggregated and contributed to the BPDC in an effort to establish an open publicly accessible data commons for the global liquid biopsy community. In addition to developing standards and aggregating data, BloodPAC works collaboratively with stakeholders in the field to broaden awareness and implementation of the suggested guidelines and establish a wider chain of feedback and discussion in the community.

Next Steps

By convening a connected community of global 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 meeting, CureSearch works collaboratively with meeting participants and contributors to identify action items and move the topic toward resolutions of the challenges discussed.

To support the implementation of liquid biopsy, CureSearch will convene a working group to further elucidate the remaining challenges and identify solutions to progressing liquid biopsy into regular practice. CureSearch will solicit the input of liquid biopsy providers, the U.S. Food and Drug Administration (FDA), the National Institutes of Health Cancer Therapy Evaluation Program (NIH CTEP), the Children's Oncology Group (COG), committed academics and advocacy groups, as well as patients and families. Goals of this group may include but will not be limited to:

- Establishing and disseminating standard operating procedures for the collection, handling, and storage of liquid biopsy samples
- Determining mechanisms for funding of collection and handling of specimens
- Identifying best practices in evaluating factors and determining time points for sampling
- Building relationships with other consortia so that data can be combined and shared
- Establishing mechanisms to commercialize panels that can address pediatrics and build relationships to test panels

CureSearch aims to identify the pediatric-specific challenges associated with liquid biopsy adoption and partner with existing groups to creatively and collectively address challenges in a non-duplicative efforts. 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 the first 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	Rutgers Cancer Institute of New Jersey
	Professor of Pediatrics	Rutgers-Robert Wood Johnson Medical School
Lia Gore, MD	Co-Director, Developmental Therapeutics Program	University of Colorado Cancer Center
	Ergen Family Chair in Pediatric OncologySection 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 New Technologies for Maximizing Analysis of Solid Tumors.

PANELIST	DESIGNATION	AFFILIATION
Kelli Bramlett, MS	Senior Director of R&D, Clinical Sequencing	Thermo Fisher Scientific
Brian Crompton, MD	Research Co-Director, Solid Tumor Center & Physician	Dana-Farber Cancer Center
	Assistant Professor of Pediatrics	Harvard Medical School
Ryan Hartmaier, PhD	Associate Director, Translational Science	AstraZeneca
Matthew Hiemenz, MD	Senior Pathologist and Associate Medical Director	Foundation Medicine
Sarah Leary, MD	Attending Physician	Cancer and Blood Disorders Center, Seattle Children's Hospital
	Associate Professor of Pediatrics	University of Washington School of Medicine

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