CHILDHOOD CANCER GENOMICS GAPS AND OPPORTUNITIES: IDENTIFICATION OF RESEARCH PRIORITIES

February 4-5, 2015, Workshop Summary

DIVISION OF CANCER TREATMENT AND DIAGNOSIS
AND THE OFFICE OF CANCER GENOMICS,
NATIONAL CANCER INSTITUTE

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CHILDHOOD CANCER GENOMICS GAPS AND OPPORTUNITIES: IDENTIFICATION OF RESEARCH PRIORITIES

Executive Summary

NCI convened a workshop February 4-5, 2015, of representative research teams that have been leaders in defining the genomic landscape of childhood cancers to discuss the influence of genomic discoveries on the future of childhood cancer research. Workshop participants also included clinical researchers, members of regulatory agencies, and members of the childhood cancer research advocacy community. The participants are listed at the end of this document. The workshop focused on the identification of gaps in current understanding and opportunities for future research.

Workshop participants identified the following research gaps and opportunities as areas that warrant future research focus:

- continued discovery research to more comprehensively characterize the genomic and epigenomic alterations that are present in childhood cancers and their clinically relevant subsets;
- clinical research protocols focused on identifying the genomic landscape of childhood cancers at relapse and on evaluating therapeutic strategies for genomically-defined patient subsets at relapse;
- a childhood cancer Genomic Data Commons to facilitate collaboration across research teams and to facilitate the identification and clinical relevance of low-frequency genomic alterations;
- preclinical models that faithfully replicate the relevant genomic alterations of childhood cancers;
- identification of treatments to directly or indirectly target pediatric cancer driver genomic alterations for which there are currently no available targeted agents, including the fusion genes that characterize selected pediatric sarcomas (e.g., Ewing sarcoma, synovial sarcoma, and alveolar rhabdomyosarcoma) and childhood leukemias (e.g., the *MLL* gene-fusion leukemias), the mutated histones found in pediatric high-grade gliomas, and the *SMARCB1* alterations found in rhabdoid tumors; and
- further definition of germline dominant and recessive lesions that predispose to cancer and the maintenance of this information within accessible databases, and the enhancement of the genetic counseling capabilities of institutions that treat children with cancer.

The workshop summary provides details of the key issues addressed at the workshop and focuses on the future research opportunities highlighted by workshop participants. The summary is provided to inform the childhood cancer community about important areas that warrant further research investment. NCI will be supporting research in many of these areas through President Obama's Precision Medicine Initiative and through other research activities.

INTRODUCTION

NCI convened a workshop February 4-5, 2015, of representative research teams that have been leaders in defining the genomic landscape of childhood cancers to discuss the influence of genomic discoveries on the future of childhood cancer research. Workshop participants also included clinical researchers, members of regulatory agencies, and members of the childhood cancer research advocacy community. The workshop focused on the identification of gaps in current understanding and opportunities for future research.

Specific objectives of the workshop included: to survey recent progress in genomic studies of childhood cancers; to consider the need for extensions of these studies; to identify scientific questions raised by the genomic work and consider strategies for pursuing them; and to identify new opportunities created by molecular studies that might allow more effective diagnosis and treatment of childhood cancers.

The workshop concentrated on four major disease categories (leukemias, embryonal tumors, sarcomas, and CNS tumors) and included brief summaries of the current understanding of the genomic landscape for specific cancers within each category. Clinical translation of genomic discoveries for childhood cancers was also discussed.

The text that follows summarizes the key issues addressed at the workshop and focuses on the future research directions highlighted by workshop participants.

CONCLUSIONS TO DATE FROM CHILDHOOD CANCER GENOMICS PROJECTS

Research teams from around the world have made remarkable progress in the past decade in elucidating the genomic landscape of the more common childhood cancers. While the discoveries presented at the workshop will not be detailed here, published reports have documented these advances for low-grade gliomas (1-3), high-grade gliomas (4-7), medulloblastoma (8-14), supratentorial primitive neuroectodermal tumors (PNETs) (15), ependymomas (16-18), neuroblastoma (19-23), Wilms tumor (24-27), retinoblastoma (28), rhabdoid tumors (29, 30), hepatoblastoma (31-34), osteosarcoma (35, 36), Ewing sarcoma (37-39), rhabdomyosarcoma (40-43), acute lymphoblastic leukemia (ALL) (44), and acute myeloid leukemia (AML) (45, 46).

A decade ago it was possible to hope that oncogenes known to be targetable, such as activated tyrosine kinases, might be identified in a high percentage of childhood cancers. However, it is now clear that, with notable exceptions, this is not the case and that the genomic landscape of childhood cancers is highly varied. Not unexpectedly, the mutation frequency in pediatric tumors is much lower on average than in adult cancers (47). Additionally, for a number of these diseases, the cancer-relevant alterations are quite distinctive from those of the common adult cancers, and, even for diseases that occur in both children and adults (e.g., AML and high-grade glioma), the spectrum of mutations in children is distinctive from that observed in adults (46, 48).

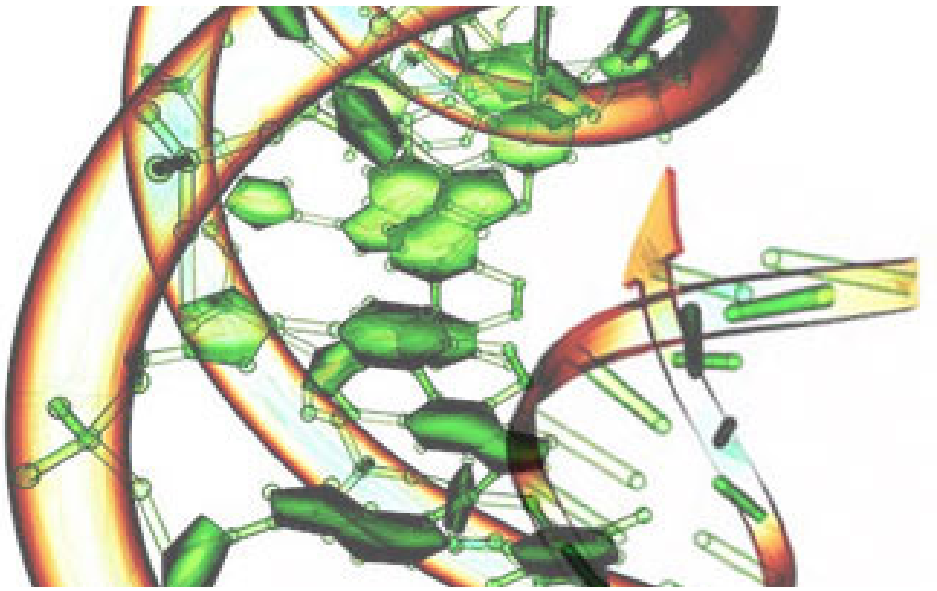
There are examples of genomic lesions that have provided immediate therapeutic direction, including the *NPM-ALK* fusion gene for anaplastic large cell lymphoma (49), *ALK* point mutations for a subset of neuroblastoma (50), *BRAF* and other kinase genomic alterations for subsets of pediatric glioma (51), Hedgehog pathway mutations for a subset of medulloblastoma (52-54), and *ABL* family genes activated by translocation in a subset of ALL (55, 56). Clinical trials designed to take advantage of the therapeutic opportunities created by these activated oncogenes are ongoing or in development. However, these diagnoses and disease subsets represent a small percentage of childhood cancer cases. A caveat is that the genomic landscape of childhood cancers at relapse is underexplored, and, therefore, therapeutic opportunities may be present for existing "targeted" agents that are not apparent based on genomic studies using diagnostic specimens.

For some cancers, the genomic findings have been highly illuminating in identifying genomically defined subsets of patients within histologies that have distinctive biological features and distinctive clinical characteristics (particularly in terms of prognosis). For example, the WNT subgroup of medulloblastoma has excellent outcome, and, in future clinical trials, it will be studied separately so reductions in therapy can be evaluated, with the goal of maintaining favorable outcome while reducing long-term morbidity (57). However, the prognostic significance of recurring genomic lesions for many other cancers remains to be defined.

A key finding from genomic studies is the extent to which the molecular characteristics of childhood cancers correlate with their tissue (cell) of origin. As with most adult cancers, mutations in childhood cancers are not randomly

distributed across diseases. Instead, distinctive oncogenic insults are associated with specific susceptible cell types and time windows of vulnerability. Examples include the presence of H3.3 and H3.1 K27 mutations almost exclusively among pediatric midline high-grade gliomas (58-60), the loss of *SMARCB1* in rhabdoid tumors (29, 30), the presence of *RELA* translocations in supratentorial ependymomas (16), and the presence of specific fusion genes in pediatric sarcomas (37-40, 61). Another theme across multiple childhood cancers is the contribution of mutations and copy number alterations of genes involved in normal development of the tissue of origin of the cancer (25, 27, 42, 62, 63), as well as the contribution of genes involved in epigenomic regulation (64).

Structural variations play an important role for many childhood cancers. Particularly in the leukemias and sarcomas, translocations resulting in oncogenic fusion genes or overexpression of oncogenes play a central role. However, for other childhood cancers (e.g., osteosarcoma) that are primarily characterized by structural variations, recurring fusion genes have not been found. Mechanisms by which recurring structural variations can have oncogenic effects have been identified for osteosarcoma (translocations confined to the first intron of *TP53*) and medulloblastoma (juxtaposition of *GFI1* or *GFI1B* coding sequences proximal to active enhancer elements leading to transcriptional activation ['enhancer hijacking']) (14, 35). However, the oncogenic mechanisms of action for the recurring structural variations of other childhood cancers (e.g., the segmental chromosomal alterations in neuroblastoma) remain to be elucidated.



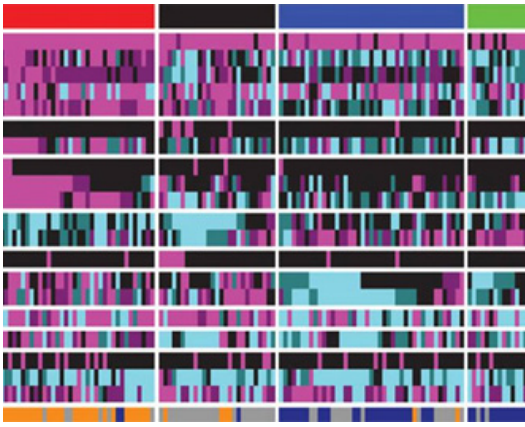
CONTINUED NEED FOR CHILDHOOD CANCER GENOMICS DISCOVERY RESEARCH

A key conclusion from the workshop was that the discovery phase is not over for childhood cancer genomics and that more discovery genomics/epigenomics studies are needed. The areas identified for future study include the less common cancers and rare subtypes, tumors at relapse to define heterogeneity and evolution of clones over time, tumors from multiple sites to define intrapatient spatial heterogeneity, systematic evaluations of noncoding regions to define their role for pediatric cancers, and epigenomic evaluations to determine how the genomic alterations of specific cancers create a chromatin architecture that maintains the transformed phenotype.

Pediatric genomic sequencing projects for some cancers (e.g., ALL, AML, medulloblastoma, and neuroblastoma) have included hundreds of cases (primarily using specimens from the time of diagnosis). However, for other cancers the number of well characterized specimens is much lower. In addition, there are now biologically defined subsets for some childhood cancers (e.g., the four subtypes of medulloblastoma), and for some cancers only small numbers of relevant subsets have been comprehensively characterized. Therefore, while the primary oncogenic alterations affecting most patients in these populations have been identified, alterations affecting up to 10% or even more of patients may have been missed for some diagnoses or subsets of patients. These yet to be discovered alterations may provide important prognostic and/or therapeutic information.

The role of noncoding genomic alterations for childhood cancers remains relatively unexplored. Childhood cancer researchers have been leaders in applying whole genome sequencing (WGS) and integration with transcriptome and chromatin immunoprecipitation sequencing (ChIP-Seq) data to identify oncogenic roles for recurring noncoding genomic alterations. As examples, structural variants affecting a common region that resulted in "enhancer hijacking" and GFI1 and GFI1B overexpression were identified in a subset of medulloblastoma cases (14). Insertion and deletion mutations in the enhancer region of *TAL1* were identified as a recurring event in T-cell ALL that leads to *TAL1* overexpression (65). A small number of childhood cancers have been identified as having *TERT* promoter mutations that lead to TERT overexpression (31, 66, 67). While these examples illustrate the potential importance of noncoding alterations, due to the limited number of cases systematically studied, they may represent only a small proportion of the number of oncogenic noncoding genomic alterations that will eventually be discovered.

Another area for future discovery is defining the contribution of epigenomics to childhood cancers and the role of mutations in chromatin remodeling erasers/writers/readers. The recent description of the ability of EWS-FLI1 multimers to induce chromatin opening and create de novo enhancers that physically interact with their target promoters—while at the same time displacing wild-type ETS transcription factors from canonical ETS motifs—highlights the potential utility of this line of research to contribute to understanding the chromatin blueprint that maintains the cancer phenotype (68). However, there remains a very limited understanding for most cancers of the chromatin structure required for maintaining transformation, and uncertainty remains about how best to



Gene sequence

systematically characterize the epigenome in cancers.

The clonal heterogeneity of childhood cancers (both spatial and temporal) and the contribution of this heterogeneity to treatment failure also remain relatively unexplored. For ALL, the study of paired diagnostic and relapsed specimens has allowed the identification of clonal heterogeneity at both time points, which in turn has demonstrated that minor clones at diagnosis can become major clones at relapse (69). The extent of spatial heterogeneity (i.e., cells at different locations in a tumor or in different metastatic tumors having different genomic alterations) remains underexplored. Systematic genomic characterization of tumors obtained for clinical purposes can contribute to these types of studies, as can programs for obtaining tumor tissue at autopsy for research purposes (70, 71). The utility of circulating nucleic acids and circulating tumor cells for providing clinically useful information about the genomic composition of tumors, for assessing tumor evolution over time, and for quantifying molecular residual disease is an understudied area for childhood cancers. Studying circulating tumor cells for childhood cancers will require assay development independent of adult efforts that are based on identifying epithelial antigens, as these markers are not useful for most pediatric tumors.

ELUCIDATING THE GENOMIC LANDSCAPE OF CHILDHOOD CANCERS AT RELAPSE

Most genomic characterization of childhood cancers to date has been performed on specimens obtained at diagnosis, and hence the majority of conclusions about the genomic landscape of childhood cancers are for the time of diagnosis. A critical area for future discovery research is defining the genomic landscape at relapse and identifying for the various types of childhood cancers the genomic alterations that are selected for between diagnosis and relapse. The most work to date for pediatric genomic characterization at relapse has been for ALL, and the identification of mutations not detectable at diagnosis and present at relapse illustrates the potential contribution of this strategy. For ALL at relapse, recurring mutations in *NT5C2* and *CREBBP* and *USH2A* have been identified (69, 72-74). Mutations in *NT5C2* likely contribute to resistance to thiopurines, an important component of maintenance therapy for children with ALL (72, 73). Mutations in *CREBBP* are associated with resistance to glucocorticoids, which are a mainstay of therapy for pediatric ALL (74). Studies of relapsed ALL have been possible because of the larger numbers of children with ALL compared to other pediatric cancers and because of the standard clinical practice in ALL of obtaining tissue confirmation of relapse.

For pediatric solid cancers, there is much more limited genomic data for specimens obtained at relapse. Eleveld et al. applied WGS to paired diagnostic and relapse samples from 23 cases of neuroblastoma to define somatic genetic alterations associated with relapse (23). They observed enrichment in the relapse specimens of mutations in genes associated with RAS-MAPK signaling, with 15/23 relapse samples containing somatic mutations in genes involved in this pathway, each mutation consistent with pathway activation. In addition, three relapse specimens showed structural alterations involving MAPK pathway genes consistent with pathway activation, so aberrations in this pathway were detected in 18/23 relapse samples (78%). Seven of the 18 alterations were not detectable in the primary tumor, highlighting the importance of genomic evaluations of tissue obtained at relapse.

Progress in understanding the genomic landscape of pediatric solid tumors and brain tumors at relapse will require a change in philosophy

Challenges in studying solid tumors at relapse include the practice of not consistently obtaining tissue confirmation at relapse and the observation that, even when tissue confirmation at relapse is obtained, specimens are limited in size. Progress in understanding the genomic landscape of pediatric solid tumors and brain tumors at relapse will require a change in philosophy and clinical practice around the role of tissue confirmation of relapse, which in turn will require collaboration with radiologists, interventional radiologists, and molecular pathologists to assure safe and high-quality specimen procurement. Technological advances in obtaining circulating tumor cells and/or tumor DNA in blood could make some of the challenges easier, although this approach will not work for every cancer. For cancers of the bone, such as osteosarcoma, incorporating methods of pathology analysis that do not require routine acid

decalcification will contribute to genomic advances, as current practice for decalcification limits genomic analysis.

Multiple research projects involving the genomic characterization of childhood cancers at relapse are ongoing or in the planning stages. A common theme of these studies is combining the research objective of cataloguing the genomic alterations present at relapse with the therapeutic objective of identifying "targetable" alterations to provide information that can be used for individualized therapeutic interventions for study participants.

Stefan Pfister, Dr. Med., German Cancer Research Center (DFKZ), presented the INFORM registry (**IN**dividualized Therapy **FO**r **R**elapsed **M**alignancies in Childhood) project, which is genomically characterizing the cancers of patients with relapsed/progressive or refractory disease from the clinical centers of the Society for Pediatric Oncology and Hematology (GPOH). The pilot phase of the study does not include a formal treatment component, although results are returned to treating physicians and can be used as medically indicated. After the pilot phase is completed, the plan is to assign patients to specific treatments based on the genomic results. The INFORM molecular diagnostics workflow provides data on copy number variation (CNV) from low-coverage WGS, single nucleotide variants (SNV) and insertions-deletions (in-dels) from WES, gene fusions and alternatively spliced transcripts from RNA-Seq, identification of outlier transcripts from gene expression profiling, and methylation-based tumor DNA classification from 450K methylation arrays. Results from the molecular diagnostics workflow are reviewed by a tumor board that develops a prioritized list of therapeutic targets based on the level of clinical and preclinical evidence supporting the potential targets identified. As examples, findings range from "very high" priority for confirmed oncogenic drivers (e.g., *PTCH1* mutation in sonic hedgehog [SHH] medulloblastoma) to "borderline" priority for potential overexpressed drivers (e.g., ALK/MET/FGFR4 overexpression in alveolar rhabdomyosarcoma). To date, 48 cases have been fully characterized and approximately 50% have had targets identified with borderline or higher priority.

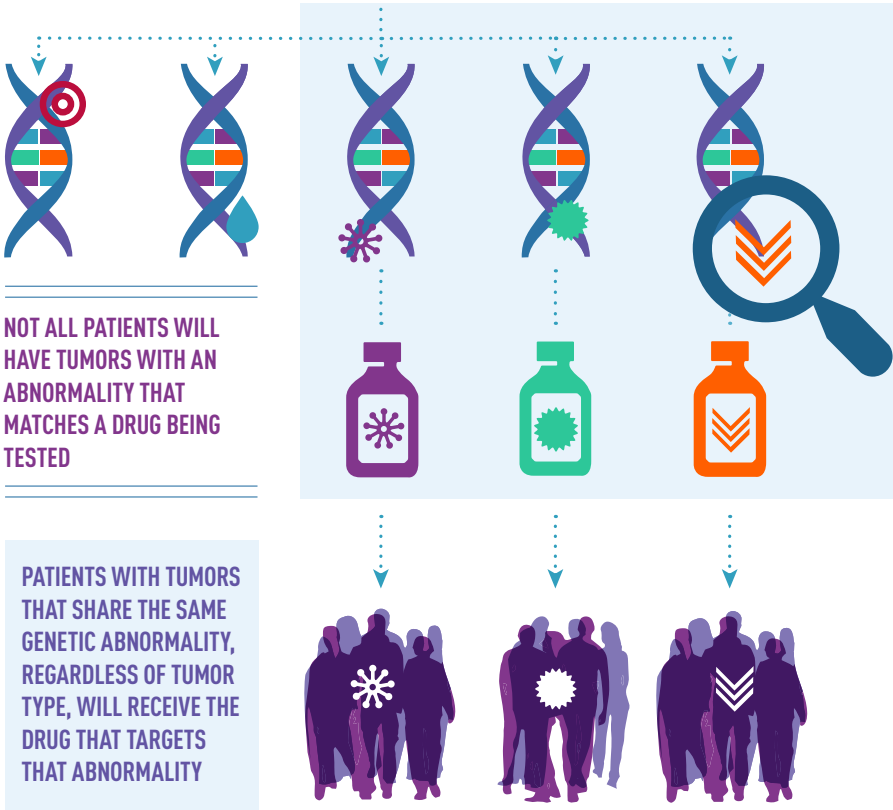
Dr. Pfister also described a European harmonization program involving research teams in Paris (Institut Gustave-Roussy and Institute Curie), Amsterdam (Academic Medical Center, University of Amsterdam), London (Great Ormond Street Hospital), and Heidelberg (DFKZ). The harmonization process includes reaching consensus on identical nucleic acid extraction procedures, sequencing and microarray platforms, and bioinformatics pipelines. Additional objectives include development of a joint target-drug database, a joint clinical documentation database, and a joint repertoire of investigator-initiated clinical trials.

Katherine Janeway, M.D., M.M.Sc., Dana Farber Children's Hospital Cancer Center, described the iCat (**i**ndividualized **ca**ncer **t**herapy) protocol, a multicenter study assessing tumor molecular profiles in advanced pediatric solid tumors. Tumor profiling consisted of mutation detection initially with a Sequenom assay (OncoMap: >450 known oncogenic mutations in >40 genes) and later with a targeted sequencing assay (OncoPanel: 275 genes with 91 introns in 30

genes), copy number assessment with array comparative genomic hybridization (aCGH) and, in some cases, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) validation of genetic findings. Tumor profiling results were reviewed by a panel of experts in pediatric oncology, molecular pathology, genetics, cancer biology, and developmental therapeutics. iCat recommendations were made if a potentially targetable variant was present and a matched targeted drug was available via a clinical trial or as a Food and Drug Administration (FDA)-approved agent with an age-appropriate dose and formulation. Recommendations were tiered from 1 (strongest) to 5 (weakest) based upon the strength of the supporting evidence. Tiers 1 and 2 correspond to clinical data in support of the recommendation, tiers 3 and 4 to pre-clinical data in support of the recommendation, and tier 5 to consensus of opinion. With four participating institutions, 100 patients were enrolled in 14 months. Ninety-three patients have completed testing and review to date, and 27 (29%) patients received an iCat recommendation, with most being tier 3 or 4. Examples of iCat recommendations included: a CDK4/6 inhibitor for *CDKN2A/B* deletion or *CCND1*, *CDK4*, or *CDK6* gain; a BET bromodomain inhibitor for *MYC* or *MYCN* gain; a MEK inhibitor for *HRAS*, *NRAS*, or *BRAF* mutations; and an ALK inhibitor for *ALK* mutations.

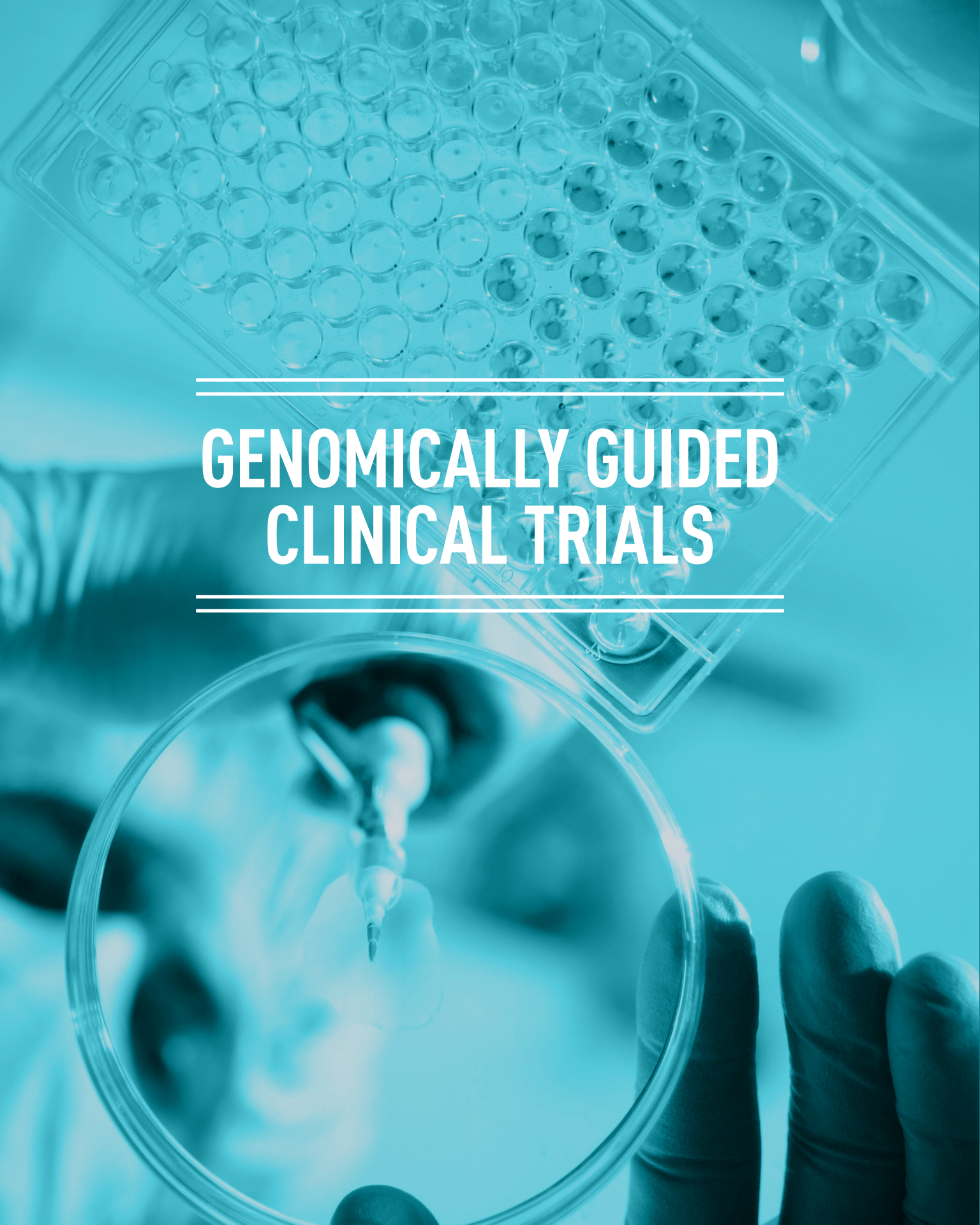
Building upon the iCat protocol is the **G**enomic **A**ssessment **I**nforms **N**ovel Therapy (GAIN) Consortium, a collaboration of 12 institutions. The GAIN Consortium will investigate the clinical impact of a precision cancer medicine approach in recurrent/refractory pediatric cancers and plans to enroll 825 patients with recurrent/refractory or high-risk solid tumors over 3 years. The measures of clinical impact will include the frequency of genomic alterations indicating potential activity of a matched targeted therapy, patient access to a matched targeted therapy, and the effect of genomic, disease, and therapeutic factors on patient outcomes. A pediatric leukemia clinical genomics trial will be conducted in parallel with the GAIN Consortium solid tumor trial.

NCI and the Children's Oncology Group (COG) are planning a clinical trial (NCI Pediatric MATCH) to both advance precision medicine for children with cancer and to increase knowledge about the genomics of relapse for pediatric cancers. The NCI Pediatric MATCH clinical trial is being modeled after a similar trial for adults (NCI-**M**olecular **A**nalysis for **T**herapy **Ch**oice, or NCI-MATCH) that uses an "umbrella" design with multiple molecularly-based



A portion of the NCI-MATCH clinical trial infographic on Cancer.gov

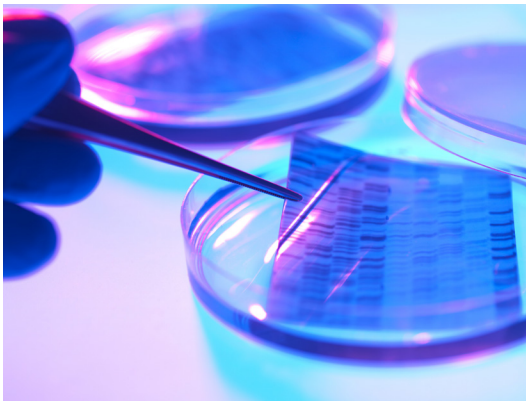
phase II studies embedded within the overall clinical trial (75). Patients with a solid tumor undergo biopsy at disease recurrence so they can have their tumors characterized for pre-defined "actionable" genomic alterations. Patients with a genomic alteration that matches the activity profile of one of the study agents are assigned to the treatment arm for this agent. While sequencing for eligibility to receive a study agent will be restricted to a set of genes for which there are relevant agents, the tissue specimens will additionally be submitted for comprehensive genomic analysis for research purposes. Hence, the trial will both provide a mechanism for access to agents for children with actionable mutations while at the same time contributing to defining the genomic landscape of childhood cancers at relapse.



GENOMICALLY GUIDED CLINICAL TRIALS

Basing diagnosis and treatment plans on selected molecular characteristics of cancer cells is standard practice for some childhood cancers, but recent genomic discoveries provide further opportunities for enhancing diagnosis and treatment decisions. In addition to the relapse-focused projects described above, other projects presented at the workshop described incorporating comprehensive genomic characterization as a standard component of clinical research protocols as described below.

Will Parsons, M.D., Ph.D., Texas Children's Cancer Center (TCCC), described the Baylor Advancing Sequencing into Childhood Cancer Care (BASIC^3) project and clinical trial that is designed to integrate information from Clinical Laboratory Improvement Amendments (CLIA)-certified germline and tumor WES into the care of newly diagnosed solid tumor patients at the TCCC and to perform parallel evaluation of the impact of tumor and germline exomes on families and physicians. The germline exome results are assessed for their impact on cancer surveillance and genetic testing of family members. The tumor exome somatic variant results are also evaluated for their impact on treatment decisions at relapse. A separate component attempts to utilize observations of physicians and families participating in the study to develop an ethical framework to guide shared decision-making for parents and pediatric specialists around use of exome data. To date, over 190 patients have enrolled in the study, with families showing high interest and high participation rates. "Actionable" somatic mutations have been identified in a minority of pediatric CNS and non-CNS solid tumor patients, with the most common mutations identified being *CTNNB1* (7%), *TP53* (5%), and *BRAF* (3%). In 5% to 10% of patients, WES identifies germline alterations associated with dominant cancer predisposition syndromes. As genomic testing becomes more widely available, it will become increasingly important to enhance the capabilities for genetic counseling at institutions that treat children with cancer. A related matter is the need to develop a comprehensive compendium of the germline dominant and recessive lesions that predispose to childhood cancer and to maintain a readily accessible database of these lesions.



Yael Mosse, M.D., Children's Hospital of Philadelphia, presented a disease-specific approach to precision medicine in neuroblastoma. For neuroblastoma, the most obvious therapeutic target identified to date is ALK, which is activated by mutation in approximately 10% of newly diagnosed high-risk cases and amplified in smaller percentage of cases (50). The most common activating mutations are at R1275, F1174, and F1245 (50). High-risk neuroblastoma patients with an activating *ALK* mutation or amplification have significantly lower event-free survival (EFS) compared to cases without these alterations (50). Among the factors that complicate the application of ALK inhibitors for the treatment of neuroblastoma is that, while the most common *ALK* mutations are transforming, not all clinically observed ALK mutations are functionally defined (50). Furthermore, different *ALK* mutations show differential sensitivity to kinase inhibition, with some ALK mutations not responding. For example, the F1174L and F1245C amino acid substitutions, which together comprise nearly 40% of *ALK* mutations observed in clinical specimens, show intrinsic resistance to crizotinib (50). One strategy for translating ALK inhibitors to the clinic is to combine an ALK inhibitor with chemotherapy, and a clinical trial utilizing this strategy is under development by

the COG for children with newly diagnosed high-risk neuroblastoma. A second strategy is developing and utilizing ALK kinase inhibitors that show more uniform activity across the range of *ALK* mutations observed in neuroblastoma. A third strategy is identifying combinations of "targeted" agents that show more robust activity than single agents against biologically defined subtypes. Identifying these combinations requires genomically characterized cell lines and xenografts that faithfully recapitulate the characteristics of the clinical disease.

James Downing, M.D., St. Jude's Children's Research Hospital (SJCRH), described the SJCRH Genomes for Kids program that will apply WGS, WES, and RNA-seq to specimens from all new cancer patients admitted to SJCRH during a single year, with a planned start date in 2015. All sequencing and data analysis will be performed in the SJCRH CLIA-certified laboratory. The entire genome and transcriptome will be analyzed through an integrated analysis pipeline incorporating the WGS, WES, and RNA-seq data. Clinical reports will include information on pathologically significant gene alterations, which for tumor specimens includes 565 cancer genes and for normal tissue includes 60 autosomal dominant cancer predisposition genes (the 26 genes recommended by the American College of Medical Genetics and Genomics [ACMG] (76) and an additional 34 genes felt to be important for the medical management of children with cancer). Based on results from the Pediatric Cancer Genome Project, approximately 8% of cases are anticipated to have pathologic or likely pathologic germline mutations in one of these 60 hereditary cancer predisposition genes.

While "typing" genomic alterations or molecular characteristics to diagnose specific cancers is important, one question to be resolved for multi-institutional clinical trials is the extent to which this testing will be centralized at one (or a few) sites versus being widely performed at local institutions. Complex tests for rare populations benefit by centralization, and this approach is being followed in the German INFORM study, Pediatric MATCH, and the GAIN Consortium study. However, an infrastructure for more generally performing central molecular testing for childhood cancer clinical trials does not currently exist in North America, and there are resource and practice constraints that create challenges to establishing this capability.

Key Finding

A key issue in accelerating the pace at which genomic characteristics are utilized in clinical decision-making is the extent to which these characteristics are used to define specific diagnoses and to classify patients for therapy. As an example, World Health Organization (WHO) criteria for classifying AML now include specific molecular characteristics that have therapeutic and/or prognostic significance (e.g., *NPM1*, *CEBPA*, and *FLT3* mutation for AML, as specified in the 2008 WHO classification) (77). Efforts are underway now to create a consensus for a molecular and histopathologic classification for pediatric low-grade gliomas, low-grade glioneuronal tumors, and other brain tumors with the upcoming update of the WHO Classification of Tumors of the Central Nervous System. Similarly, the diagnosis of alveolar rhabdomyosarcoma for COG clinical trials has transitioned from a histology-based diagnosis to a molecular diagnosis requiring presence of the *PAX-FKHR* gene fusion (78, 79). An argument can be made for applying a similar approach for Ewing sarcoma by requiring the presence of an *EWSR1* and *ETS* family gene fusion for the diagnosis of this disease.

OTHER GENOMIC RESEARCH ISSUES

A relatively large number of childhood cancer specimens have been sequenced, and the pace of sequencing (both comprehensive and targeted) is accelerating. While databases for individual projects exist and while deposition of data is required at publication, workshop participants were concerned that existing resources for the collection and analysis of data across projects are inadequate. In particular, databases that link genomic data and that include rich clinical annotation for multiple research projects are lacking. This inadequacy is particularly problematic for childhood cancers, given the limited numbers of cases comprehensively characterized for most cancer types. A resource that collected clinical and genomic data in a standardized manner would allow the clinical significance of uncommon genomic alterations (e.g., *STAG2* mutation in Ewing sarcoma) to be determined more quickly and reliably and would allow historical controls to be established for molecularly defined subsets of specific cancers (e.g., *BRAF* mutated high-grade gliomas).

NCI is developing the NCI Genomic Data Commons (GDC) database to foster the molecular diagnosis and treatment of cancer. The GDC is housed at the University of Chicago and will have the following functionalities:

- Importing and standardizing genomic and clinical data from large-scale, NCI-managed legacy programs, including TARGET;
- Harmonizing the mapping of sequence data to the genome/transcriptome;
- Implementing state-of-art methods for derived data, including mutation calls, copy number, structural variants, and digital gene expression;
- Maintaining data security and managing authorized access;
- Providing data for download and, potentially in the future, for computation on a co-localized compute cluster; and
- Developing a robust process to upload new genomic data to the GDC for comparison with existing data and shared access.

In the near future, the GDC will be able to support research teams in identifying low-frequency cancer drivers, defining genomic determinants of response to therapy, and composing clinical trial cohorts sharing targeted genetic lesions. For the GDC to have a meaningful impact for childhood cancers, the research teams generating the data will have to be willing to submit their datasets with the relevant corresponding clinical data, which will require substantial time and effort.

A recurring observation at the workshop was the relatively low number of mutations in childhood cancers that have transcription factor fusion genes as their oncogenic drivers. Examples include Ewing sarcoma (*EWS-FLI1*), alveolar rhabdomyosarcoma (*PAX-FKHR*), synovial sarcoma (*SS18–SSX*), and *MLL-AF4* for infant leukemias (*MLL*-fusion genes). Application of precision medicine principles to these cancers will require ways to directly target the fusion genes or alternatively to identify susceptibilities created by the fusion genes. One strategy is to develop small molecule inhibitors directly targeting the transcriptional fusion oncoprotein or its obligatory interactors. Examples of this strategy include the

small molecule YK-4-279 that blocks EWS-FLI1 from interacting with RNA helicase A (RHA) (80), inhibitors of DOT1L that block the leukemogenic activity of MLL fusion proteins (81), and a small-molecule inhibitor of the aberrant transcription factor CBFBeta-SMMHC that blocks binding to RUNX1 (82). Another strategy is the application of functional high through-put genomic screens to identify genes selectively involved in proliferation and survival for pediatric cancers driven by fusion proteins, such as Ewing sarcoma (83), rhabdomyosarcoma (84), and alveolar soft part sarcoma (85). Functional genomics studies are also needed to identify the biological significance of variants of unknown significance in known cancer genes, and results from these studies need to be assembled and then made available in a manner such that they are quickly available to and usable by the pediatric oncology community.

Application of precision medicine principles requires preclinical models that replicate the relevant genomic alterations present in tumor specimens of specific diseases. The ability to xenograft ALL specimens in non-obese diabetic/severe combined immunodeficient (NOD.Cg-Prkdc^{scid}, also termed NOD/SCID) or NOD/SCID/Il2rg^{tm1wjl}/SzJ (NSG) mice with high success rates has allowed testing of targeted agents against molecularly characterized ALL xenograft models as illustrated by research projects evaluating relevant kinase inhibitors against models with specific JAK mutations and kinase fusions (86-88). However, for most cancer types the number of comprehensively characterized models is small and information about these models is not readily available. A central repository for molecular characterization data for preclinical models could create virtual panels of well-credentialed models that could expedite development of targeted agents for childhood cancers, assuming a mechanism for distribution of the models to qualified researchers. The NCI-supported Pediatric Preclinical Testing Program (PPTP) has models for which WES has been performed with data available through the TARGET Data Coordinating Center. The PPTP observed that its panels of xenograft models have low response rates to many targeted agents, even when there is evidence of pathway activation from pharmacodynamic studies (e.g., phospho-ERK expression for the MAPK pathway). However, for the small number of models that do respond, a mutation in a gene relevant to the agent's target has often been observed, as illustrated by the presence of the *BCR-ABL1* fusion gene in a model responding to the SRC-ABL inhibitor dasatinib (89), a *PALB2* mutation in a model responding to the PARP inhibitor talazoparib (90), and a *BRAF* V600E mutation in an astrocytoma xenograft responding to the MEK inhibitor selumetinib (91). Having large panels of genomically characterized models will allow drug/gene relationships such as these to be identified/confirmed in the context of childhood cancers.

Regulatory agencies will play an important role in determining how genomic characterization is developed for clinical use for childhood cancers (92, 93). Elizabeth Mansfield, Ph.D., FDA, described the proactive approach taken by the agency in developing a regulatory framework in which to promote rapid innovation in genomic characterization while at the same time ensuring safety and efficacy. The FDA has developed a draft guidance document for how it proposes to regulate laboratory developed tests (LDT) (i.e., a type of in vitro diagnostic test that is designed, manufactured and used within a single

laboratory) (93, 94). Such tests will include some that are developed for use in the genomic characterization of pediatric cancers for clinically relevant alterations. Key characteristics of the regulatory framework for LDTs include a risk-based approach with greater focus on highest-risk tests and a phased-in approach in which the highest-risk tests are prioritized for action. Potentially relevant to childhood cancer genomics is the rare disease "carve out", which applies to tests offered 4,000 or fewer times per year. The FDA has proposed continued enforcement discretion for premarket review and quality system requirements for LDTs used for rare diseases. The FDA has also prepared a discussion paper regarding regulatory oversight of next-generation sequencing diagnostic tests and is seeking public comment on the options described in a preliminary discussion paper (95). Another regulatory issue relevant to clinical applications of pediatric cancer genomic characterization is the investigational use of tests in which results are returned for clinical decision making. These investigational tests are not exempt from regulation, with the extent of regulatory oversight determined by the risk level associated with use of the test. For tests associated with significant risk, an Investigational Device Exemption (IDE) must be submitted and must provide evidence (usually analytical performance on key parameters) that the test is "safe" (i.e., likely to perform as expected). Once the IDE is approved, the clinical trial in which the test is utilized is conducted under the IDE, with reporting requirements as specified by regulation.

SUMMARY

While extraordinary progress has been made in defining the genomic landscape of childhood cancers, workshop participants identified critical research gaps and opportunities to timely and effective clinical translation of genomic discoveries. There was consensus that the discovery phase has not ended and that further comprehensive molecular characterization research projects are needed to define the prevalence and clinical significance of somatic alterations for the less common childhood cancers, to determine the extent of intrapatient spatial tumor heterogeneity and its role in treatment failure, and to identify the role of noncoding genomic alterations for childhood cancers. A priority for future discovery research is determining the genomic alterations that are arise at relapse, so their contribution to treatment failure can be deciphered. A number of ongoing and planned clinical trials will be addressing these research objectives. Clinical trials such as the Pediatric MATCH study, the INFORM registry, and the GAIN Consortium study will make important contributions to understanding the genomics of relapse while at the same time supporting a therapeutic application of the principles of precision medicine for children at relapse. Given the number of research teams developing genomics data for childhood cancers and the relatively low frequency of specific childhood cancers, there is a critical need for aggregating data in a manner that allows facile analysis so sufficient numbers of cases can be obtained to define the clinical significance of recurring genomic alterations. Well-resourced collaborative efforts across institutions, countries, and continents will be needed to translate present discoveries and to make new discoveries so the full promise of precision medicine is extended to children with cancer.

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