PRECISION MEDICINE IN THE PEDIATRIC ONCOLOGY CLINIC: FROM FEASIBILITY ASSESSMENT TO CLINICAL IMPACT

Katie Janeway, MD, MMSc
Director, Pediatric Solid Tumor Program
Director, Clinical Genomics

DANA-FARBER  Boston Children’s
CANCER AND BLOOD DISORDERS CENTER
CANCER DEVELOPMENT

Genetic mutation

Cancer develops when damage to a cell’s DNA allows or causes the cell to grow and divide uncontrollably, eventually forming a malignant tumor.

SEQUENCING OR TUMOR PROFILING
READ THE DNA LETTERS TO IDENTIFY THE ERRORS OR MUTATIONS
BACKGROUND

GENE FUSION
IMPORTANT TYPE OF MUTATION IN PEDIATRIC CANCERS

BLUE RIBBON PANEL RECOMMENDATIONS

CANCER MOONSHOT
cancer.gov/brp

E. Fusion oncoproteins in pediatric cancer.
   - Improve understanding of the abnormal fusion proteins that result from chromosomal translocations and drive many pediatric cancers.
Learn from individual patient experiences to fundamentally change care for all children with cancer
REACHING THE GOAL

1. Get patients together – observe patterns
2. Identify the mutations
3. Connect mutation to a drug
4. Get the patient the drug
5. Measure and record the response
COMPLEXITY OF PRECISION CANCER MEDICINE

The goal of precision medicine is to treat patients with drugs that target the specific genetic mutations in their tumors, regardless of where the tumors are found. This approach may improve the success of treatment and reduce side effects.

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“I'm here about the details.”
DANA-FARBER PROFILE

• Enterprise level research project 3 hospitals: DFCI, BCH and BWH started 2012

• All children with cancer or suspected cancer seen at Boston Children’s or Dana-Farber offered the opportunity to participate starting in 2013

• Participation allows
  • Use of clinically acquired, leftover specimens for research
  • Bank specimens and derivatives
  • Linkage to clinical data

• Patients with > 10 FFPE unstained slides 20% tumor → tumor only sequencing performed in a clinical lab

• Results with potential to impact clinical care returned to primary oncologist and patient
ONCOPANEL REPORT

SNVs/INDELs

Tier 4 variants:
- ARHGAP35 c.2680G>A (p.D894N), exon 1 - in 3% of 635 reads ***
- BCL2L12 c.396C>A (p.S132F), exon 3 - in 44% of 704 reads ***
- DDR2 c.1508G>C (p.C503S), exon 14 - in 52% of 400 reads ***
- DNMT3A c.1706C>G (p.P569R), exon 3 - in 47% of 788 reads ***
- NRG1 c.1444C>A (p.P482T), exon 13 - in 50% of 697 reads ***
- POLE c.3778G>A (p.R1260T), exon 30 - in 55% of 418 reads ***
- PRF1 c.824A>C (p.E275A), exon 3 - in 45% of 642 reads ***
- SLX4 c.635G>A (p.R212Q), exon 3 - in 48% of 706 reads ***

Structural Variants:
A reciprocal PAX3-FOXO1 fusion is identified with 3 fusion sequences aligned (chr13:41144960 to chr2 223081811; chr2:223081833 to chr13:41144902; chr2:223081811 to chr13:41144960). All fusion sequences have breakpoints in PAX3 intron 7 and FOXO1 intron 1, which are typical (COSF248 and COSF956). All fusion sequences are consistent with respect to coding strand and direction. This result is consistent with the FOXO1 rearrangement detected by FISH on a prior case (S12-11382, CG12-M08112), and supports the diagnosis of alveolar rhabdomyosarcoma.

Mutational Signatures:

MMR-Status: Proficient (MMR-P / MSS)

Mutational Burden:

Tumor Mutational Burden/Megabase: 6.064
This is higher than 73% of all Soft Tissue Sarcoma cancers sequenced by this version of OncoPanel.
This is higher than 52% of all Profile cases sequenced by this version of OncoPanel.
A 16 month old with recurrent extra-cranial (non-brain) solid tumor enrolls on a clinical sequencing study at your institution. As part of this study a targeted next generation panel test will be run on tumor and tumor profiling will be returned to the patient’s oncologist. What is the approximate likelihood that a variant is identified for which there is some evidence linking the variant to response to targeted therapy or that a variant is identified that informs clinical management by either suggesting a possible germline cancer risk syndrome or clarifying diagnosis?

A) 85%
B) 60%
C) 40%
D) 5%
A child with a recent diagnosis of cancer is being evaluated at your institution. Part of the initial work up at your institution is a whole exome sequencing of paired tumor and normal. What is the chance that the normal whole exome sequencing will reveal an autosomal dominant germline mutation increasing the risk of developing cancer?

A) This is not known at this point
B) 1%
C) 50%
D) 10%
MULTI-INSTITUTION PCM STUDY IN PEDIATRIC ONCOLOGY: THE ICAT1 STUDY

- Aim: to determine whether it is feasible to identify key gene variants and make an individualized cancer therapy or iCat recommendation using currently available clinical sequencing tests

Eligibility: High risk extracranial solid tumors

Expert Panel
SOMATIC VARIANT CURATION

Tier 1 or 2

Tier 3 or 4

Tier 5
• High degree of physician and patient engagement

- Conducting a multi-institution study is feasible
  - 40% patients enrolled from 3 collaborating Institutions
  - >90% would participate again (Marron J., PBC, 2016)
## ICAT1 RESULTS

### iCat Recommendation Tier

<table>
<thead>
<tr>
<th>Tier</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>1</td>
</tr>
<tr>
<td>Tier 2</td>
<td>2</td>
</tr>
<tr>
<td>Tier 3</td>
<td>8</td>
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<tr>
<td>Tier 4</td>
<td>16</td>
</tr>
<tr>
<td>Tier 5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31 patients</strong></td>
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</table>

### Known or Likely Deleterious Mutation

<table>
<thead>
<tr>
<th>Gene</th>
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<th>Diagnosis</th>
<th>Tier</th>
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</thead>
<tbody>
<tr>
<td>ALK</td>
<td>p.F1174L (c.3520T&gt;C)</td>
<td>NBL</td>
<td>3</td>
</tr>
<tr>
<td>ALK</td>
<td>p.R1275Q (c.3824G&gt;A)</td>
<td>NBL</td>
<td>1</td>
</tr>
<tr>
<td>BRAF</td>
<td>p.V600E (c.1799T&gt;A)</td>
<td>DFS</td>
<td>2</td>
</tr>
<tr>
<td>FGFR4</td>
<td>p.V550L (c.1648G&gt;T)</td>
<td>ERMS</td>
<td>3</td>
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<tr>
<td>HRAS</td>
<td>p.Q61K (c.181C&gt;A)</td>
<td>ERMS</td>
<td>5</td>
</tr>
<tr>
<td>NRAS</td>
<td>p.Q61K (c.181C&gt;A)</td>
<td>ERMS</td>
<td>2</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>p.E545K (c.1633G&gt;A)</td>
<td>ERMS</td>
<td>5</td>
</tr>
<tr>
<td>ATM</td>
<td>p.V140A (c.1229T&gt;C)</td>
<td>ERMS</td>
<td>5</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>p.S45F (c.134C&gt;T)</td>
<td>ACC</td>
<td>4</td>
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</table>

### Translocation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Diagnosis</th>
<th>Tier</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK3</td>
<td>EML4-NTRK3</td>
<td>US</td>
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### Copy Number Alterations (MYC/MYCN)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Diagnosis</th>
<th>Tier</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYCN</td>
<td>High CN gain</td>
<td>NBL (n=2)</td>
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<tr>
<td>MYC</td>
<td>High CN gain</td>
<td>OST</td>
<td>4</td>
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<tr>
<td>MYCN</td>
<td>High CN Gain</td>
<td>US</td>
<td>4</td>
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</table>

### Variant of Uncertain Significance

<table>
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<th>Gene</th>
<th>Alteration</th>
<th>Diagnosis</th>
<th>Tier</th>
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</thead>
<tbody>
<tr>
<td>FGFR2</td>
<td>p.C382R (c.1147T&gt;C)</td>
<td>Sialoblastoma</td>
<td>4</td>
</tr>
<tr>
<td>PTCH1</td>
<td>p.R1113C (c.3337C&gt;T)</td>
<td>ARMS</td>
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<tr>
<td>MET</td>
<td>p.T1010I (c.3029C&gt;T)</td>
<td>CCS</td>
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<tr>
<td>MAPK1</td>
<td>p.D251N (c.751G&gt;A)</td>
<td>OST</td>
<td>5</td>
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</table>

### Copy Number Alterations (Cell Cycle)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Diagnosis</th>
<th>Tier</th>
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</thead>
<tbody>
<tr>
<td>CDKN2A/B</td>
<td>2 copy deletion</td>
<td>SS</td>
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<tr>
<td>CDKN2A/B</td>
<td></td>
<td>EWS</td>
<td>4</td>
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<tr>
<td>CDKN2A/B</td>
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<td>MPNST</td>
<td>4</td>
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<tr>
<td>CDKN2A/B</td>
<td></td>
<td>CMN</td>
<td>4</td>
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<tr>
<td>CDKN2A/B</td>
<td></td>
<td>ERMS</td>
<td>4</td>
</tr>
<tr>
<td>CDKN2A/B</td>
<td></td>
<td>EWS</td>
<td>4</td>
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</table>

### Other

<table>
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<th>Gene</th>
<th>Alteration</th>
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<th>Tier</th>
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<tbody>
<tr>
<td>SMARCB1</td>
<td>2 copy deletion</td>
<td>ES</td>
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<tr>
<td>Met</td>
<td>Expression</td>
<td>RCC</td>
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<tr>
<td>CDKN2A/B</td>
<td>Loss p16 expression</td>
<td>US</td>
<td>4</td>
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Harris M, JAMA Oncology, 2016
<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Cancer Types</th>
<th>Patient Population</th>
<th>No. of Patient</th>
<th>% Actionable alterations</th>
<th>Year</th>
<th>PMID</th>
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<tbody>
<tr>
<td>Peds-MiOncoSeq</td>
<td>University of Michigan</td>
<td>Solid and hematologic malignancies</td>
<td>Relapsed/refractory, high-risk newly diagnosed</td>
<td>91</td>
<td>46%</td>
<td>2015</td>
<td>26325560</td>
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<tr>
<td>iCat</td>
<td>Dana-Farber Cancer Institute and others</td>
<td>Extracranial solid tumors</td>
<td>Relapsed/refractory, high-risk newly diagnosed</td>
<td>89</td>
<td>34%</td>
<td>2016</td>
<td>26822149</td>
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<tr>
<td>BASIC3</td>
<td>Baylor College of Medicine</td>
<td>Solid</td>
<td>Newly diagnosed</td>
<td>150</td>
<td>39%</td>
<td>2016</td>
<td>26822237</td>
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<tr>
<td>INFORM</td>
<td>German Cancer Research Center and others</td>
<td>Solid and hematologic malignancies</td>
<td>Relapsed/refractory</td>
<td>52</td>
<td>50%</td>
<td>2016</td>
<td>27479119</td>
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<tr>
<td>MBB Program</td>
<td>Institut Curie, France</td>
<td>Solid</td>
<td>Relapsed/refractory, high-risk newly diagnosed</td>
<td>58</td>
<td>40%</td>
<td>2016</td>
<td>27896933</td>
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<tr>
<td>PIPseq</td>
<td>Columbia University Medical Center</td>
<td>Solid and hematologic malignancies</td>
<td>Relapsed/refractory, high-risk newly diagnosed</td>
<td>101</td>
<td>38%</td>
<td>2016</td>
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<tr>
<td>MOSCATO-01</td>
<td>Gustave Roussy, France</td>
<td>Solid</td>
<td>Relapsed/refractory</td>
<td>69</td>
<td>61%</td>
<td>2017</td>
<td>28733441</td>
</tr>
</tbody>
</table>

Forrest SJ, et al, Curr Op Peds
DF/BC PRECISION CANCER MEDICINE PROJECTS

BY THE NUMBERS

iCat included 100 patients with relapsed and/or treatment-resistant pediatric solid tumors.

In 31% of patients, the team recommended a new targeted treatment option based on the tumor's sequencing data.

In another 12% of patients, the team found evidence supporting a different diagnosis or suggesting a predisposition to cancer.

75 patients

What is Profile?

Profile, launched by scientists at Dana-Farber/Brigham and Women's Cancer Center and Dana-Farber/Boston Children's Cancer and Blood Disorders Center, is one of the nation's most comprehensive precision cancer medicine research initiatives.

3 Institutions
All patients
Current test:
- Tumor only
- 500 genes; 60 for fusions, signatures
30,000 samples sequenced
1,025 pediatric patient samples

Learn more: http://www.danafarberbostonchildrens.org/innovative-approaches/precision-medicine.aspx

Yana Pikman and Kim Stegmaier
In Precision Medicine, Pioneering Young Patient Teaches Veteran Doctor

METASTATIC ANAPLASTIC ASTROCYTOMA
BRAF ALTERATION → DABRAFENIB
FIRST CHILD WITH BRAIN TUMOR ON THE TRIAL

Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors

Mimi Bandopadhayay

Transitioning from research to clinical care
• 3 of 31 received targeted therapy matched to the iCat recommendation
  • Reasons matched therapy (MTT) not received assessed by survey
    • Clinical trial not available: completed accrual or patient ineligible
    • Clinical status: patient in second remission or disease too advanced or deceased
  • Similar results in Mody et al., JAMA, 2015 (NHGRI, CSER)

We need more trials targeted therapy in pediatric oncology
A 15 year old with recurrent and refractory rhabdomyosarcoma at your institution has their tumor sequenced and a potentially actionable variant is identified. This gene variant is likely to alter the protein function in a way that would promote cancer. There is a drug targeting the gene affected in this case that is approved for a different cancer indication. However, the drug has not been studied in a clinical trial in children, for rhabdomyosarcoma or for this particular variant. There is no open clinical trial of the drug for which your patient is eligible. There is a “standard” treatment option for this child as well but it is not expected to cure the patient. What statement best represents how you would think about the treatment options in this case.

A) The tumor mutation profile matches a targeted therapy. The targeted therapy is very likely to work and have fewer side effects and we should figure out a way to get it for the patient.

B) Both treatment options are reasonable but the matched targeted therapy is more likely to work and less likely to have side effects so that treatment should be recommended more strongly.

C) Both treatment options are reasonable but the standard therapy is more likely to work so that treatment should be recommended more strongly.

D) Both treatment options are reasonable and it is not known which will work better. Other issues like expected side effects, administration and availability should be considered in determining which to recommended more strongly.

E) Only the standard option is viable because the likelihood of getting the non-approved matched targeted therapy is low. Thus only the standard therapy should be presented.
NCI-COG PEDIATRIC MATCH: STUDY DESIGN

Co-Chairs: Will Parsons and Nita Seibel

APEC1621SC: Screening protocol

Children with relapsed and refractory solid tumors and lymphomas ≥ 1 year

- Modular format
- Single stage phase II studies
- N=20 per arm
- Small expansion cohorts
- 7 arms (agents) to start
- Non-histology driven
- Estimated 200-300 subjects/year

APEC1621A-Z: Phase 2 treatment protocols

Available MATCH study agents

- SD, CR or PR
- Continue until progression
- PD

Measurable disease 12 wks from report

- Another actionable mutation detected?
  - Yes
  - No

Off study

Slide thanks to Will Parsons
# NCI-COG Pediatric Match Subprotocols

**NCI-COG PEDIATRIC MATCH: TARGET AND AGENT PRIORITIZATION COMMITTEE (CO-CHAIRS KATIE JANEWAY AND JAE CHO)**

Charge: prioritize most relevant molecular targets and corresponding agents to recommend for inclusion

<table>
<thead>
<tr>
<th>Agent Class</th>
<th>Agent</th>
<th>Subarm Chair/VC</th>
<th>Protocol ID</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>TRK inhibitor</td>
<td>Larotrectinib</td>
<td>Janeway/Dubois</td>
<td>APEC1621-A</td>
<td>Activated</td>
</tr>
<tr>
<td>FGFR inhibitor</td>
<td>Erdaftinib</td>
<td>Lee/Chou</td>
<td>APEC 1621-B</td>
<td>Activated</td>
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<tr>
<td>EZH2 inhibitor</td>
<td>Tazemetostat</td>
<td>Chi/Yi</td>
<td>APEC 1621-C</td>
<td>Activated – currently on FDA hold</td>
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<tr>
<td>PI3K/mTOR inhibitor</td>
<td>LY3023414</td>
<td>Laetstch/Ludwig</td>
<td>APEC 1621-D</td>
<td>Activated</td>
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<tr>
<td>MEK inhibitor</td>
<td>Selumetinib</td>
<td>Allen/Eckstein</td>
<td>APEC 1621-E</td>
<td>Activated</td>
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<tr>
<td>ALK inhibitor</td>
<td>Ensartinib</td>
<td>Irwin/Greengard</td>
<td>APEC 1621-F</td>
<td>Activated</td>
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<tr>
<td>BRAF inhibitor</td>
<td>Vemurafenib</td>
<td>Kim/Nelson</td>
<td>APEC 1621-G</td>
<td>Activated</td>
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<tr>
<td>PARP inhibitor</td>
<td>Olaparib</td>
<td>Glade-Bender/Pinkney</td>
<td>APEC 1621-H</td>
<td>Activated</td>
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<tr>
<td>CDK4/6 inhibitor</td>
<td>Palbociclib</td>
<td>Mody/Macy</td>
<td>APEC 1621-I</td>
<td>Activated</td>
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<tr>
<td>ERK1/2 inhibitor</td>
<td>Ulixertinib</td>
<td>Vo/Sabnis</td>
<td>APEC1621-J</td>
<td>Activated 10/1/18</td>
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</table>

**Dosing strategy:** Adult RP2D if it is not the MTD; 1 dose level below if adult RP2D=M TD

Allen C, et al, JNCI 2017
# PRECISION TRIALS IN PEDIATRIC ONCOLOGY

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Examples of Precision Trials</th>
<th>Sponsor</th>
<th>ClinicalTrials ID</th>
</tr>
</thead>
</table>
| **Basket in Relapsed/Refractory Cancers Across Multiple Diagnoses** | ▪ NCI-COG Pediatric MATCH  
▪ AcSé-eSMART | COG/NCI Gustave Roussy | NCT03155620  
NCT02813135 |
| **Disease-specific Umbrella in Patients with Progressive Disease** | ▪ Ruxolitinib or Dasatinib with Chemotherapy in Ph-Like ALL  
▪ NEPENTHE (Neuroblastoma) | MD Anderson CHOP | NCT02420717  
NCT02780128 |
| **Single-Agent Targeted Therapy in Advanced Cancers** | ▪ Larotrectinib in NTRK Fusion Positive Tumors  
▪ EZH2 Inhibitor Tazemetostat in INI-1 Negative tumors  
▪ Crizotinib for Tumors with an ALK, MET or ROS1 alteration  
▪ LDK378 (Ceritinib) in ALK-activated Pediatric Tumors  
▪ Dabrafenib with Trametinib for BRAF V600 Positive Tumors  
▪ Afatinib in Pediatric Tumors with ErbB Pathway Deregulation | LOXO Oncology Epizyme UNICANCER Novartis Novartis Boehringer Ingelheim | NCT02637687  
NCT02601937  
NCT02034981  
NCT01742286  
NCT02684058  
NCT02372006 |
| **Disease-specific Trials in Newly Diagnosed Patients** | ▪ Total Therapy XVII JAK/STAT Mutations in ALL and Lymphoma  
▪ Addition of Dasatinib for ALL with TKI-targetable Fusions  
▪ Combination Therapy Plus Dasatinib for Ph-Like B-ALL  
▪ Clinical and Molecular Risk-Directed Therapy (Medulloblastoma)  
▪ BIOMEDE (DIPG) | St. Jude DFCI COG/NCI St. Jude Gustave Roussy | NCT03117751  
NCT03020030  
NCT02883049  
NCT01878617  
NCT02233049 |

Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

A. Maximum Change in Tumor Size, According to Tumor Type

B. Outcomes

Drylon A, Laetsch, T et al, NEJM, 2018
12 institutions collaborate on precision oncology studies in children with difficult to cure cancers in children, adolescents and young adults
Extracranial solid tumors: HR, unclear, recurrent
Planned N=825

- Eligibility
  - Remote consent

All: T+(N) targeted NGS panel
Selected: WES, RNA Seq, WGS

- Tumor Profiling
  - OR Data Collection

Additional Variant Assessment
Clinical Impact
Therapy Recommendation
Classify drug availability

- Curation
  - Clinical interpretation
  - “GAIN Report”

Vital Status
Treatment Response

- Prospective Clinical Data Element Annotation

COHORT STUDY TO EVALUATE OUTCOMES AFTER RECEIPT OF TARGETED THERAPY MATCHED TO AN INDIVIDUALIZED CANCER THERAPY (ICAT) RECOMMENDATION IN CHILDREN AND YOUNG ADULTS: THE GAIN CONSORTIUM/ICAT2 STUDY (NCT02520713)
THE GAIN/ ICAT2 STUDY: ENROLLMENT

Accrual

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Osteosarcoma</td>
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</tr>
<tr>
<td>Singular / Other Rare Diagnosis</td>
<td>71</td>
</tr>
<tr>
<td>Ewing Sarcoma</td>
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<tr>
<td>Undifferentiated Malignant Neoplasm</td>
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<tr>
<td>Alveolar Rhabdomyosarcoma</td>
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<tr>
<td>Neuroblastoma</td>
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<tr>
<td>Wilm’s Tumor</td>
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<tr>
<td>DSRCT</td>
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<tr>
<td>Malignant Rhabdoid Tumor</td>
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<tr>
<td>Hepatoblastoma / HCC</td>
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<td>ERMS</td>
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<tr>
<td>Synovial Sarcoma</td>
<td>8</td>
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<tr>
<td>Renal Cell Carcinoma</td>
<td>6</td>
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</table>

Accrual 360

348 GAIN Reports
CASE EXAMPLES

BRAF-KHDRBS2 fusion identified → MEK inhibitor (trametinib)

13 yo relapsed, progressive neuroendocrine carcinoma
- Weight loss, abdominal pain, nausea, distention, and constipation
- Low albumin, poor kidney function

“He’s 3 weeks on Trametinib and his tumor is clearly smaller. Energy, appetite, activity all improved, playing basketball again… albumin improving as well… clearly responding…”

Later progressed, ERK inhibitor
Single patient IND

5 weeks
TCF12-NOTCH1 Fusion identified → impact on the tumor?
→ gamma secretase inhibitor

7 yo with malignant glomus tumor originally in the neck now recurrent with lung metastases

2 months later
COHORT STUDY TO EVALUATE OUTCOMES AFTER RECEIPT OF TARGETED THERAPY MATCHED TO AN INDIVIDUALIZED CANCER THERAPY (iCAT) RECOMMENDATION IN CHILDREN AND YOUNG ADULTS: THE GAIN CONSORTIUM/iCAT2 STUDY (NCT02520713)

Extracranial solid tumors: HR, unclear, recurrent
Planned N=825

- Eligibility
- Remote consent

All: T+(N) targeted NGS panel
Selected: WES, RNA Seq, WGS

Tumor Profiling
- OR Data Collection

Additional Variant Assessment
Clinical Impact
Therapy Recommendation
Classify drug availability

Curation
- Clinical interpretation

Vital Status
Treatment Response

1) Describe OS, PFS in each group
2) Identify factors associated with outcome
3) For subset with measurable disease, ORR and PFS by group

No iCat
iCat, Unmatched therapy
iCat, Matched therapy
Extraordinary responder

Prospective Clinical Data
Element Annotation
• MD Anderson phase I program
  – 534 patients with one targetable variant, 143 received matched targeted therapy

## DATA SHARING: ONGOING EFFORTS IN PEDIATRIC ONCOLOGY

<table>
<thead>
<tr>
<th>Data Repository</th>
<th>Notes</th>
<th>Cases</th>
<th>More Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude</td>
<td>- Multiple data sources - Less clinical annotation</td>
<td>4,469</td>
<td><a href="https://pecan.stjude.org/home">https://pecan.stjude.org/home</a></td>
</tr>
<tr>
<td>GENIE</td>
<td>- Clinical sequencing labs in hospitals - Targeted gene panels - Potential extensive clinical annotation and access historical cases</td>
<td>1,163 ≤ 18 18 - 516 DFCI - 392 MSKCC</td>
<td><a href="http://www.cbioportal.org/genie/">http://www.cbioportal.org/genie/</a></td>
</tr>
<tr>
<td>Foundation Medicine</td>
<td>- Limited clinical information - Real world data set</td>
<td>1,215</td>
<td><a href="https://pediatric-data.foundationmedicine.com">https://pediatric-data.foundationmedicine.com</a></td>
</tr>
</tbody>
</table>

EXPANDING SCOPE OF PRECISION ONCOLOGY


\( gBRCAm \) Newly dx metastatic br ca Olaparib


Molecular Biomarkers for Targeted Therapy
The goal of precision medicine is to treat patients with drugs that target the specific genetic mutations in their tumors, regardless of where the tumors are found. This approach may improve the success of treatment and reduce side effects.

- AQUEOUS HUMOR
- PLASMA
- FUSION SIGNATURE
- COPY NUMBER IMMUNE INFILTRATE
- CHECKPOINT INHIBITORS
- EPIGENETIC MODIFIERS
- COMBINATION WITH CHEMO
- Malignant cell growth
ACKNOWLEDGEMENTS

Boston Children's / pathology and molecular pathology
Marian Harris
Alanna Church
Mark Fleming

Dana-Farber/Boston Children's / cancer biology, DVL
Brian Crompton, MD
Lisa Diller, MD
Suzanne Shusterman, MD
Kimberly Stegmaier, MD
Steven Dubois, MD, MS
Jon Marron, MD
Suzanne Forrest, MD

Staff: Catherine Clinton, Erin Parker, Stephanie Meyer, Giana Strand, Abigail Ward, Alma Imamivoc-Turco, Alex Lee, Laura Corson, Deirdre Reidy, research coordinators, computational biology

Former members: Carlos Rodriguez-Galindo, MD, Charlie Roberts, MD, PhD

Collaborators:
Columbia University Medical Center: Julia Glade-Bender, MD
Children's National Medical Center: AeRang Kim, MD, PhD
University of Chicago: Sam Volchenboum, Mark Applebaum
UT Southwestern: Ted Laetsch
Seattle Children's: Navin Pinto, Julie Park, Jeffrey Stevens
CHOP: Rochelle Bagatell
Montefiore: Jonathan Gil
Children's Hospital Colorado: Meg Macy
UCSF: Amit Sabnis
Utah Huntsman Cancer Center: Joshua Schiffman, Luke Maese
MSKCC: Andrew Kung

PATIENTS AND FAMILIES!

Funders:
iCat1 Funding:
Friends for Life Foundation
Hyundai Hope on Wheels
Gillmore Fund

GAIN Funding:
Division Hematology-Oncology Consortium Funding
Medel Fund
C&S Grocers
Pan Mass Challenge – Precision for Kids
### CASE EXAMPLES

<table>
<thead>
<tr>
<th>GAIN PATIENT 194 (Utah)</th>
<th>I yo sarcoma in thigh – unclear diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAIN result</strong></td>
<td>BRAF-ERC1 fusion</td>
</tr>
<tr>
<td><strong>Significance for patient</strong></td>
<td>New treatment option: Trametinib</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Just got insurance approval for treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GAIN PATIENT 101 (Seattle)</th>
<th>20 yo Metastatic papillary thyroid cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAIN result</strong></td>
<td>SQSTM1-NTRK1 fusion</td>
</tr>
<tr>
<td><strong>Significance for patient</strong></td>
<td>New treatment option: Larotrectinib</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Patient currently doing well, treatment not needed yet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GAIN PATIENT 201 (Seattle)</th>
<th>7 yo Relapsed rhabdomyosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAIN result</strong></td>
<td>High tumor mutational burden</td>
</tr>
<tr>
<td><strong>Significance for patient</strong></td>
<td>New treatment option: Pembrolizumab</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>No current need for anti-cancer therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GAIN PATIENT 158 (Dana-Farber)</th>
<th>17 yo relapsed osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAIN result</strong></td>
<td>BCOR-CCNB3 fusion</td>
</tr>
<tr>
<td><strong>Significance for patient</strong></td>
<td>Definitive diagnosis</td>
</tr>
<tr>
<td></td>
<td>Understand full spectrum of rare disease</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Explanation for prior disease course</td>
</tr>
</tbody>
</table>