NCI-COG
Pediatric Molecular Analysis for Therapy Choice (MATCH) Study
APEC1621

A phase 2 precision medicine cancer trial
Co-developed by the Children's Oncology Group and the National Cancer Institute

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CTAC
July 12, 2017

What is Pediatric MATCH?

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NCI-Children's Oncology Group Pediatric MATCH Trial*

This precision medicine clinical trial, funded by NCI and conducted by COG, matches children and adolescents with treatment based on genetic changes in their tumors.

Pediatric MATCH is for patients ages 1 to 21 who have both:

- Solid tumors, including lymphomas and brain tumors, or histiocytoses
- Tumors that no longer respond to standard treatment or that have come back after treatment

ABOUT 200-300 PEDIATRIC PATIENTS EACH YEAR ARE EXPECTED TO ENROLL IN THE SCREENING PORTION OF THE STUDY

We expect to screen a total of 1,000 patients.

TUMOR TISSUE WILL UNDERGO TESTING FOR CHANGES IN MORE THAN 160 GENES

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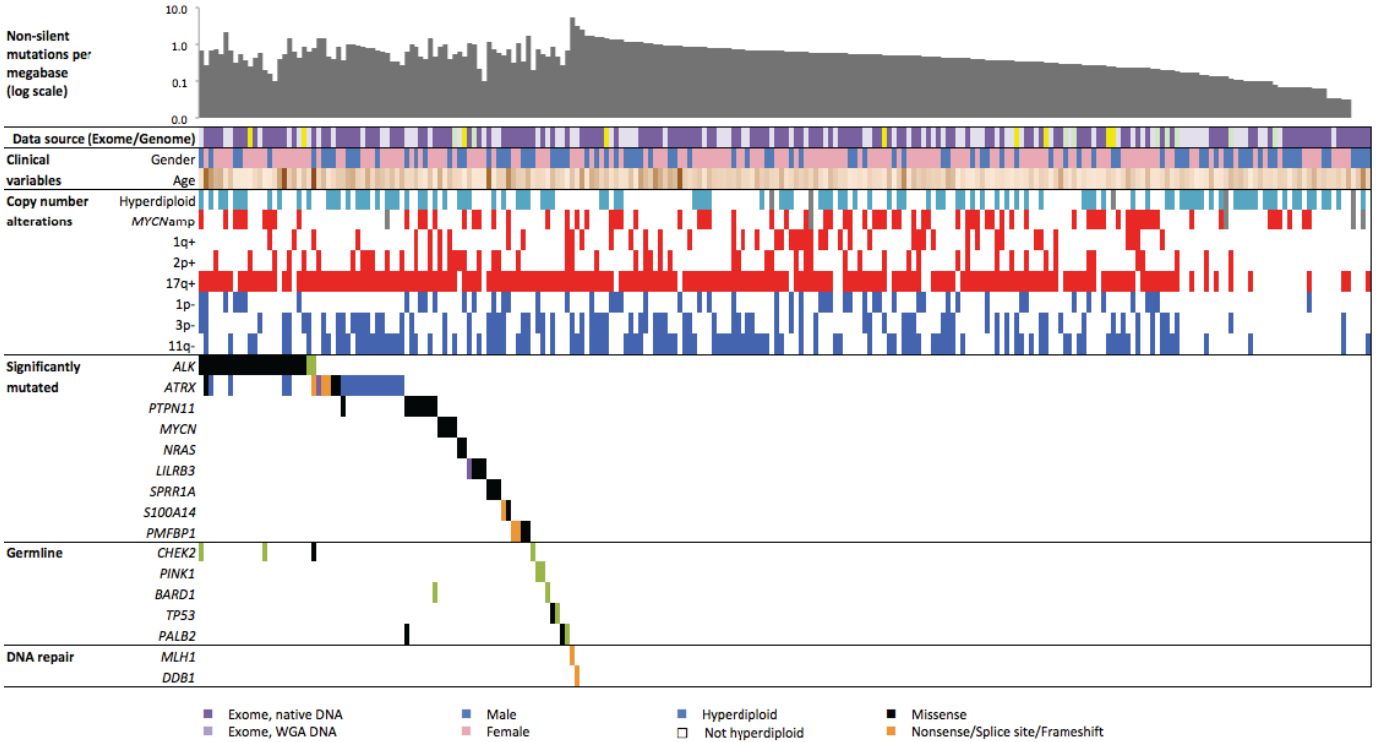
Hypothesis

By identifying genetic changes affecting pathways of interest in refractory and recurrent pediatric cancers, we will be able to deliver targeted anticancer therapy that produces a clinically meaningful objective response rate.

The Genomic Landscape of High-Risk Neuroblastoma



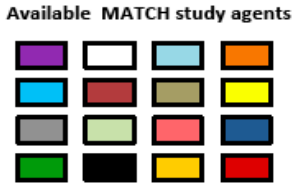
- 240 matched tumor and normal pairs (age > 18 mos and Stage 4 disease) by WES (221 cases), WGS (18 cases), or both (1 case)

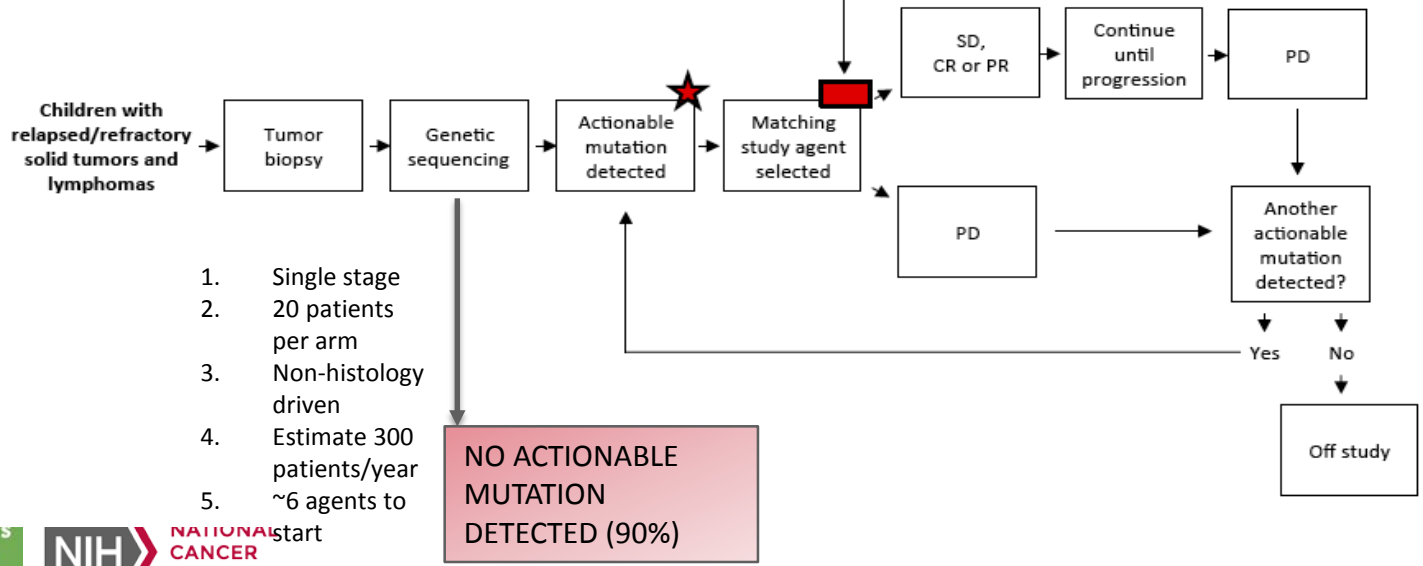
Pugh TJ, et al. Nature Genetics 2013:45(3):279-284

NCI-COG Pediatric MATCH

BRAF inhibitor
PI3K-mTOR inhibitor
MEK inhibitor
FGFR inhibitor
CDK4/6 inhibitor

TRK inhibitor
EZH2 inhibitor
ALK inhibitor
PARP inhibitor





1. Single stage
2. 20 patients per arm
3. Non-histology driven
4. Estimate 300 patients/year
5. ~6 agents to start

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Levels of Evidence for Target Selection in NCI-COG Pediatric MATCH

- Level 1: Gene variant credentialed for selection of an approved drug (e.g.BRAF V600E and vemurafenib)
- Level 2a: Variant is eligibility criteria for an ongoing clinical trial
- Level 2b: Variant identified in an N of 1 response(s)
- Level 3: Preclinical inferential data
  - Models with variant respond; without variant do not
  - Gain of function mutation demonstrated in preclinical model
  - Loss of function (tumor suppressor genes or pathway inhibitor e.g. NF1); stop codon or demonstrated loss of function in pre-clinical model

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Levels of Evidence for Drugs in NCI-COG Pediatric MATCH

- Level 1: FDA approved for any indication for that target
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS) with evidence of target inhibition
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition at some level

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Target and Agent Prioritization (TAP) Committee

- Members: COG, NCI, MATCH trial in adults, CTEP, FDA
- Charge: prioritize most relevant molecular targets and corresponding agents to recommend for inclusion
- Initial process (2/2015-5/2015)
  - List of high priority targets/agents developed
  - Detailed assessment of the target/agent pair (lit review, expert opinion), priority score assigned
    - Frequency of target in childhood malignancies
    - Level of evidence linking target to agent response
      - At least clinical case report and supporting evidence of mechanism
    - Agent availability and viability of agent class
  - Presented to committee, voting
  - Recommend to MATCH leadership and engage industry

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OXFORD

JNCI J Natl Cancer Inst (2017) 109(5): djw274

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Review

REVIEW

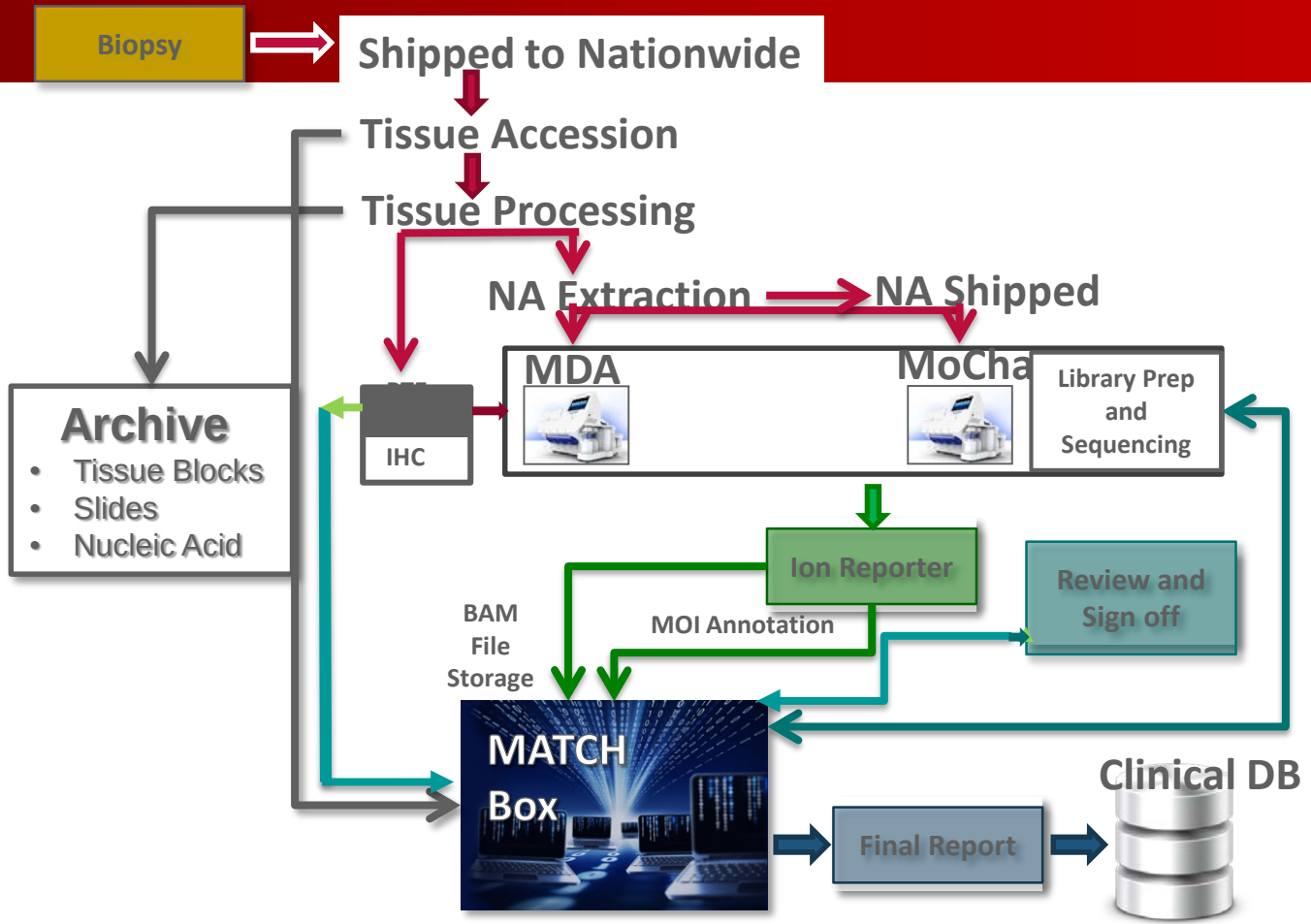
Target and Agent Prioritization for the Children's Oncology Group—National Cancer Institute Pediatric MATCH Trial

Carl E. Allen, Theodore W. Laetsch, Rajen Mody, Meredith S. Irwin, Megan S. Lim, Peter C. Adamson, Nita L. Seibel, D. Williams Parsons, Y. Jae Cho, Katherine Janeway; on behalf of the Pediatric MATCH Target and Agent Prioritization Committee*

Pediatric MATCH Therapeutic Arms

Arm	Agent Class	aMOI Frequency	Agent
APEC1621 A	Pan-TRK inhibitor	2-3%	Larotrectinib (LOXO-101)
APEC1621 B	FGFR inhibitor	2-3%	Erdafitinb
APEC1621 C	EZH2 inhibitor	2-3%	Tazemetostat
APEC1621 D	PI3K/mTOR inhibitor	5-10%	LY 3023414
APEC 1621 E	MEK inhibitor	10-20%	Selumetinib
APEC 1621 F	ALK inhibitor	2-3%	Ensartinib
APEC 1621 G	BRAF inhibitor	5%	Vemurafenib
APEC 1621 H	PARP inhibitor	2-3%	Olaparib
APEC 1621 I	CDK4/6 inhibitor	2-3%	Palbociclib

Pediatric MATCH Specimen Work Flow Schema



NCI-COG Pediatric MATCH
Design Features

- Requirement for biopsy: must obtain tissue post-relapse for study eligibility except for brain stem glioma patients
  - Rationale: Tumor genomes evolve. To identify potential targets for therapy a “current” relapsed sample is needed
- Most patients screened will be biomarker negative and will not match to a treatment arm
- Inclusion of agents with adult RP2D

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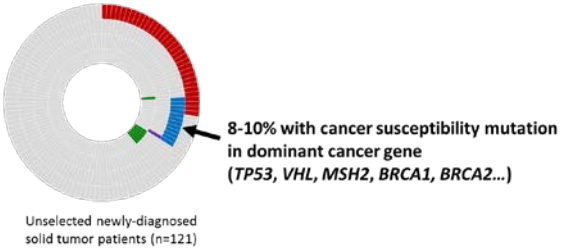
NCI-COG Pediatric MATCH
Design Features

- Response rate (tumor regression) will be primary efficacy measure
- Possibility of assignment of patients with non-target-bearing tumors to selected agents that have demonstrated activity in target-bearing tumors
- Evaluation of germline DNA



Parsons DW et al. JAMA Oncol, 2015

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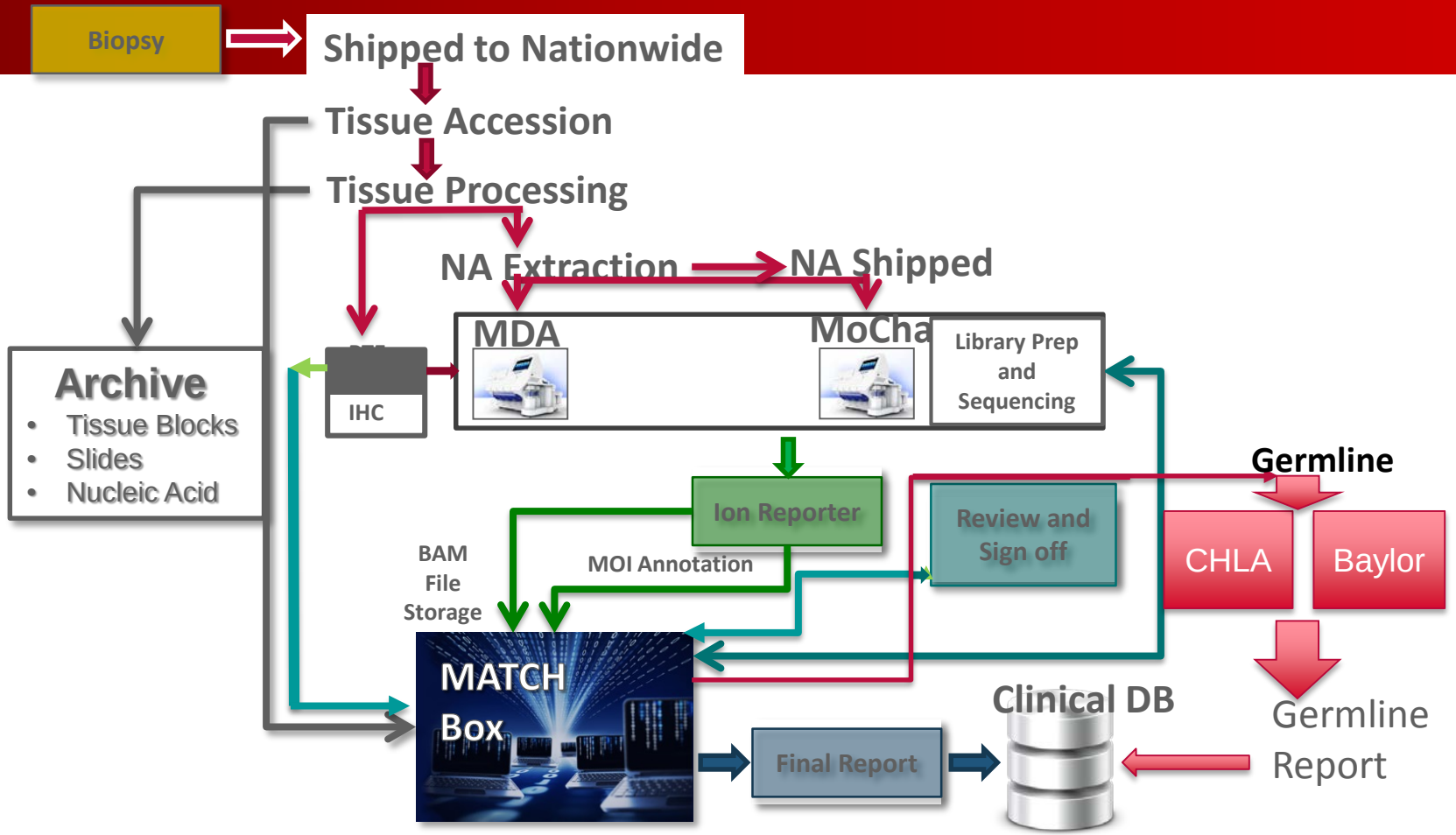
Pediatric MATCH Specimen Work Flow Schema



Challenges in Developing Pediatric MATCH

- Risk determination
- Analytical performance of assay on pediatric tissues
- Incorporation of germline testing and validation
- Process for interpreting germline results and sharing with families
- Specimen processing at NCH and incorporation within the lab system
- Agents available for treatment arms and formulations
- Developing Pediatric MATCHBox to support a new study design and workflow
- Approach to NY state regulations
- Standardizing procedures across labs
- Education and reassurance of advocates
- Managing expectations with families
- Timing with NCI-MATCH
- Efficient and timely PedCIRB protocol reviews
- Building a cohesive informatics team with multiple partners

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Questions???

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https://www.childrensoncologygroup.org

https://cancer.gov/pediatricmatch