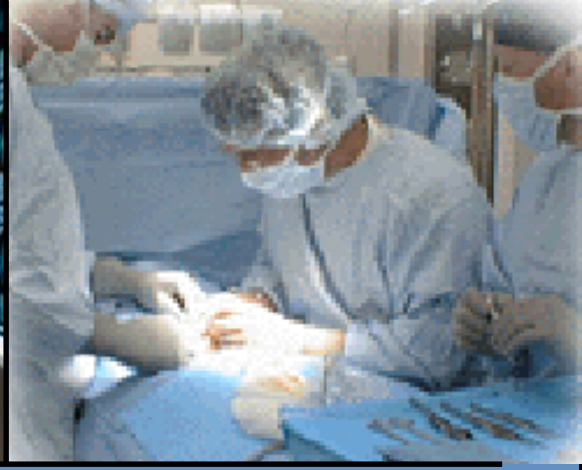
National Cancer Institute



Update on Adult & Pediatric MATCH Trials and Plans for Future Basket & Umbrella Trials in the NCI National Clinical Trials Network (NCTN)

NCAB Subcommittee on Clinical Investigations Meeting - 12/2/2019

Meg Mooney, MD
Acting Associate Director & Chief, Clinical Investigations Branch
Cancer Therapy Evaluation Program, DCTD, NCI

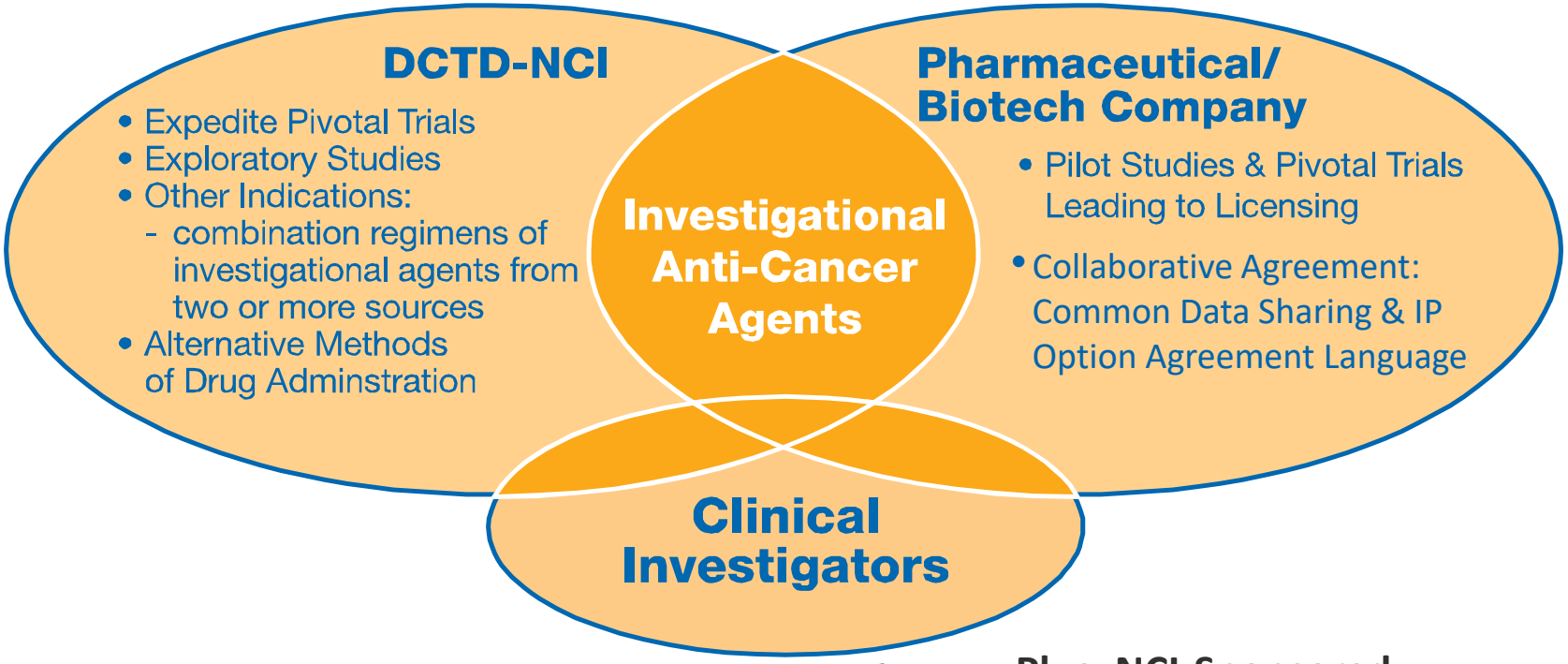
Presentation Agenda

- Overview and Update on NCI NCTN Adult MATCH & Pediatric MATCH Trials
- Lessons Learned – Focus on 2 Main Areas
  - Use of Laboratory Network for Testing for Rare Mutations/Variants
  - Need for Simplification of Protocol Structure
- Future Directions

CTEP's Role in Drug Development for National Program

- **Combinations of targeted agents a high priority**
  - Based on evidence that resistance to initially effective single agents often develops quite rapidly in many adult tumors
  - More than 100 combination trials initiated since 2000
  - Facilitated by the Intellectual Property (IP) language in CTEP-industry agreements
- **Molecular-targeted effects:**
  - Mechanism of Action/Proof of Principle
  - Biomarker assessment and evaluation, assay development & qualification

Doing Battle Against Cancer: A Collaborative Effort



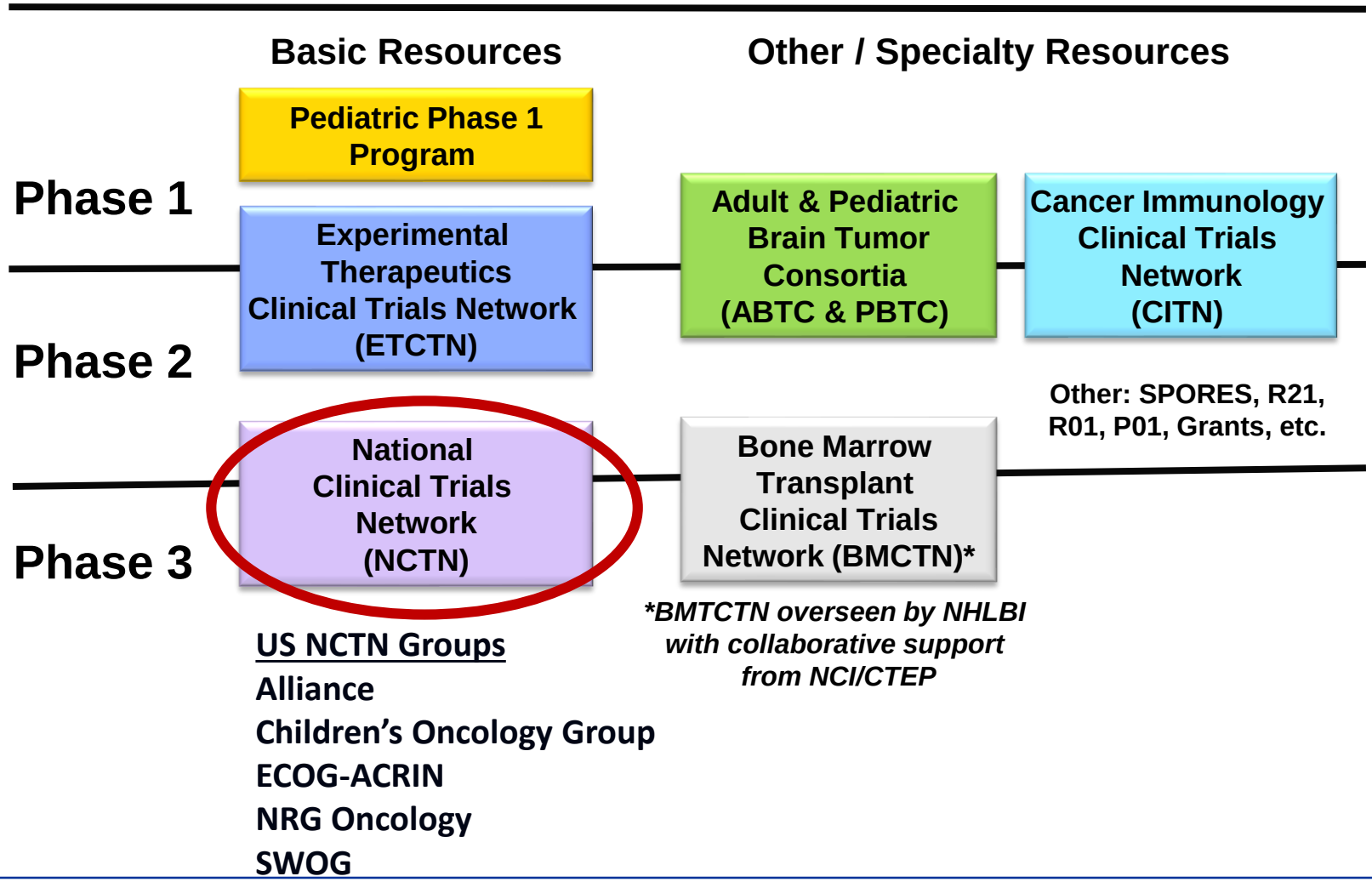
IND & Clinical Trials

Novel Cancer Therapies

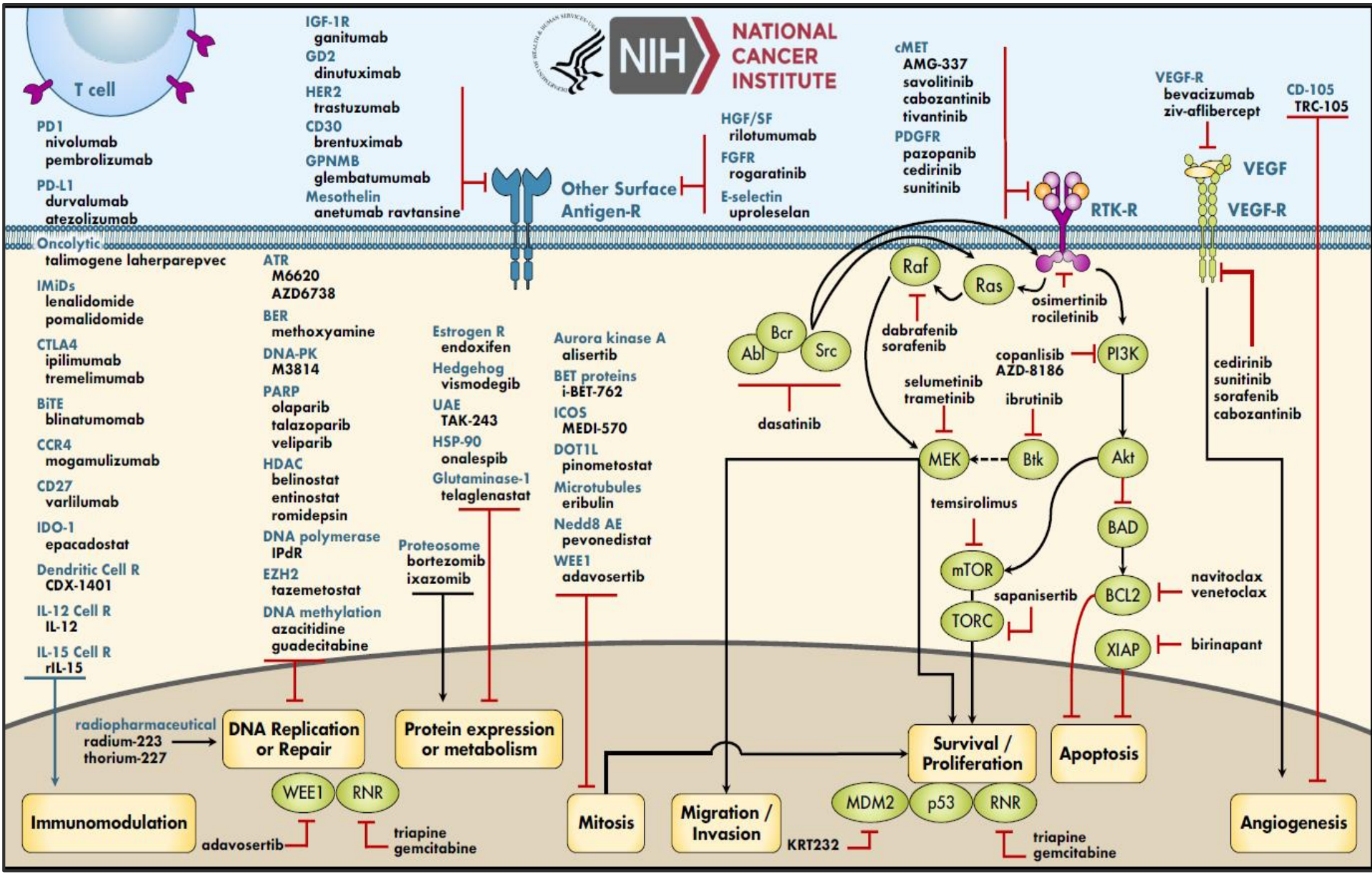
Plus: NCI-Sponsored Infrastructure for Clinical Trials

- Investigator Credentialing & Registration
- CTEP IND Sponsor / Monitoring
- Medidata Rave Data Mgt System
- NCI Central IRB
- CTSU Enrollment & Study Access
- CTSU Regulatory Support

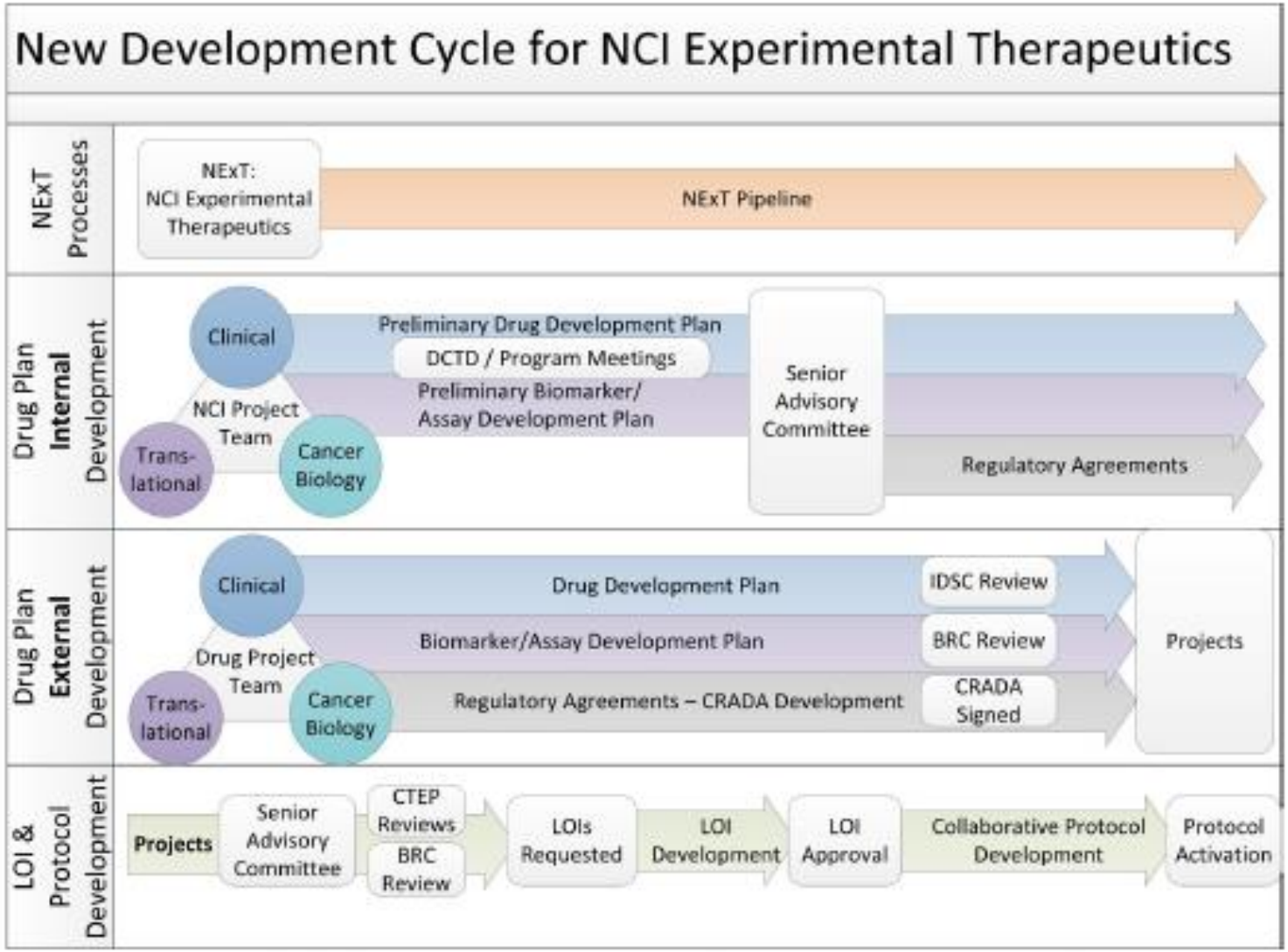
CTEP/DCTD Clinical Trials
Clinical Trials Programs



High Priority Targets & CTEP/DCTD Agents



Project Team-Driven Approach to NCI Early Phase Clinical Trials Associated with Drug Development Plans



CRADA: Cooperative Research and Development Agreement **IDSC**: Investigational Drug Steering Committee **BRC**: Biomarker Review Committee

NCI-Molecular Analysis for Therapy Choice

NCI-MATCH / EAY131: A phase II precision medicine cancer trial
Co-developed by the ECOG-ACRIN Cancer Research Group and the National Cancer Institute

NCI-MATCH Objective:
A Large national "signal-finding" trial

- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of the cancer type

- This is a signal-finding trial in patients with advanced/refractory disease; treatments that show promise can advance to larger, more definitive trials

Molecular Analysis for Therapy CHoice

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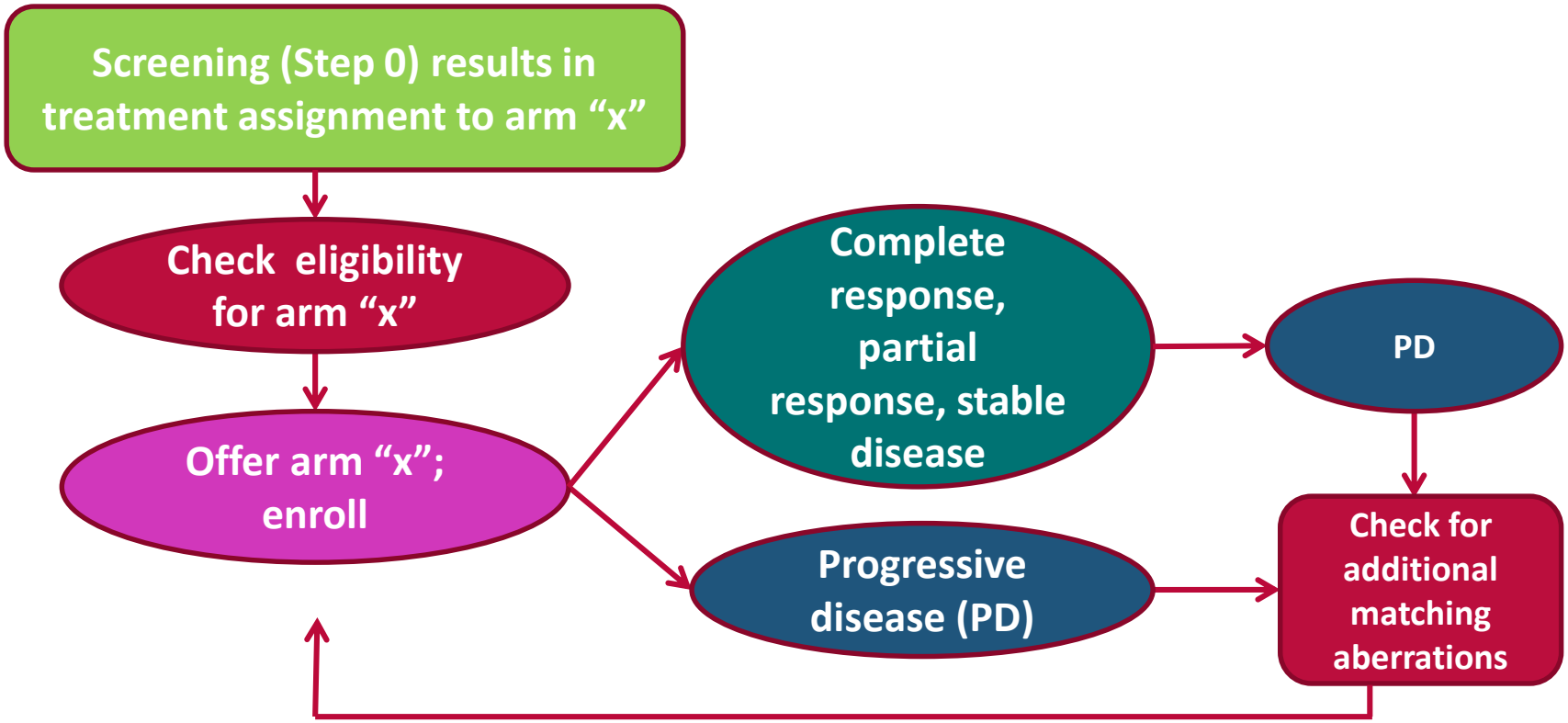
ECOG-ACRIN cancer research group
Reshaping the future of patient care

Design of NCI MATCH
(Multiple Phase II Trials – Multiple Cancer Types)

- Master protocol w/ individual arms that open & close independently
- Genomic testing directs patients to molecularly-targeted treatments
- Each arm evaluates activity of a treatment in tumors with relevant actionable mutations in refractory malignancies ("basket" type trial)
- Goal to include at least 25% less common or rare cancers (Other than breast, colon, lung, prostate)
  - Trial started August 2015 with 10 treatment arms with a built in "pause" after 500+ patients screened for full assessment of all trial phases for feasibility
  - Trial reopened in May 2016 with a total of 24 treatment arms
  - **As of 11/29/2019, screened 6,898 patients & matched 1,049 pts to 37 tx arms** using Laboratory Network with high concordance in assay performance
  - If Objective Response Rate (primary endpoint) is ≥ 5/31 (16%), agent considered worthy of potential further study

NCI-MATCH Treatment Arm Overall Design (*Multiple Single-Arm Phase II Trials*)



- Target 25% "rare" tumor histologies; Target Match rate of 23% to 25%
- Endpoint ORR of 5% *versus* 25%

MATCH Assay Oncomine Cancer Panel gene list

Hotspot genes (n=66)

ABL1
AKT1
ALK
AR
BRAF
BTK
C15orf23
CBL
CDK4
CHEK2
CSF1R
CTNNB1
DNMT3A
EGFR
ERBB2
ERBB3
ERBB4
ESR1
EZH2
FGFR2
FGFR3
FLT3
FOXL2
GATA2
GNA11
GNAQ
GNAS
HRAS
IDH1
IDH2
IFITM1
IFITM3
JAK1
JAK2
JAK3
KDR
KIT
KRAS
MAGOH
MAP2K1
MAPK1
MAX
MED12
MET
MPL
MTOR
MYD88
NFE2L2
NRAS
PAX5
PDGFRA
PIK3CA
PPP2R1A
PTPN11
RAC1
RAF1
RET
RHEB
RHOA
SF3B1
SMO
SPOP
SRC
STAT3
U2AF1
XPO1

Copy number variants (n=43)

ACVRL1
AKT1
AR
APEX1
BCL2L1
BCL9
BIRC2
BIRC3
CCND1
CCNE1
CD274
CD44
CDK4
CDK6
CSNK2A1
EGFR
ERBB2
FGFR1
FGFR2
FGFR3
FLT3
GAS6
IGF1R
IL6
KIT
KRAS
MCL1
MDM2
MDM4
MET
MYC
MYCL1
MYCN
NKX2-1
PDGFRA
PIK3CA
PNP
PPARG
RPS6KB1
SOX2
TERT
TIAF1
ZNF217

Tumor suppressors (n=25)

APC
ATM
BAP1
BRCA1
BRCA2
CDH1
CDKN2A
FBXW7
GATA3
MSH2
NF1
NF2
NOTCH1
PIK3R1
PTCH1
PTEN
RB1
SMARCB1
STK11
TET2
TP53
TSC1
TSC2
VHL
WT1

Gene fusion drivers (n=16; 156 variants)

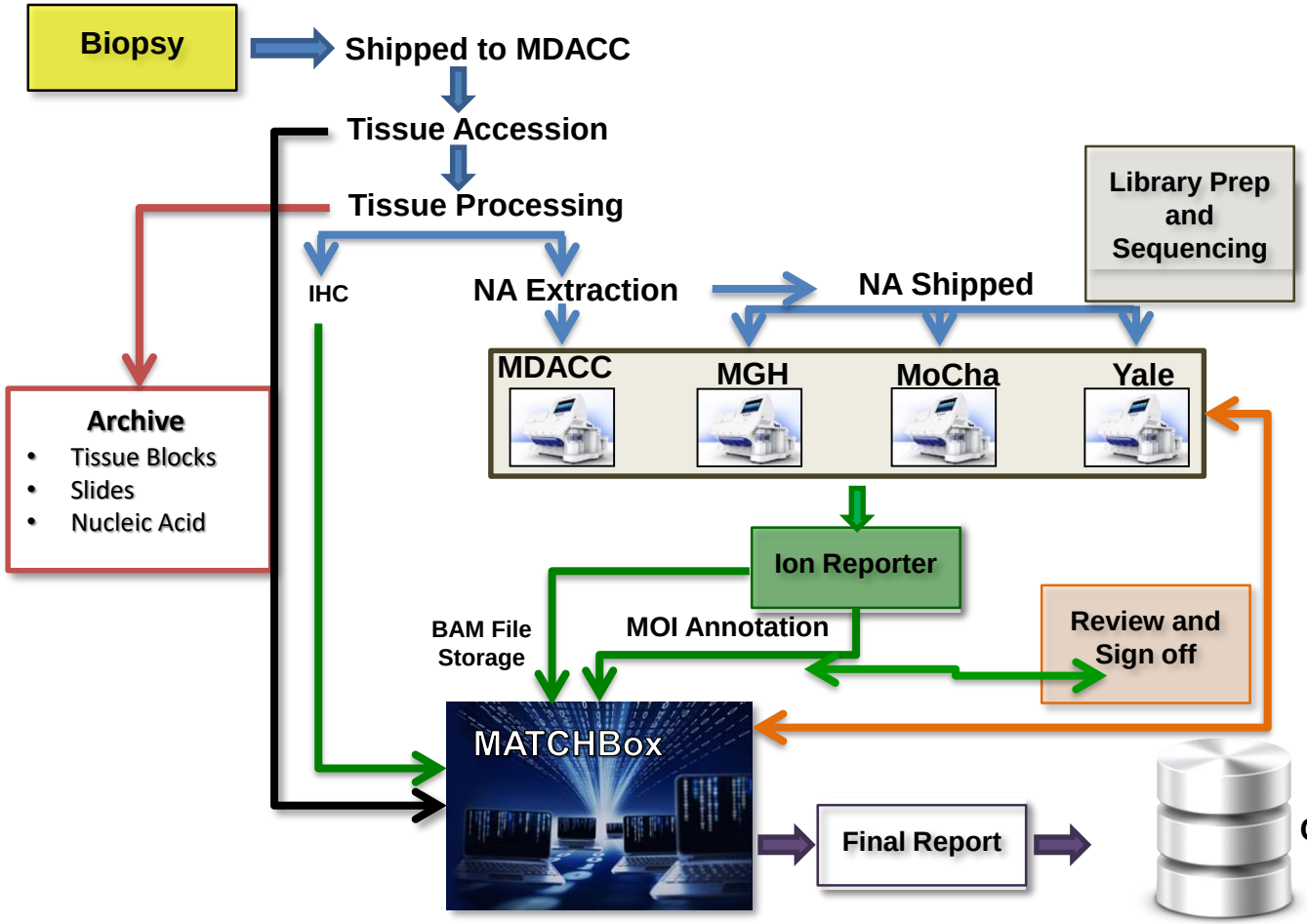
AKT3
ALK
BRAF
CDK4
ERBB2
ERG
ETV1
ETV4
ETV5
FGFR3
NTRK1
NTRK3
PPARG
RAF1
RET
ROS1

- *Tier 3 clinical evidence highlighted*
- *Gene variants associated with clinical trial enrollment (open trials)*

Highlighted genes are aMOIs which are subset of MOIs (143) with level of evidence

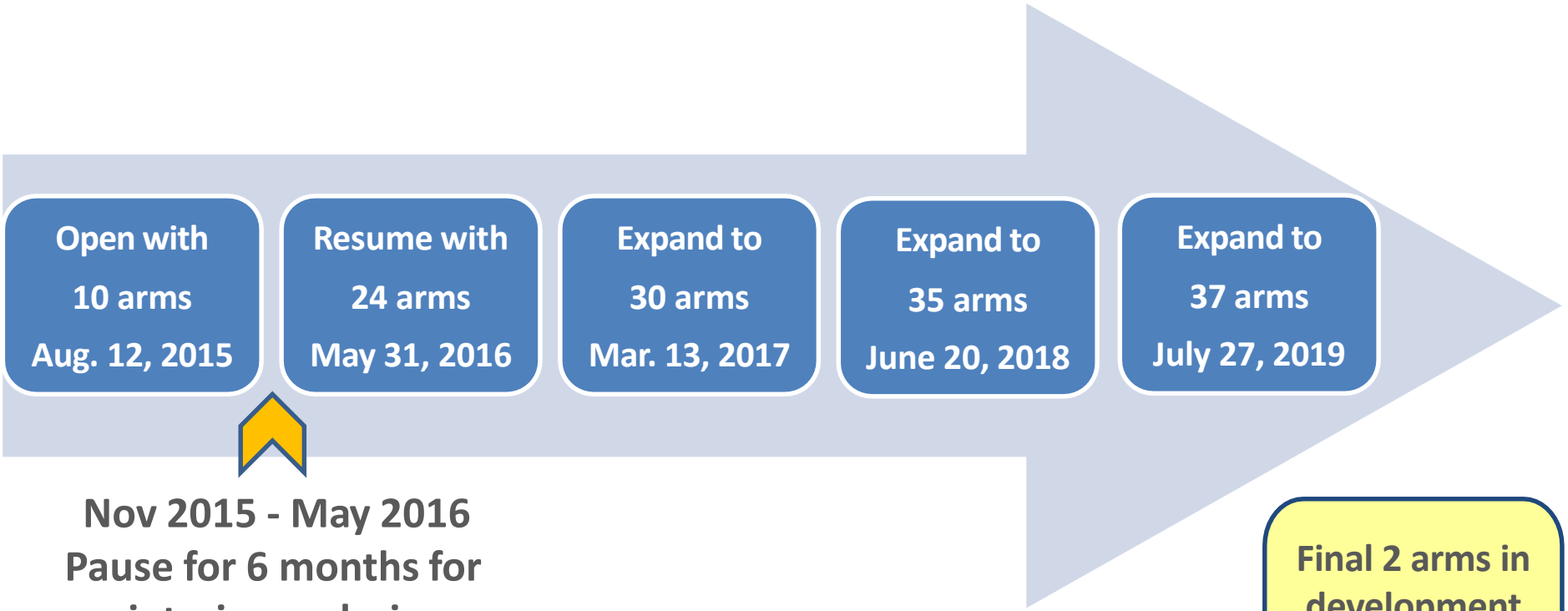
ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

NCI-MATCH Assay System & Work Flow
~ 14 Day Turnaround Time



- Expansion of NGS capacity (S5 platform)
- Versioning of NGS assay (new variants/arms)
- Mandating needle aspiration in all cases (cytology 86->98%)
- IHC's added (PTEN, MSH2, MLH1, Rb1)

Brief Timeline of NCI-MATCH Treatment Arms



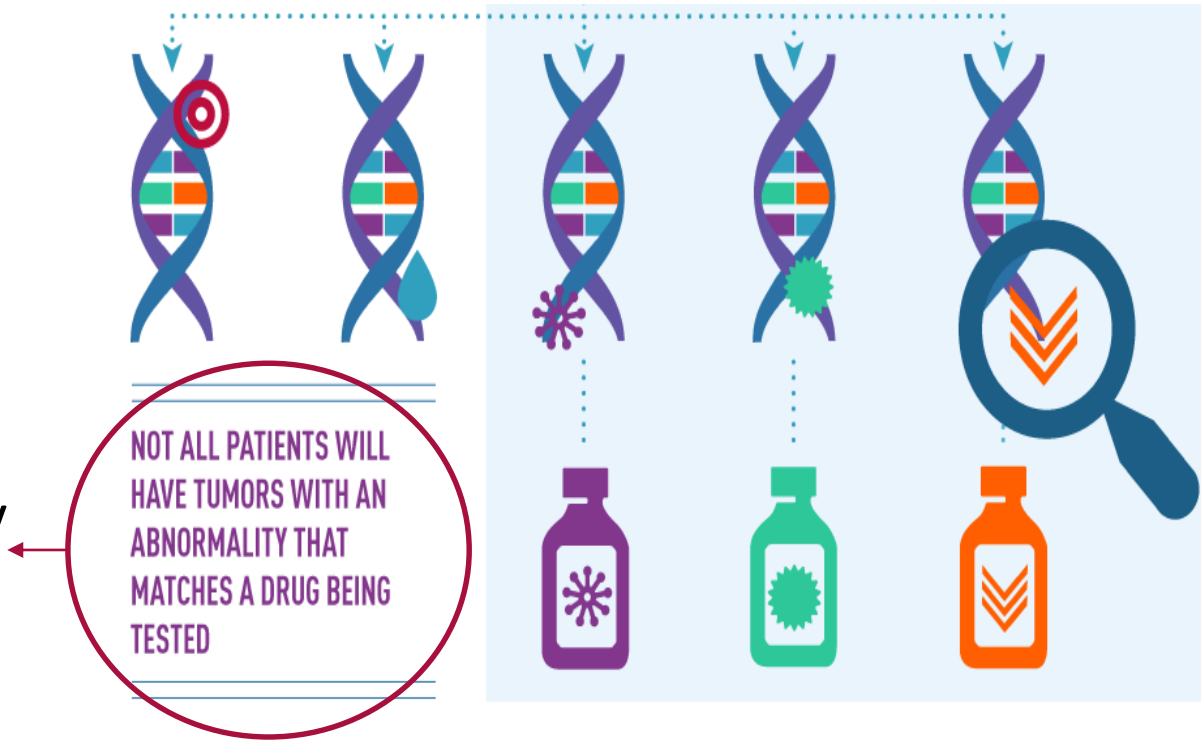
Nov 2015 - May 2016
Pause for 6 months for interim analysis
and
Lab capacity increase

Final 2 arms in development

39 total arms by end 2019

NCI-MATCH Important Discovery Required an Additional Change in the Study

In the first 6,000 patients tested, the tumor gene variants we are studying occurred less frequently than expected in this study population, **ranging from 3.47 percent to zero**



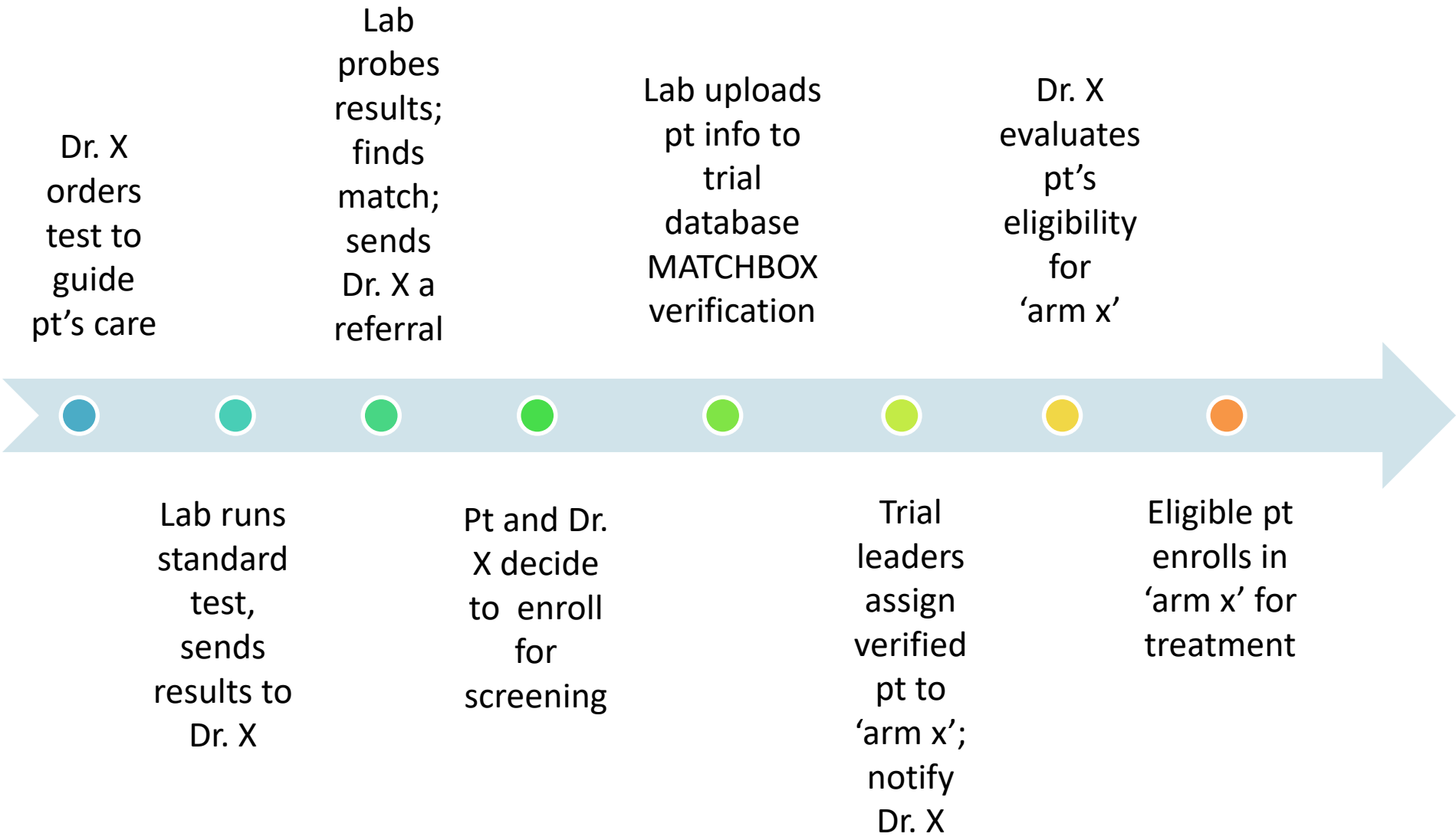
Conventional clinical trial design approach may not be feasible
Need to broaden the patient population screening process

Current Genetic Testing Process MATCH Eligibility

- After screening fresh tumor biopsies from 6,000 patients, 19 treatment arms did not meet accrual due to low prevalence of eligibility variants.
- NCI-MATCH now identifies patients utilizing an external laboratory network of CLIA-certified academic & commercial labs that perform NGS assays **as part of their routine care** at NCI-MATCH participating sites.
- Candidate labs were recruited through notice in Federal Register (FRN)
- Each candidate lab submitted a letter of interest for the NCI-MATCH team review to meet baseline criteria for FRN, if so, they were invited to submit an application to become an **NCI-MATCH Designated Laboratory.**
- Accepted laboratories sign a collaboration agreement and undergo concordance/qualification (CQ) testing.

Patient Pathway onto NCI-MATCH - Commercial Lab

Applies only to patients at ~1100 participating trial sites



Commercial Labs Referring Patients to NCI-MATCH

Caris Life Sciences®	OmniSeq, Inc.
CellNetix Pathology and Laboratories	PathGroup
Foundation Medicine, Inc.	Strata Oncology, Inc.
GenPath (BioReference Laboratories, Inc.)	Tempus Labs, Inc.
NeoGenomics Laboratories, Inc.	The Jackson Laboratory

Academic Labs Referring Patients to NCI-MATCH

Generally, cancer center labs test their own patient population

Augusta University	University of Chicago
City of Hope	University of Colorado
Cedars-Sinai Medical Center	University of Michigan
Columbia University	Weill Cornell Medicine
Johns Hopkins University	Yale University
Massachusetts General Hospital	
Memorial Sloan Kettering Cancer Center	
MD Anderson Cancer Center	

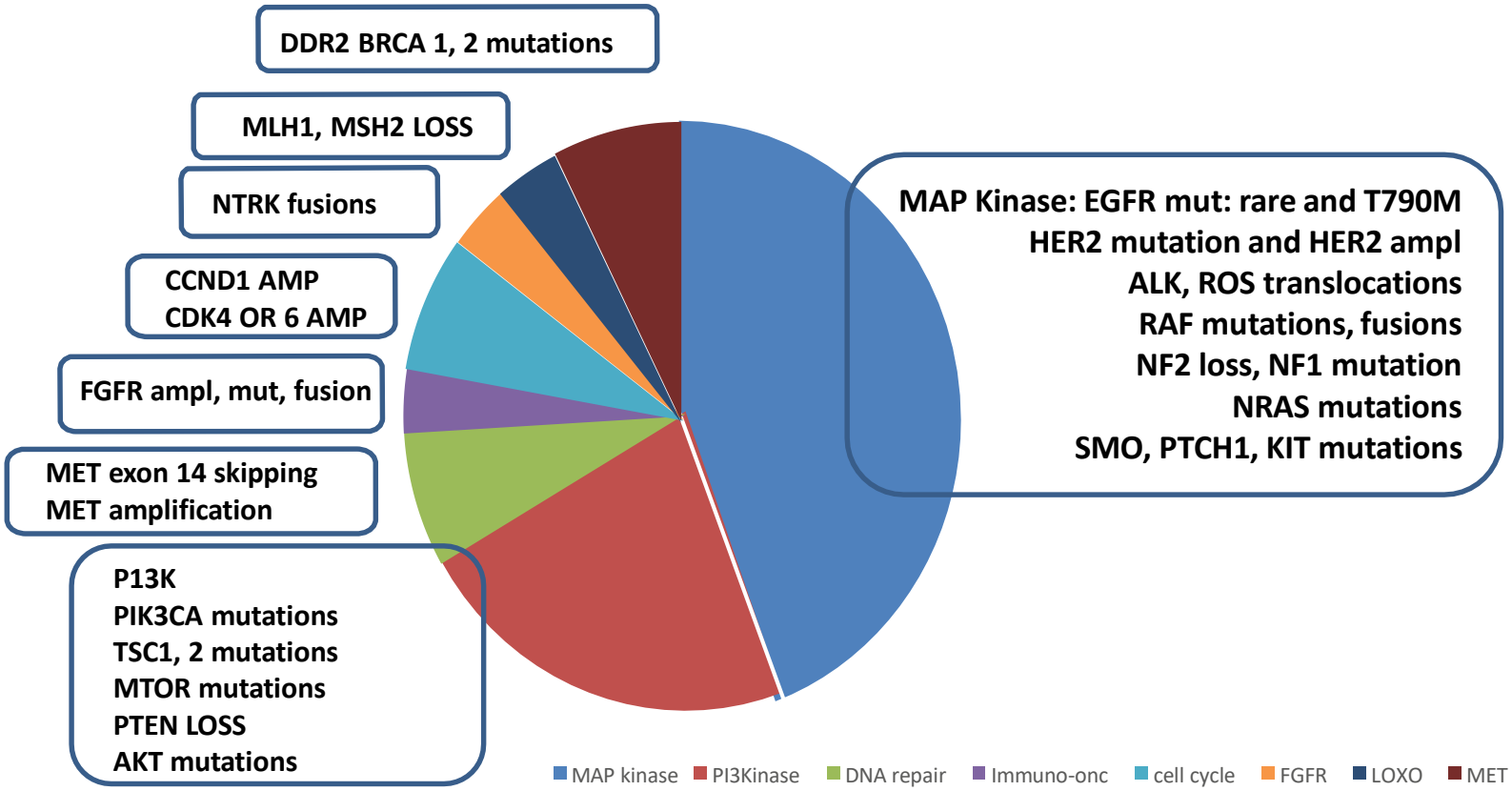
- More labs to come
- Learn more: ecog-acrin.org/nci-match

NCI-MATCH Treatment Arms with Results

Updated June 2019

Drug	Drug / Variant	Arm	Primary Result (ORR)	Publication / Presentation
Ado-trastuzumab emtansine	HER2 amplification	Q	8%	Jhaveri KL, ASCO 2018 (oral)
AZD4547	FGFR pathway aberrations	W	8%	Chae YK, ASCO 2018 (oral)
Taselisib	PIK3CA mutations	I	0%	Krop IE, ASCO 2018 (oral)
GSK2636771	PTEN expr or loss by IHC	N & P	5% arm N (mut/del) 0% arm P	Janku FM, ESMO 2018 (poster discussion)
Capivasertib	AKT mutations	Y	23%	Kalinsky KM, EORTC-NCI-AACR 2018 (oral plenary)
Nivolumab	dMMR status	Z1D	24%	Azad N, SITC 2018 (oral plenary)
Afatinib	HER2 activating mutations	B	2.7%	Bedard PL. AACR 2019
Palbociclib	CCND1, 2, and 3 amplifications and Rb protein expression by IHC	Z1B	0%	Clark AS. AACR 2019
AZD1775	BRCA1 or BRCA2 mutations	Z1I	3.2%	Kummar S. AACR 2019
Dabrafenib/trametinib	BRAFV600	**H**	**33%**	Salama AKS ASCO 2019

Treatment Arms in NCI-MATCH by Molecular Pathway



NCI-MATCH Resources

Main Webpages:	ecog-acrin.org/nci-match-eay131
	cancer.gov/nci-match
Protocol Documents:	ctsu.org (password required)
Spanish:	cancer.gov/espanol/nci-match
Email Inquiries:	match@jimmy.harvard.edu
NCI Contact Center:	1-800-4-CANCER and cancer.gov/contact

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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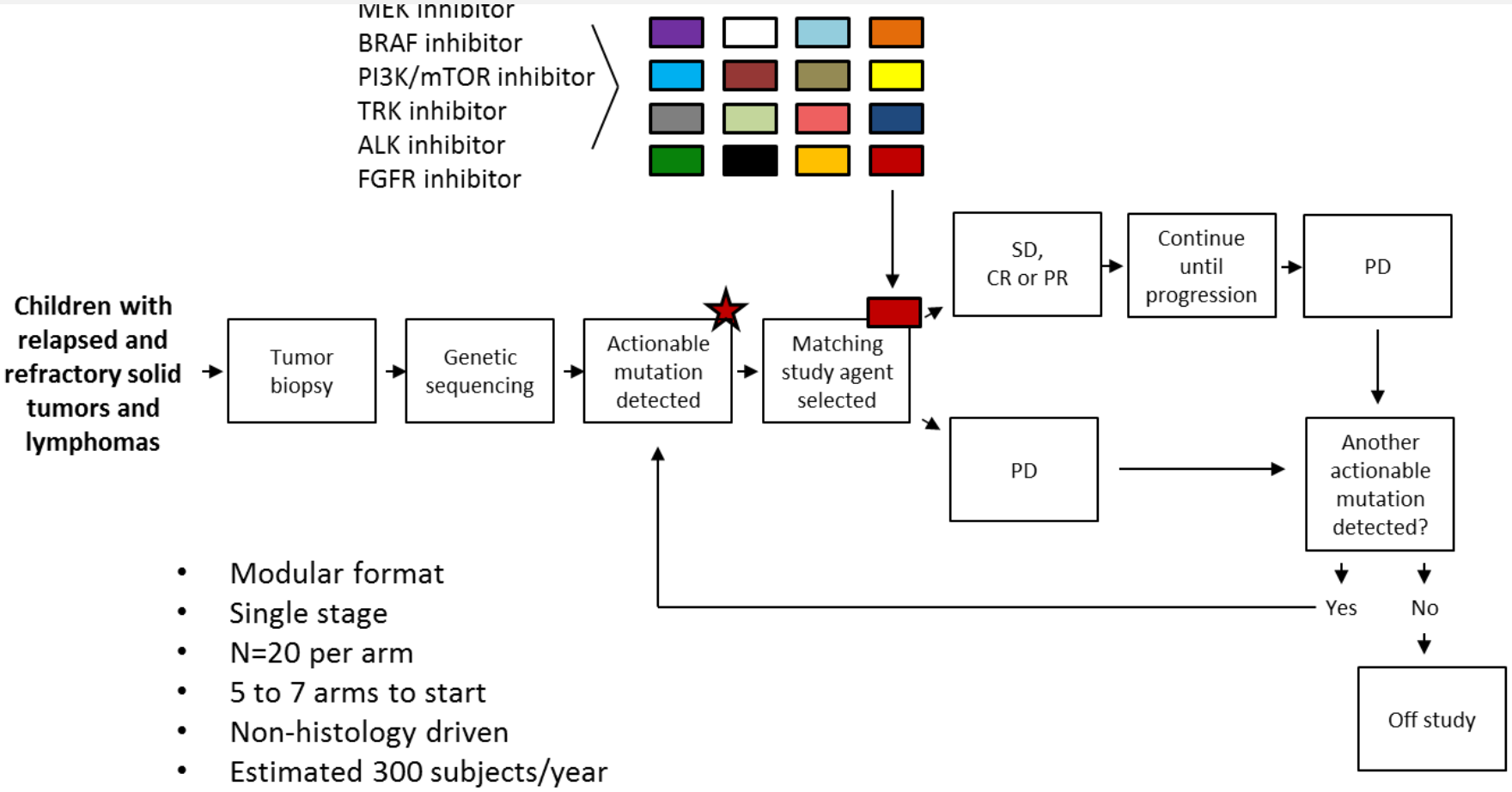
NCI-COG Pediatric MATCH Study



- Modular format
- Single stage
- N=20 per arm
- 5 to 7 arms to start
- Non-histology driven
- Estimated 300 subjects/year

Goal: 1,000 screened patients with ~ 300 enrolled on a treatment arm

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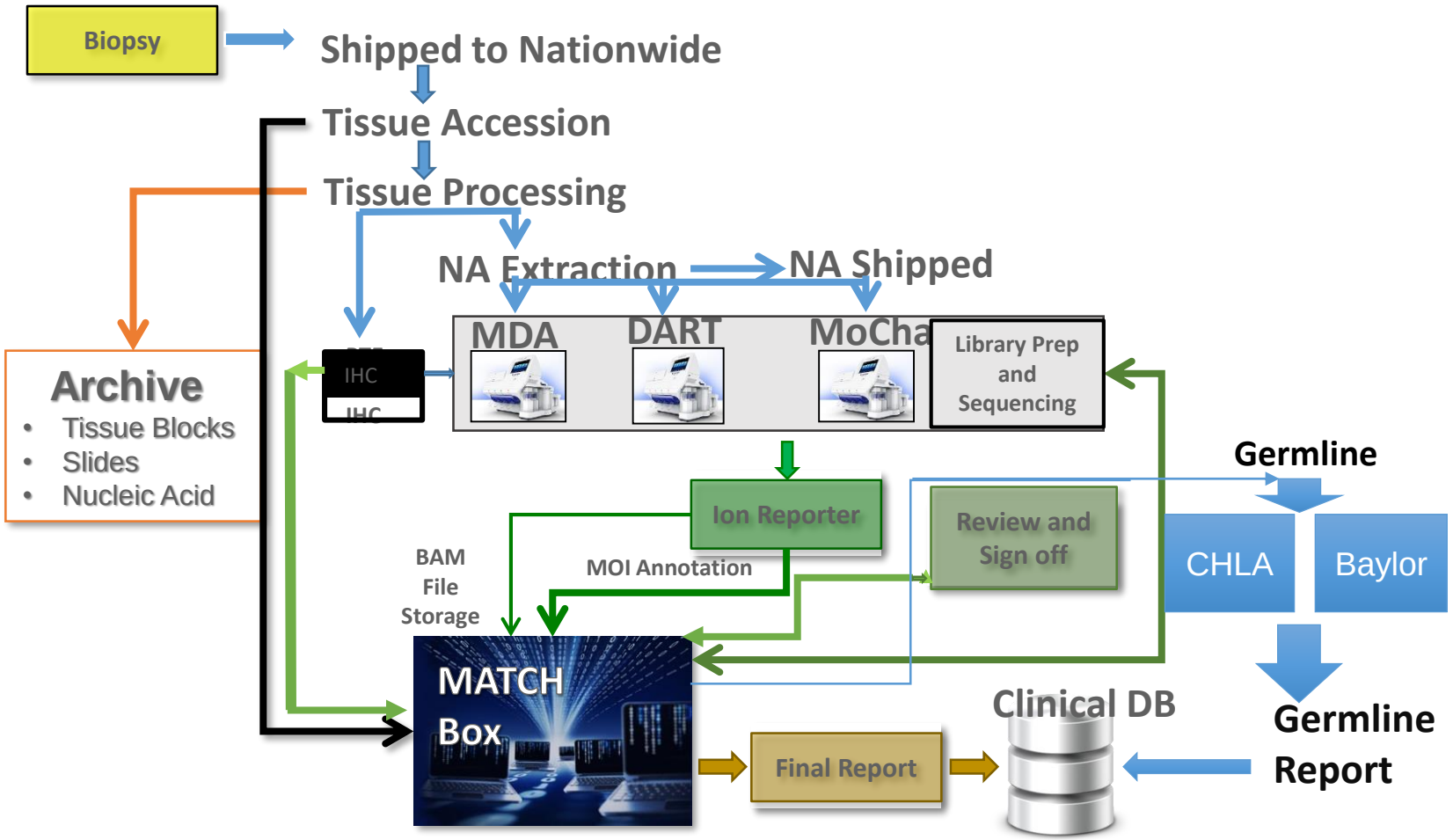
Pediatric MATCH Specimen Work Flow Schema Mirrors Initial Adult NCI MATCH Work



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NCI-COG Pediatric MATCH

Design Features-Differences from Adult NCI MATCH

A similar signal finding study to NCI Adult MATCH with differences:

- 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
- Inclusion of agents with adult RP2D-some never tested in pediatric previously
- 20 patients enrolled/treatment arm; Activity in 3 out of 20 patients of interest; Option to expand to enroll additional patients if responses are seen
- Different administrative structure for study protocol
- Germline DNA

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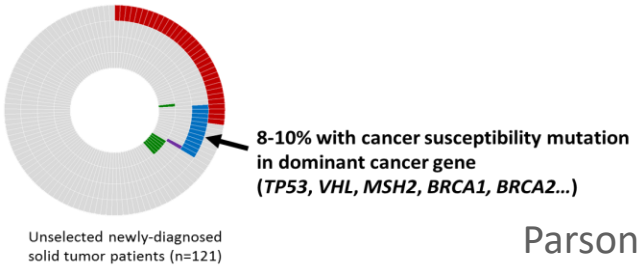


Parsons DW et al. JAMA Oncol, 2015

Germline Sequencing on Pediatric MATCH

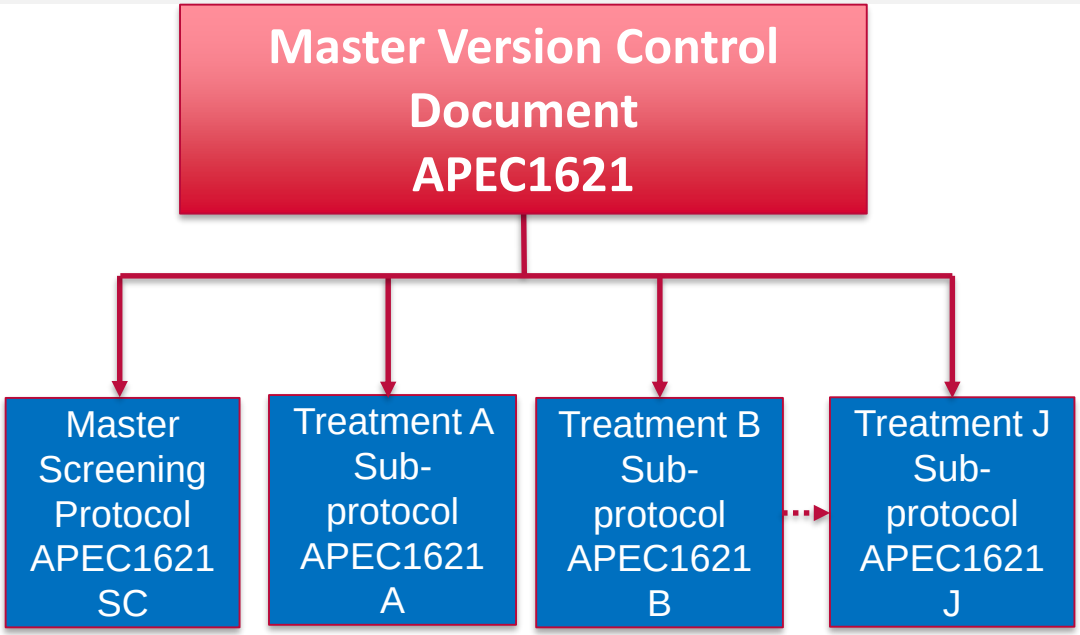
- Blood samples being sequenced using same DNA panel
- Purpose: to identify whether mutations identified by tumor sequencing are somatic or germline (not a full evaluation)
- Interpretation by study clinical geneticists
- Results returned to treating pediatric oncologist
- MATCH study genetic resources available including genetic counseling, website and online educational materials for treating physician

Administrative Structure of NCI-COG Pediatric MATCH

1 study with multiple sub-studies or explicitly broken out with a separate Master Version Control Document

Central Coordination by COG (Group leading study)

Moderate Flexibility (around 5 to 13 sub-studies)



NCTN Group Ops/SDMC: 1 study with explicitly broken out sub-studies
CTEP PIO: 1 study with explicitly broken out sub-studies
CIRB: 1 study with explicitly broken out sub-studies
CTSU: 1 study with explicitly broken out sub-studies
CTRP / Clinicaltrials.gov: Explicitly broken out sub-studies (linked references)
FDA: 1 study with 1 IND
Sites: 1 study with explicitly broken out sub-studies

Treatment Subprotocols (10 activated as of 12/31/2018)

Protocol ID	Agent	Agent Class	aMOI Frequency	Activation Date	Accrual as of 11/29/2019
APEC1621-A	Larotrectinib	TRK inhibitor	2-3%	7/24/2017	5
APEC 1621-B	**Erdafitinib**	**FGFR inhibitor**	2-3%	**11/06/2017**	11
APEC 1621-C	Tazemetostat	EZH2 inhibitor	2-3%	7/24/2017	11
APEC 1621-D	**LY3023414**	**PI3K/mTOR inhibitor**	5-10%	**7/31/2017**	10
APEC 1621-E	Selumetinib	MEK inhibitor	10-20%	7/24/2017	21 Met Accrual
APEC 1621-F	**Ensartinib**	**ALK inhibitor**	2-3%	**7/24/2017**	6
APEC 1621-G	Vemurafenib	BRAF inhibitor	5%	7/24/2017	4
APEC 1621-H	Olaparib	PARP inhibitor	2-3%	7/24/2017	5
APEC 1621-I	Palbociclib	CDK4/6 inhibitor	Variable	6/25/2018	9
APEC1621-J	**Ulixertinib**	**ERK1/2 inhibitor**	Variable	**10/01/2018**	8

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806 children screened as of 11/29/2019

Bolded agents-first time tested in children

3 Additional Treatment Subprotocols In Development

Protocol ID	Agent	Agent Class	Activation Date
APEC1621- K	Ivosidenib	IDH 1 inhibitor	Fall, 2019
APEC 1621- M	Tipifarnib	Farnesyl transferase inhibitor Target HRAS	Fall, 2019
APEC 1621- N	Loxo - 292	RET inhibitor	Fall, 2019

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Screening Protocol Enrollment Description

As of 12/32/2018, 422 patients screened

(basis for ASCO June 2019 Presentation on NCI Pediatric MATCH)

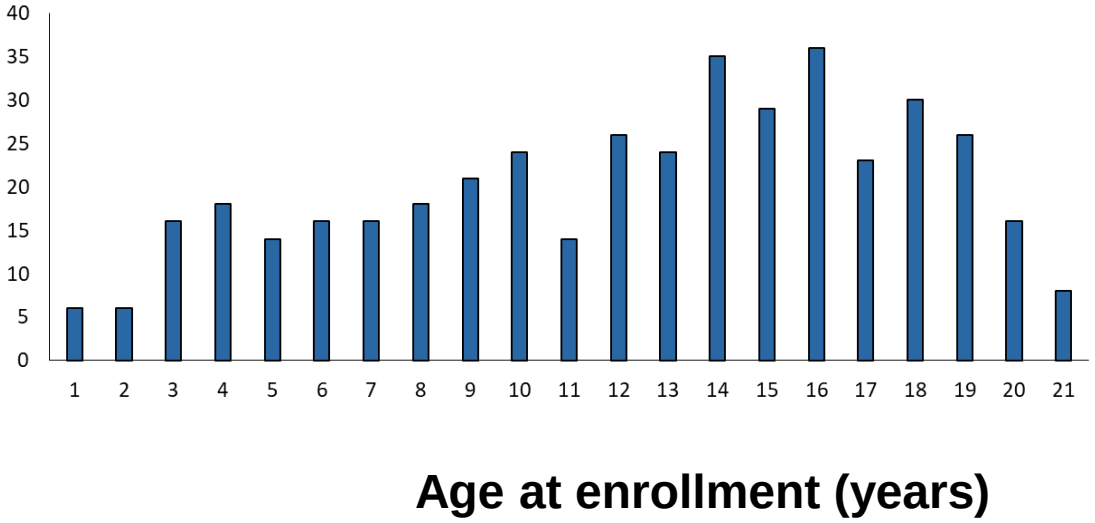
Patient sex, race, ethnicity

Characteristics	Number	Percent
Sex		
Male	248	59%
Female	174	41%
Ethnicity		
Hispanic or Latino	86	20%
Not Hispanic or Latino	320	76%
Not Reported or Unknown	16	4%
Race		
White	284	67%
Black or African American	55	13%
Native Hawaiian or Pacific Islander	4	1%
Asian	19	5%
American Indian or Alaska Native	2	1%
Multiple Races	7	2%
Not Reported or Unknown	51	12%

Patient age

- Age range 1 to 21 years (median = 13)
- 40% of patients from 15-21 years

Patients enrolled



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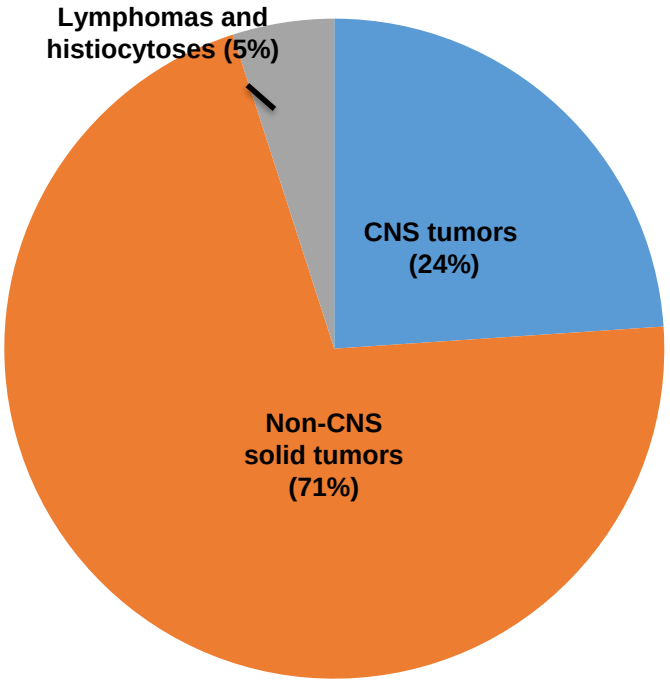
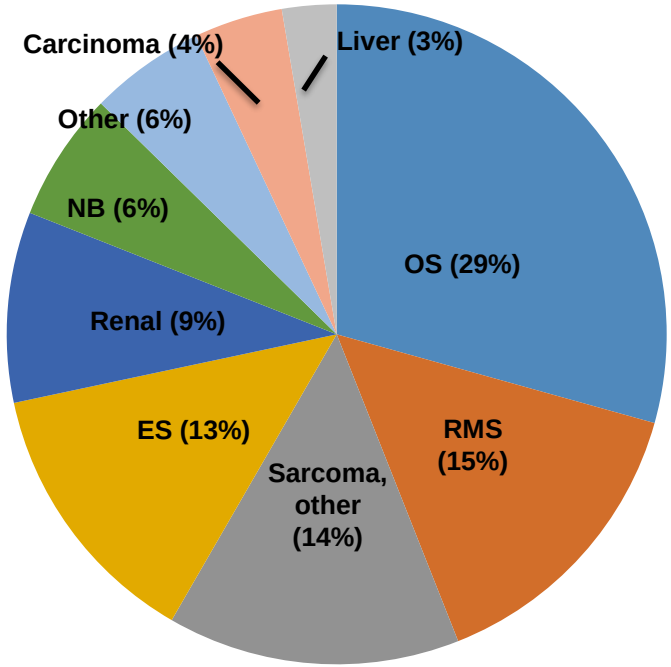
Screening protocol diagnoses

ALL DIAGNOSES



NON-CNS TUMORS



OS, osteosarcoma; RMS, rhabdomyosarcoma; ES, Ewing sarcoma; NB, neuroblastoma

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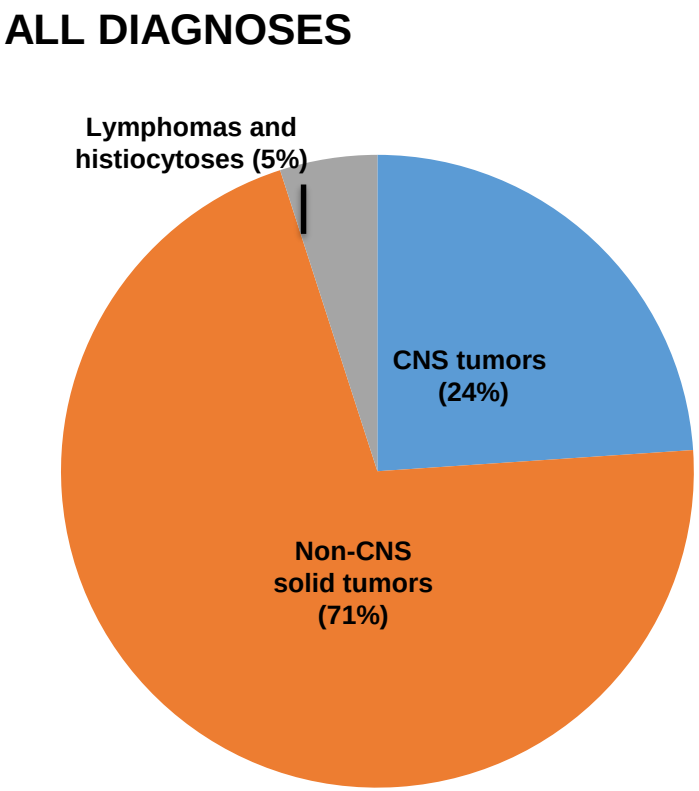
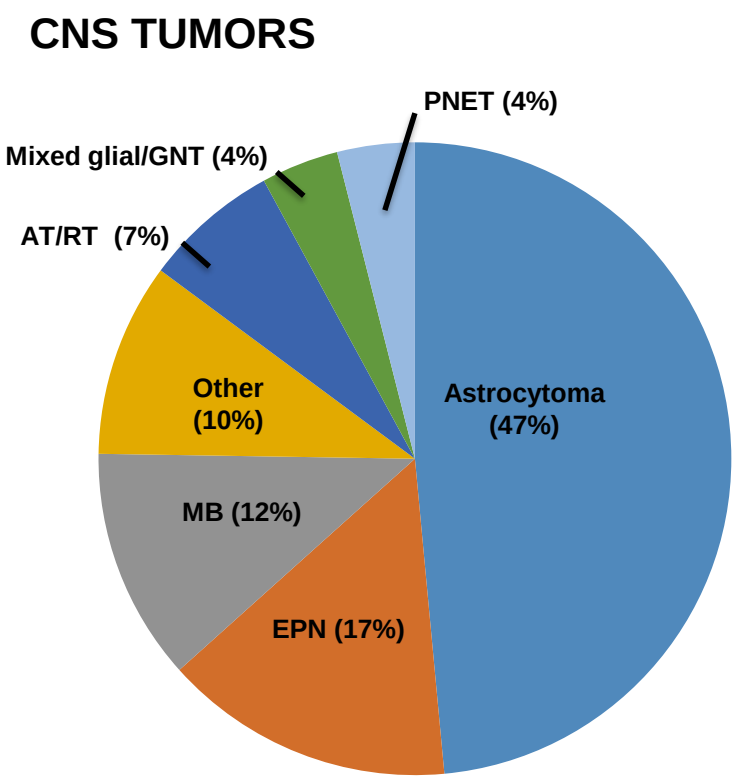
Screening protocol diagnoses





EPN, ependymoma; MB, medulloblastoma,
AT/RT; atypical teratoid/rhabdoid tumor; GNT, glioneuronal tumor;
PNET, primitive neuroectodermal tumor

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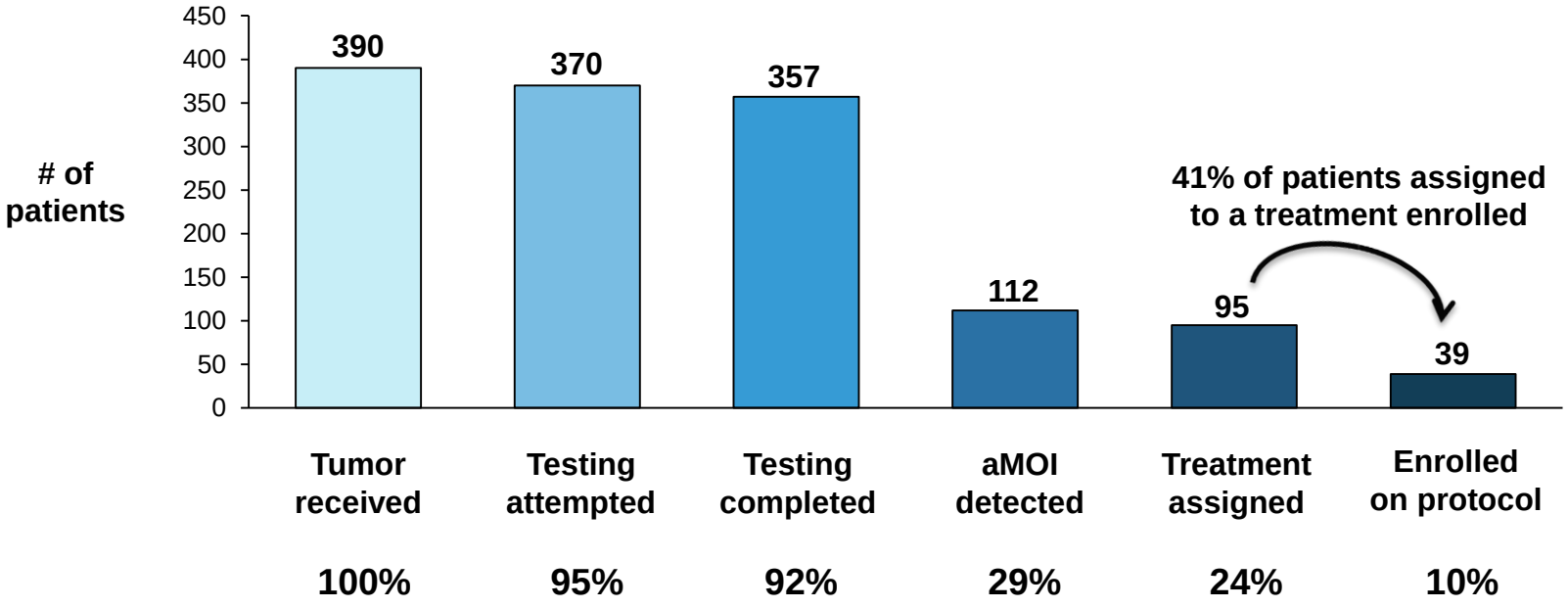
Tumor testing and matching

- **Tumor sample was received for 390/422 (92%) enrolled patients**



Median turnaround time (tumor receipt to assignment): 15 days

Parsons DW et al. ASCO 2019

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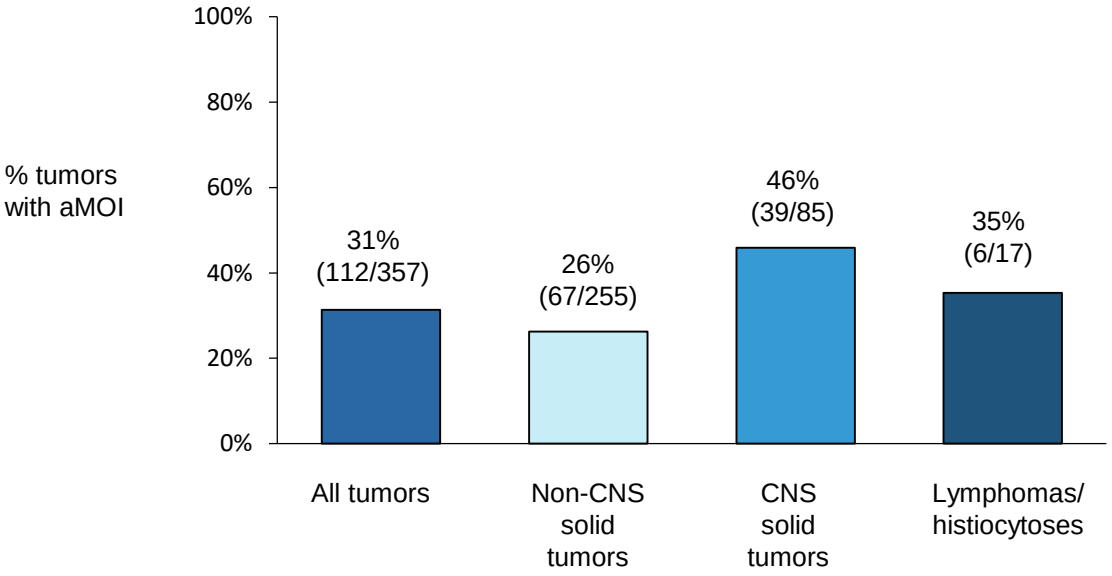
Actionable mutation detection – all tumors

- An aMOI was detected in 112/357 (31%) tumors



n=357 tumors with testing completed as of 12/31/18

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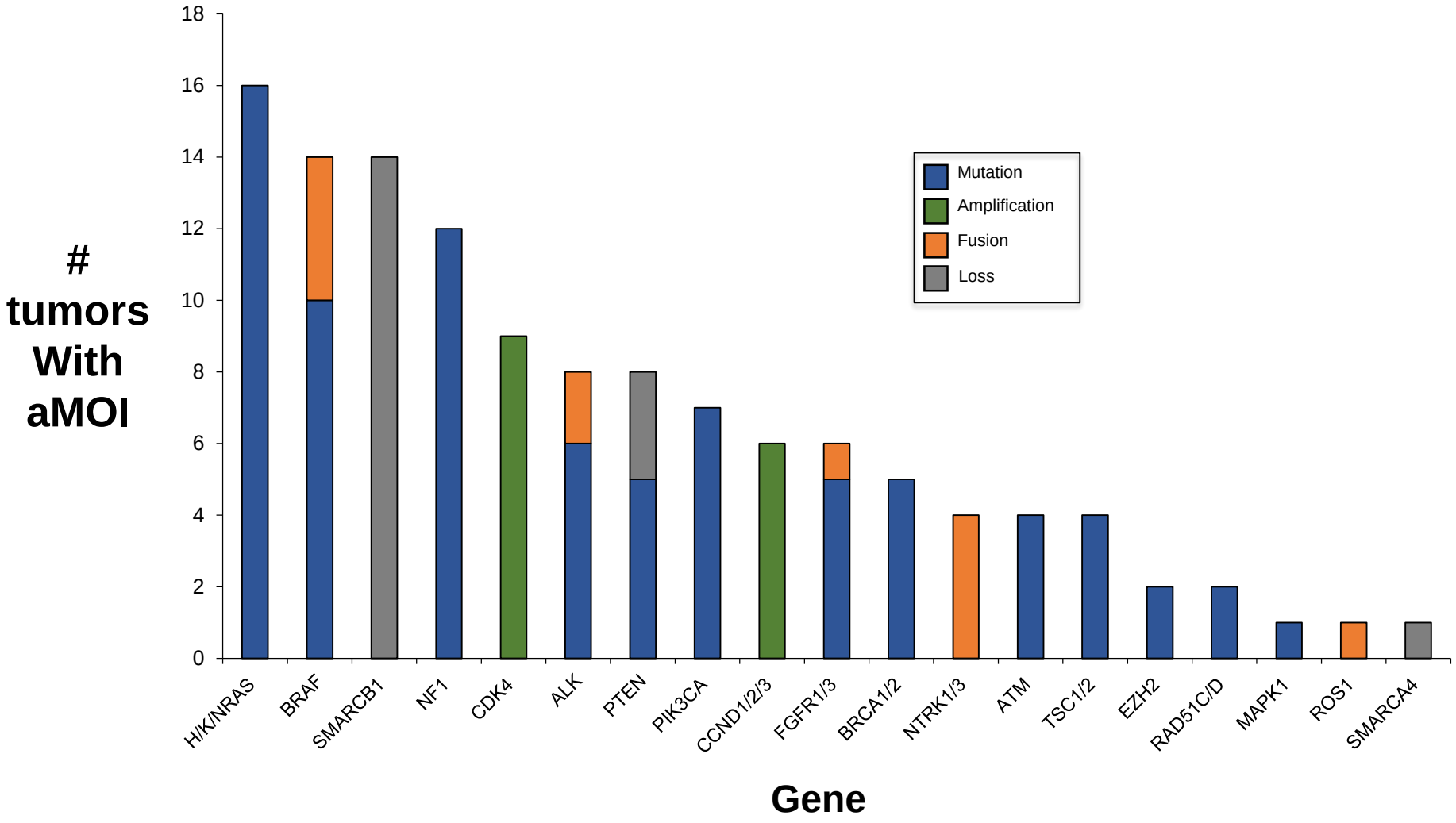
Actionable mutation detection - genes



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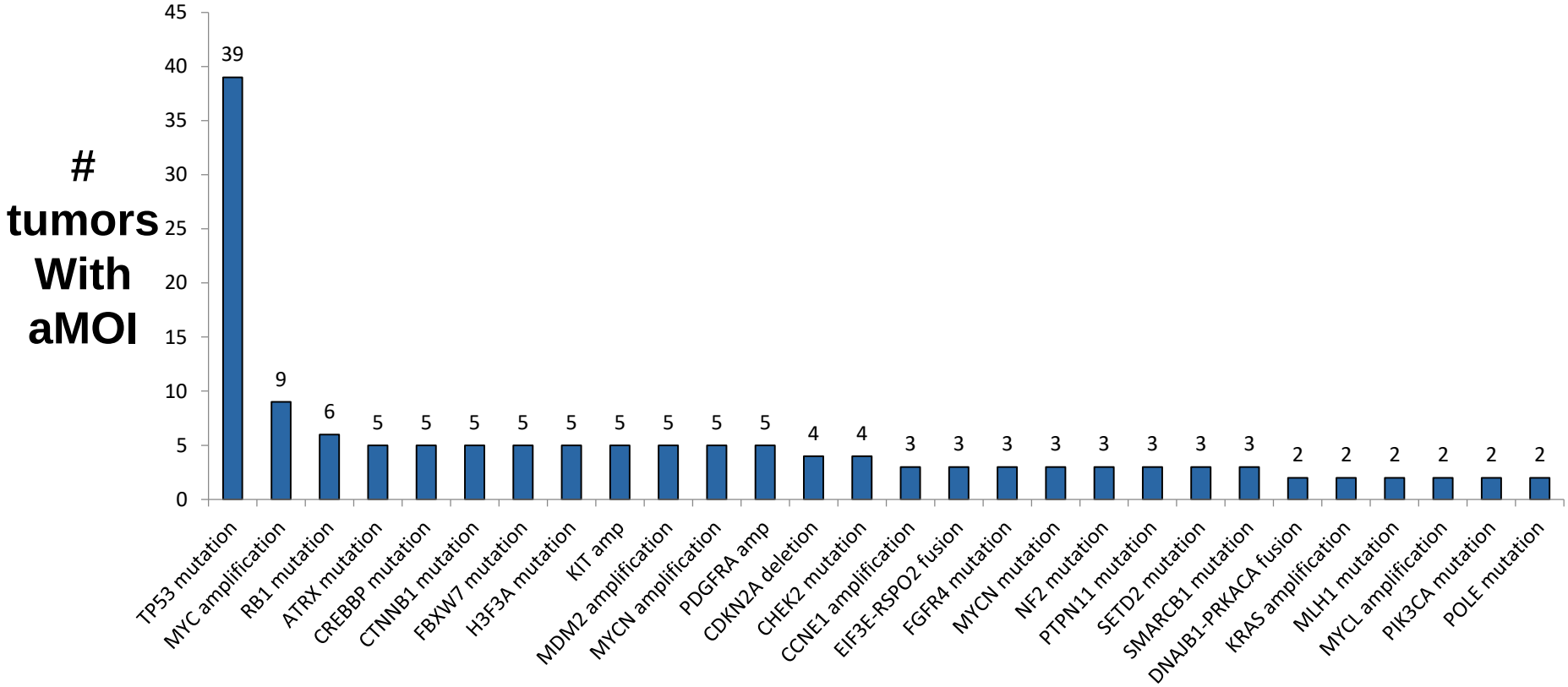
n=357 tumors with testing completed as of 12/31/18

Non-actionable mutations– recurrent genes



n=357 tumors with testing completed as of 12/31/18

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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
- Protocol configuration

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Conclusions on Pediatric MATCH to Date

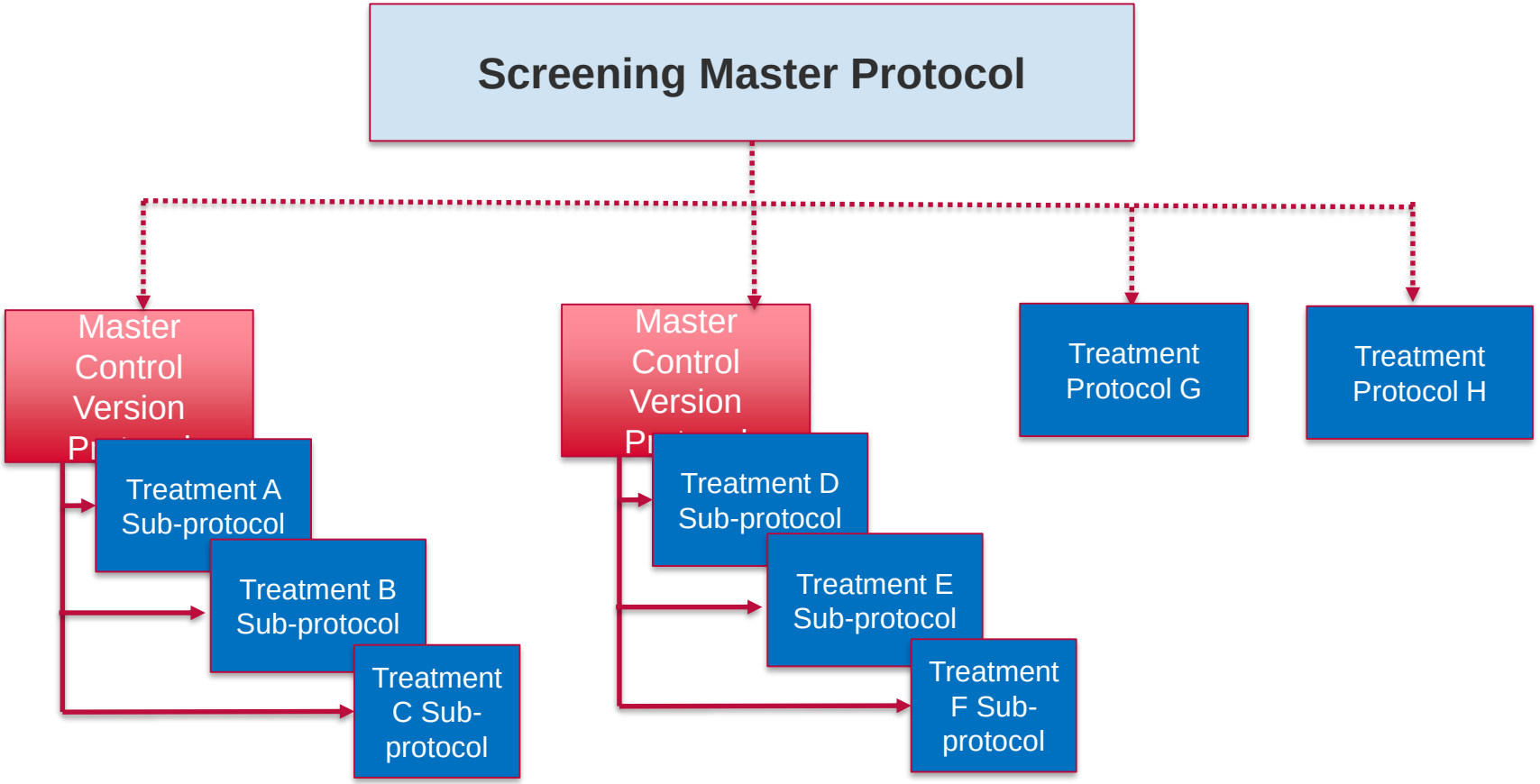
- NCI-COG Pediatric MATCH has created a collaborative framework for collection, processing, and sequencing of refractory pediatric cancers
- The modular format of the overall study (Master Control Version document with individual subprotocols) has made it easier for the sites to manage the study locally
- Study enrollment has exceeded projections, with participation from a large and diverse (and growing) group of COG institutions
- Approximately 25% of study patients with tumor submitted have been assigned to a treatment arm, with 10% enrolled on those trials to date
- The study is successfully facilitating the evaluation of molecularly-targeted agents in biomarker positive pediatric cohorts

Future Directions
National Trials to Succeed NCI-MATCH

3 potential successor trials in development

- **ComboMATCH:** Drug combinations are more likely to provide clinical benefit than single agents in most scenarios, so the successor trial to focus on drug combinations using pre-clinical data from *in vivo* models of drug combinations that predict clinical benefit in defined patient groups
- **AML/MDS Precision Medicine Initiative:** Focus on matching AML molecular subtypes to targeted therapies in different age/fitness groups as well as throughout the course of the disease
- **iMATCH:** Focus on providing prospective immunologic profiling to feed IO study arms defined by histology or molecular subgroups
- **Coordination:** Via a Network of laboratories to provide lab support for the trials and a Precision Medicine Analysis & Coordination Center to provide screening data coordination, decision-making and communications support for the trials

Alternative Administrative Design for Umbrella/Basket Trials Instead Single Protocol



1 master screening protocol and then multiple "cassettes" of Separate sub-protocols over time. The screening master is independent of the "cassettes" – but it is all centrally operated/harmonized and is under 1 or multiple INDs.

Summary

- Design as well as scientific & administrative conduct of umbrella/basket trials is challenging, but efficiencies can be identified and exploited to maintain flexibility & accelerate clinical research

- Need for study of rare gene variants requires a large network of laboratories for identifying patients

- Programmatic expansion of additional large, national, umbrella/basket trials requires coordinated use of similar administrative, laboratory, and IT systems that can be shared across trials

NCI-MATCH (Adult) Study

- **There is widespread participation across the NCI scientific community**
  - About 120 treatment arm chairs and co-chairs
  - Nearly 1100 participating sites nationwide
  - Over 150 individuals on 10 steering committees and working groups

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

NCI National Clinical Trials Network
a National Cancer Institute program

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Reshaping the future of patient care

NRG ONCOLOGY
Advancing Research. Improving Lives.™

SWOG
Leading cancer research. Together.

NCI-COG Pediatric MATCH Study

Study committees

- Study design and logistics: Stacey Berg, Beth Fox
- Target/agent prioritization: Katie Janeway (COG vice chair), Jae Cho
- Sequencing platform/analysis: Jim Tricoli
- Germline result reporting: Sharon Plon, Steven Joffe
- Biospecimens: Julie Gastier-Foster
- Informatics: Hema Chaudhary, David Patton

COG leadership and staff

- Peter Adamson, Thalia Beeles, Rita Tawdros, Jon Bennet, Wendy Martinez, Lauren Saguilig, Olga Militano, Todd Alonzo, Jin Piao, Renee Klenke, Joel Reid, Marilyn Siegel, Joyce Mhlanga, Alok Jaju, Anne Gill et al.

NCI/CTEP leadership and staff

- Nita Seibel (NCI study chair), Malcolm Smith, Mickey Williams, Naoko Takebe, Bhanu Ramineni, Brent Coffey, Cindy Winter, Jennifer Lee, adult NCI-MATCH leadership (Conley, Chen) et al.

MATCH laboratories

- Stan Hamilton, Ryan Pepper, Greg Tsongalis, Brianna Houde, Vivekananda Datta, Shahanawaz Jiwani, David Sims, Mark Routbort, Divya Panditi, Shountea Stover, Erik Zmuda et al.

FDA leadership

- Martha Donoghue, Greg Reaman

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