ACCELERATING PEDIATRIC DRUG DEVELOPMENT

A FRIENDS OF CANCER RESEARCH FORUM

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Opening Remarks

Ellen V. Sigal

Chairperson & Founder, Friends of Cancer Research

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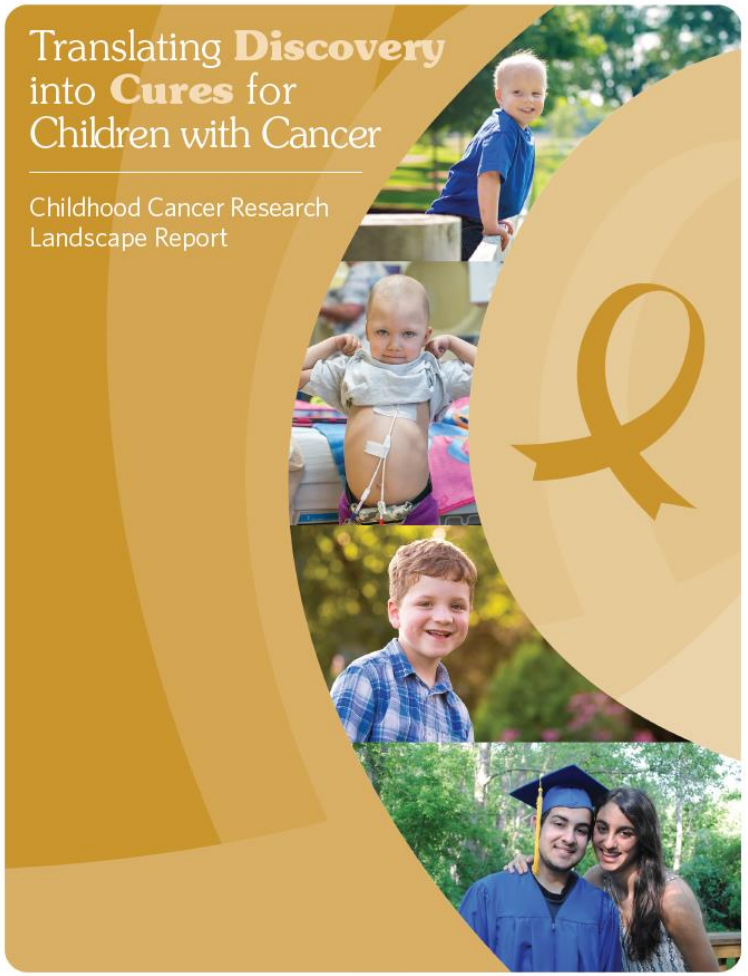
Childhood Cancer Research and Drug Development Landscape

Mark Fleury PhD

Policy Principal-Emerging Science

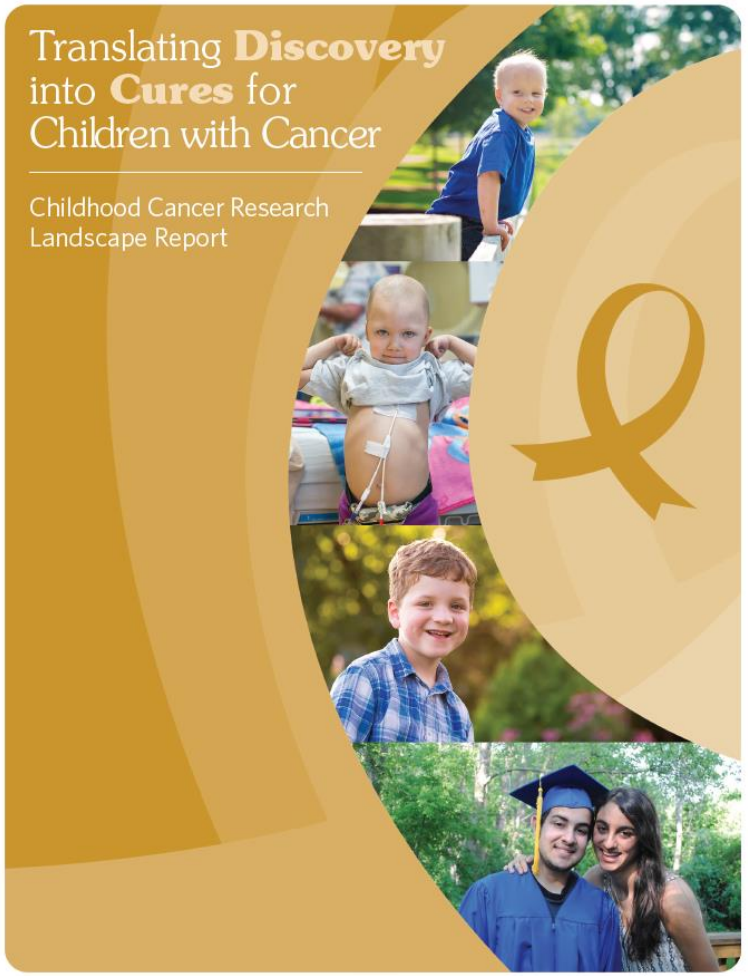
Childhood Cancer Drug Development

- Drug development of any kind shares common elements
- Unique challenges faced in childhood cancer
- Report is a joint project between ACS and the Alliance for Childhood Cancer
- Describes the process, landscape and unique challenges in childhood research
- Available at: www.cancer.org/childrensreport



Landscape Report Organization

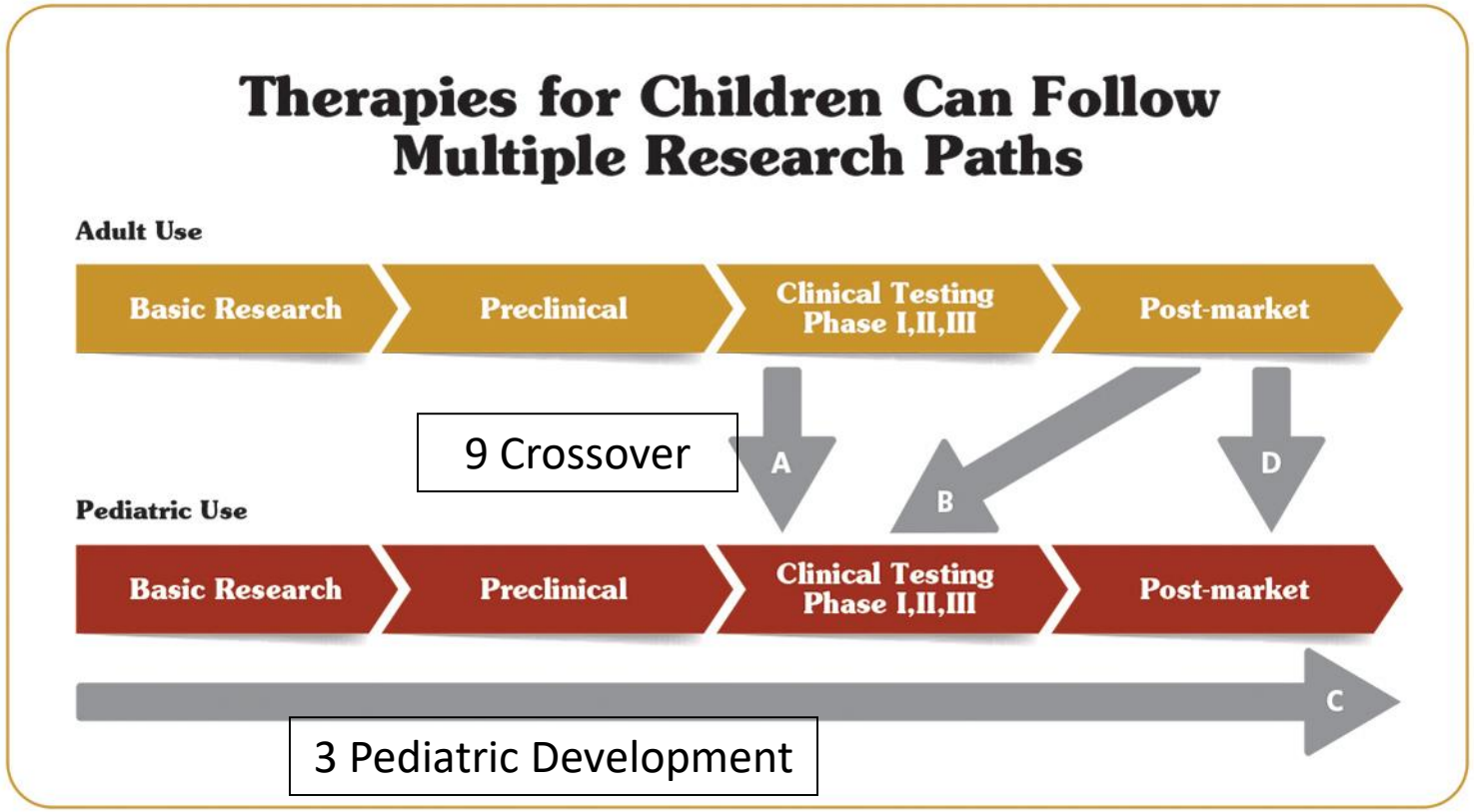
- Biology
- Preclinical Research
- Clinical Research
- Regulatory Requirements
- Funding and Economic Forces



Summary Findings

- **Childhood cancers are often biologically different than the cancers that share the same name in adults, meaning that childhood-specific research is required.**
- **Side effects from treatment cause significant health impacts on children.**
- **The rarity of childhood cancers**
  - **Can make recruiting children to participate in clinical research challenging, either due to a small number of diagnosed patients or due to competition between different research projects.**
  - **Means smaller financial incentives to develop and market drugs specifically for children with cancer. This leads to greater governmental and non-profit roles in drug development.**
- **Society has afforded special protective status for children involved in research, which changes the type of research generally considered to be ethical for children and also changes the process for approving such research.**

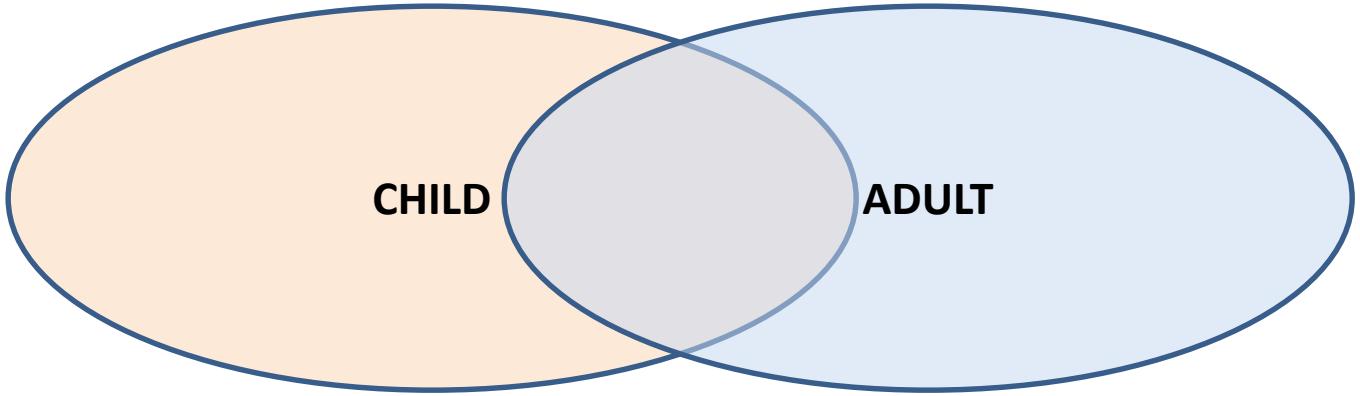
Arriving at New Therapies for Kids



12 Pediatric Label Indications since 1980

Basic Research

- **Childhood cancers are often biologically different than the cancers that share the same name in adults, meaning that childhood-specific research is required.**



Basic Research

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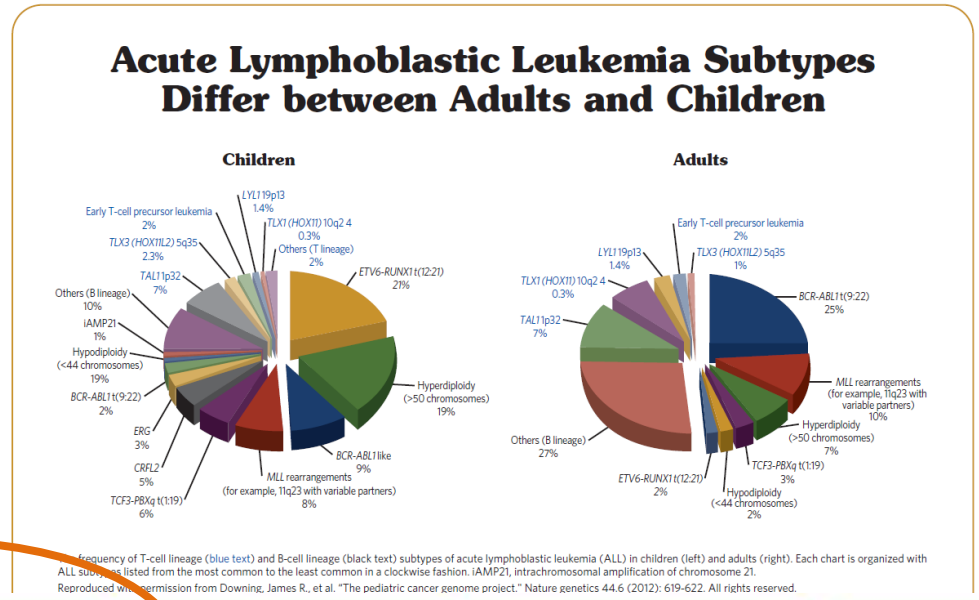


frequency of T-cell lineage (blue text) and B-cell lineage (black text) subtypes of acute lymphoblastic leukemia (ALL) in children (left) and adults (right). Each chart is organized with ALL subtypes listed from the most common to the least common in a clockwise fashion. iAMP21, intrachromosomal amplification of chromosome 21.

Basic Research → Preclinical → Clinical Testing Phase I,II,III → Post-market

Basic Research

- **Side effects from treatment cause significant health impacts on children**

Cancer Therapies Cause a Variety of Late Effects

System	Exposure	Effect
Cardiovascular	Radiation therapy Anthracyclines Platinums	Myocardial infarction or stroke Congestive heart failure Valvular disease Hypertension
Lungs	Radiation therapy Bleomycin Carmustine/Lomustine	Restrictive lung disease Pulmonary fibrosis Exercise intolerance
Kidney/urological	Radiation therapy Platinums Ifosfamide/cyclophosphamide	Renal insufficiency or failure Hemorrhagic cystitis
Endocrine	Radiation therapy Alkylating agents	Obesity Infertility and gonadal dysfunction Dyslipidemia Insulin resistance and diabetes
Central nervous system	Radiation therapy Intrathecal chemotherapy	Learning disabilities Cognitive dysfunction
Second cancers	Radiation therapy Alkylating agents Epipodophyllotoxins	Solid tumors Leukemia Lymphoma
Psychosocial	Cancer diagnosis	Affective disorders (anxiety, depression) Posttraumatic stress Sexual dysfunction Relationship problems Employment and educational problems Insurance discrimination Adaptation and problem solving

Preclinical

"There is a lack of preclinical data to justify running some trials that are proposed."

— *Dr. Gregory Reaman, Associate Director, Office of Hematology and Oncology Products, US FDA*

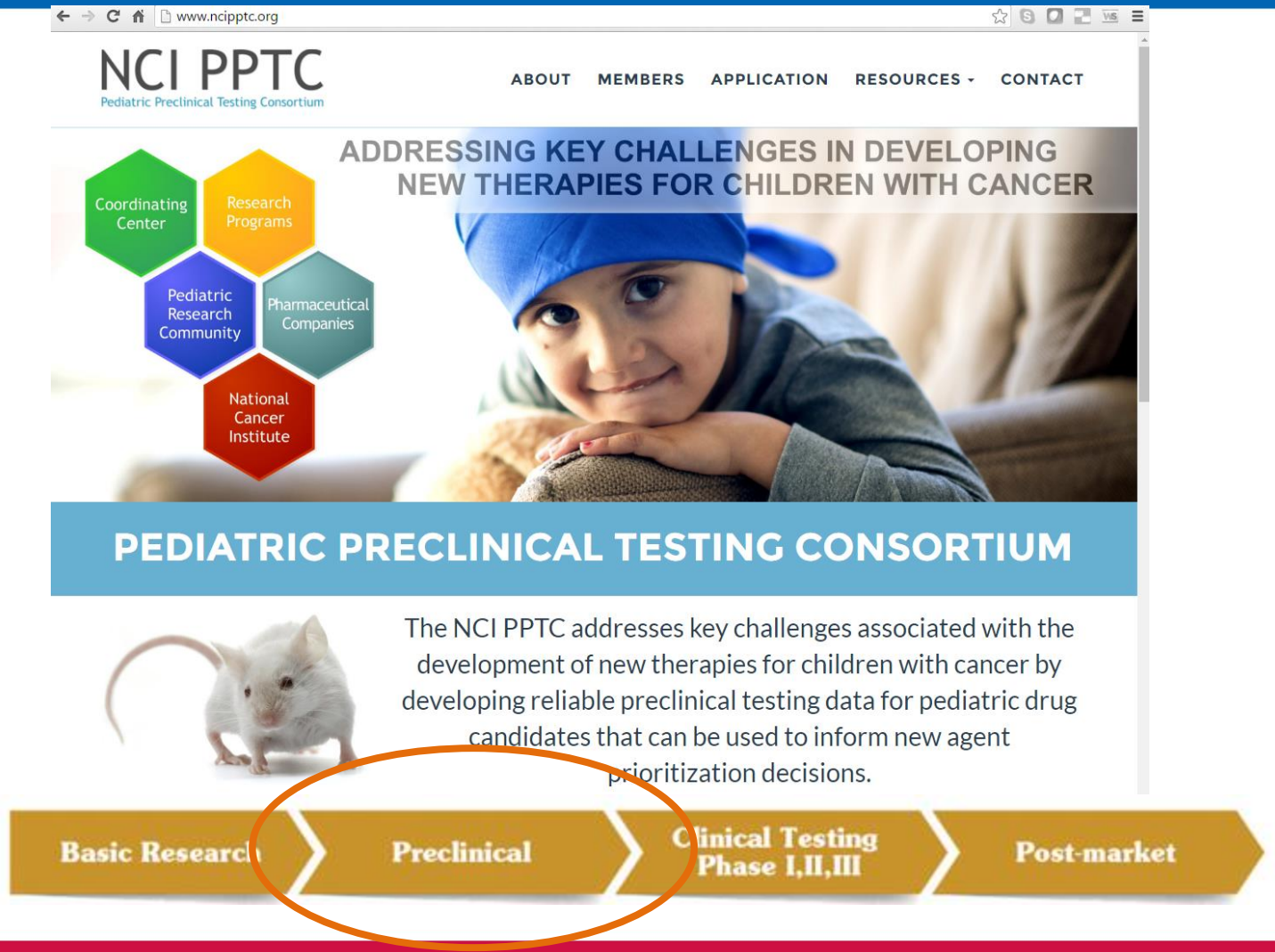
"There is a clear preclinical funding gap. Deprioritizing the thorough and expensive kind of preclinical studies that have depth of biological replicates and appropriate statistical power can leave many trials vulnerable to misinformed conclusions at their foundation. "

— *Dr. Charles Keller, Scientific Director, Children's Cancer Therapy Development Institute*

"Unless we can generate meaningful preclinical data, we won't be able to develop a treatment that is a home run. At present, people use weak rationales to justify taking a drug for adults and using it on kids without strong preclinical justification."

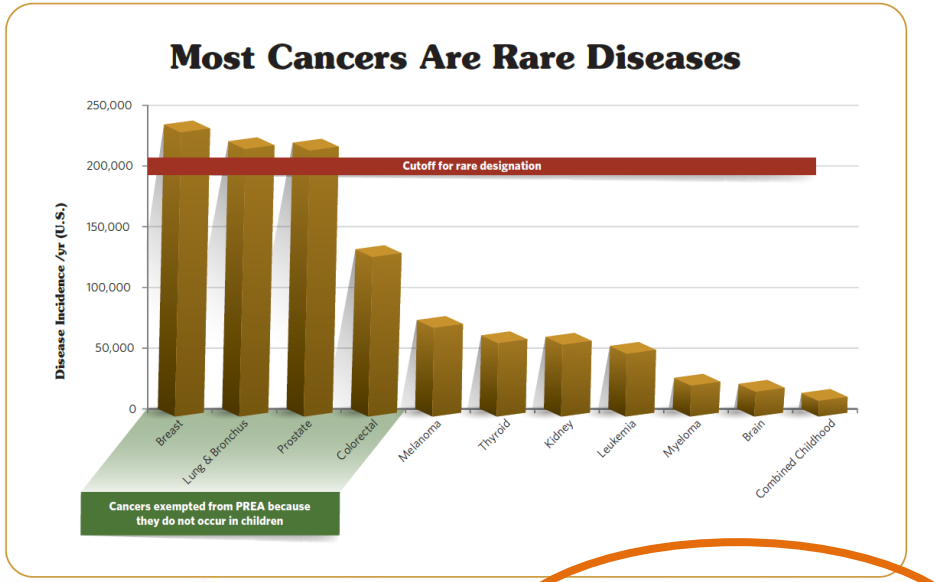
— *Dr. Girish Dhall, Director, Neuro-oncology program, Children's Hospital Los Angeles*

Preclinical



Challenges with Low Numbers

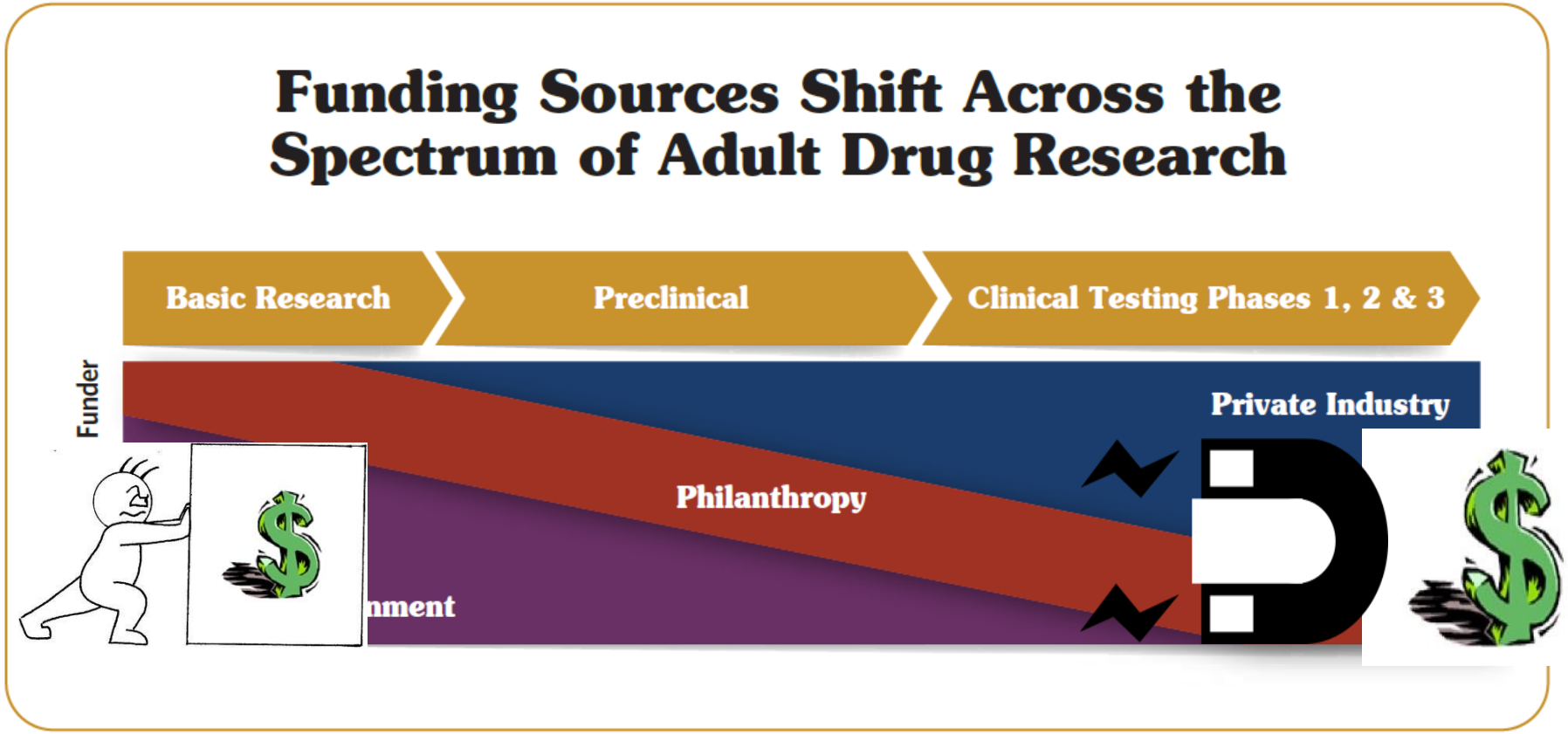
- **The rarity of childhood cancers**
  - **Can make recruiting children to participate in clinical research challenging, either due to a small number of diagnosed patients or due to competition between different research projects.**



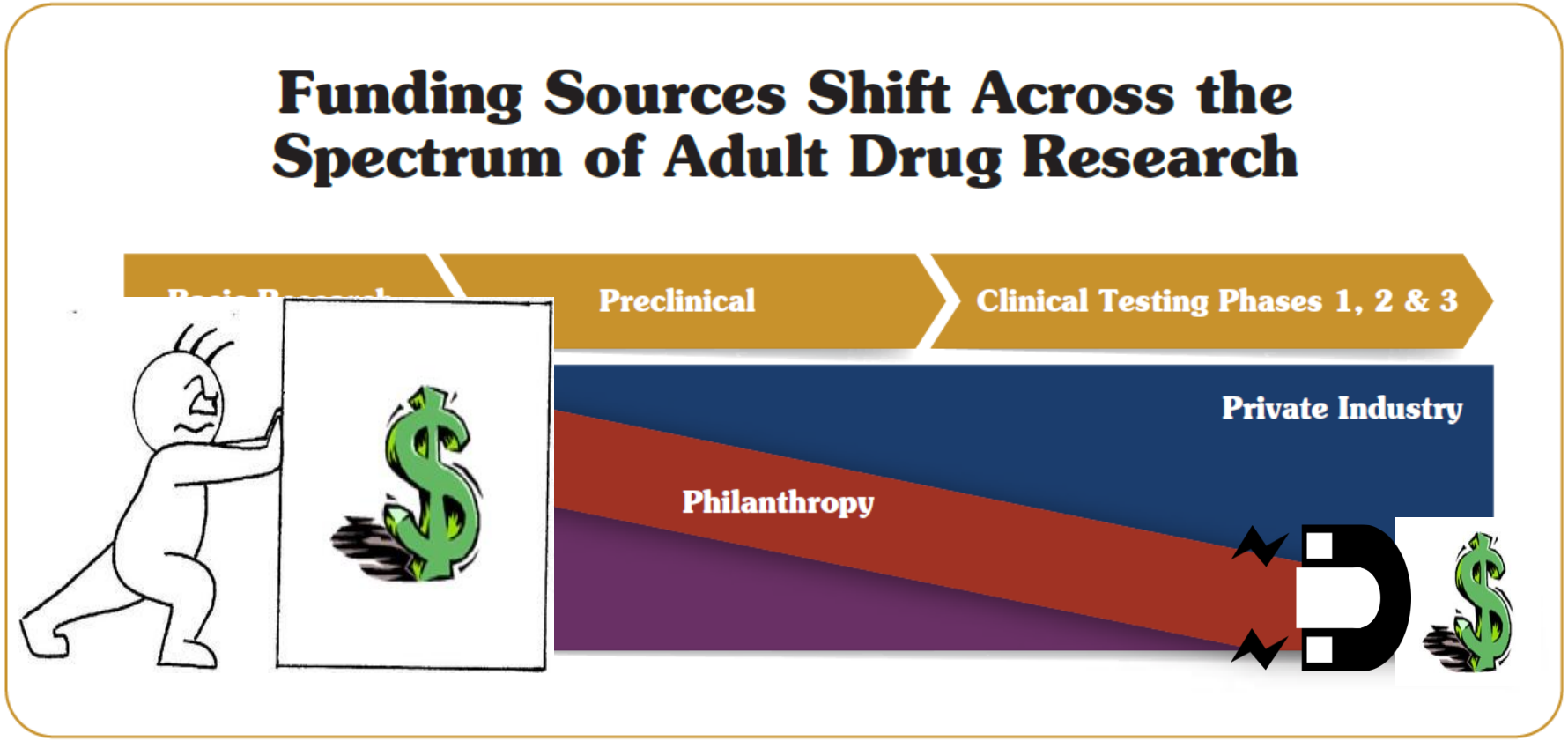
Low Numbers but High Participation

- 90% of children with cancer are treated at a Children's Oncology Group (COG) facility
- 50%-60% Enroll on some type of trial (therapeutic and non-therapeutic)
- 20%-30% Enroll on a therapeutic trial
- COG funded at ~$30 M/yr by NCI

Who Drives Research?



Who Drives Research?



Challenges with Low Numbers

- **The rarity of childhood cancers**
  - **Means smaller financial incentives to develop and market drugs specifically for children with cancer. This leads to greater governmental and non-profit roles in drug development.**

Regulatory programs to change the natural incentives—BPCA, PREA, Creating Hope

Summary Findings

- **Childhood cancers are often biologically different than the cancers that share the same name in adults, meaning that childhood-specific research is required.**
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Summary

- **Challenges ranging from biological to logistical to ethical and economic require enhanced collaboration among stakeholders who share the common goal of advancing treatments to cure childhood cancers.**

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

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

NIH NATIONAL CANCER INSTITUTE

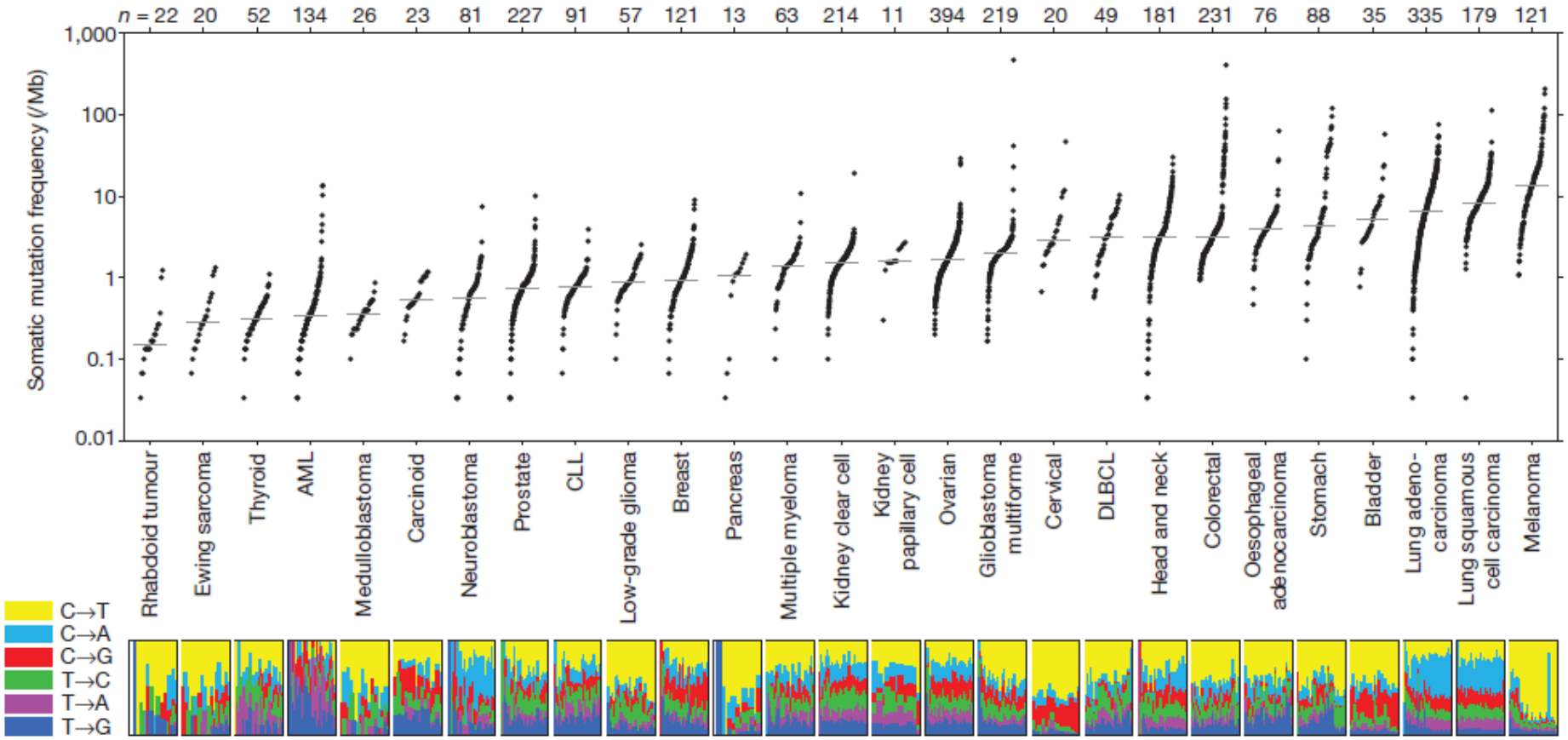
February 21, 2017

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.

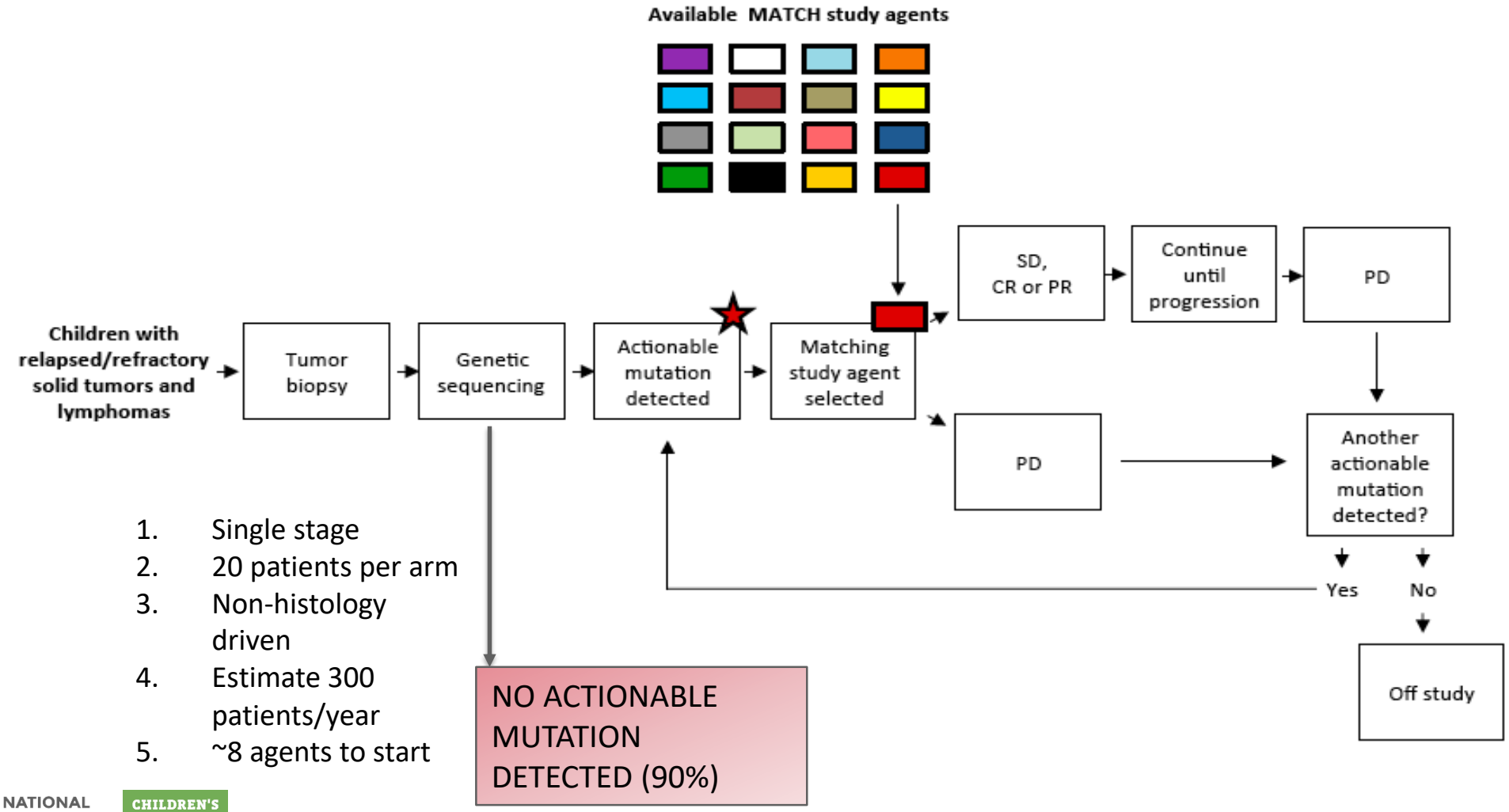
Number of Somatic Mutations in Human Cancers

- Childhood cancers generally have lower mutation rates than adults cancers



Lawrence MS, et al. Nature 2013:499(7457):214-218

NCI-COG Pediatric MATCH

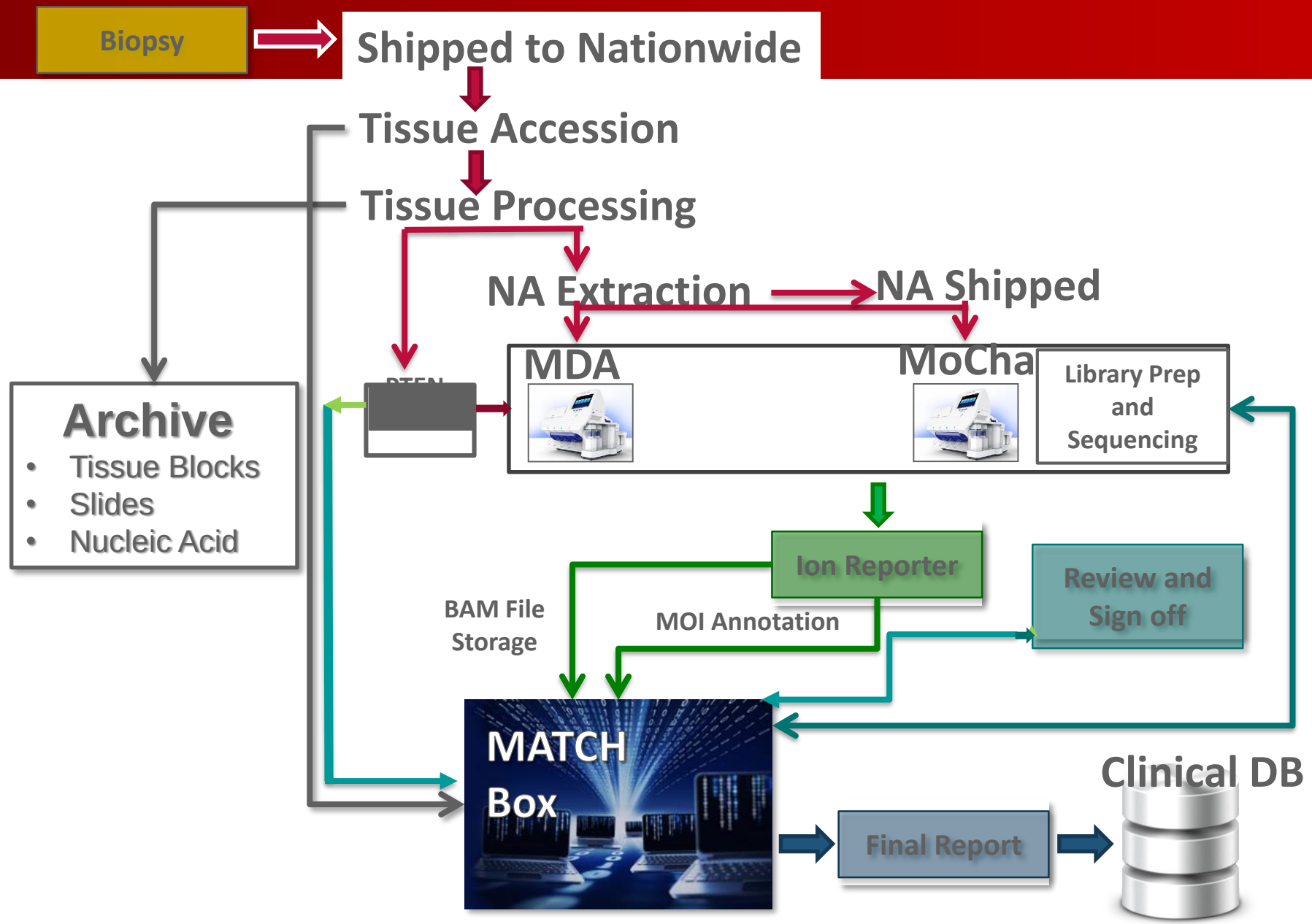


1. Single stage
2. 20 patients per arm
3. Non-histology driven
4. Estimate 300 patients/year
5. ~8 agents to start

NIH NATIONAL CANCER INSTITUTE

CHILDREN'S ONCOLOGY GROUP

Pediatric MATCH Specimen Work Flow Schema

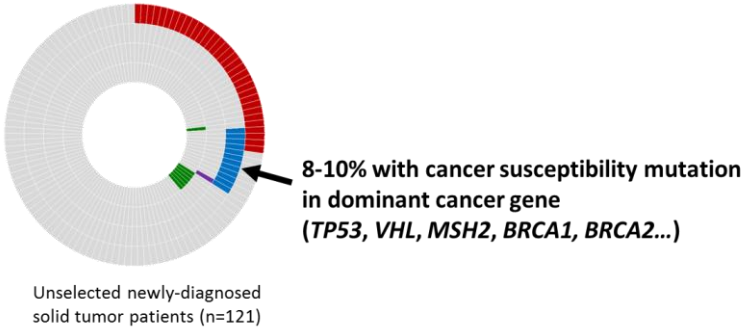


NCI-COG Pediatric MATCH
Design Features

- Test many children and adolescents to find widely distributed genetic alterations
- 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

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

Thank you!

seibelnl@mail.nih.gov

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Bringing Genomics to the Pediatric Oncology Clinic: The TAPUR Study

Katherine A. Janeway, MD, MMSc
February 21, 2017

Friends of Cancer Research

DANA-FARBER Boston Children's

CANCER AND BLOOD DISORDERS CENTER

The Significance of Precision Cancer Medicine (PCM)

2 ½ year old with metastatic inflammatory myofibroblastic tumor with *ALK* rearrangement

- Key variants known for only a few pediatric cancers
- Is it possible to extend successes of precision medicine to pediatric cancers where the key variants are not yet known?

Multi-Institution PCM Study in Pediatric Oncology: the iCat1 Study

- Goal: to determine whether it is feasible to identify key gene variants and make an **i**ndividualized **ca**ncer **t**herapy or **iCat** recommendation using currently available clinical sequencing tests

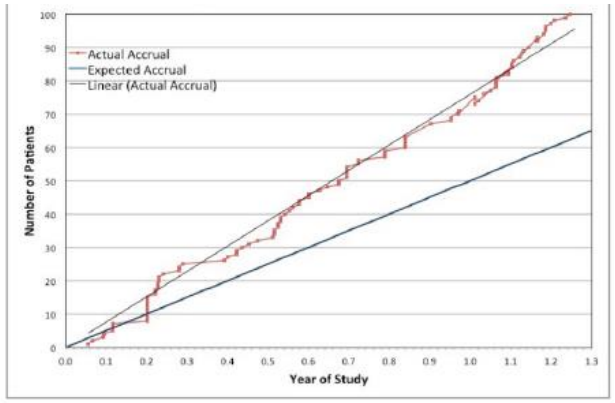
Eligibility: High risk extra-cranial solid tumors

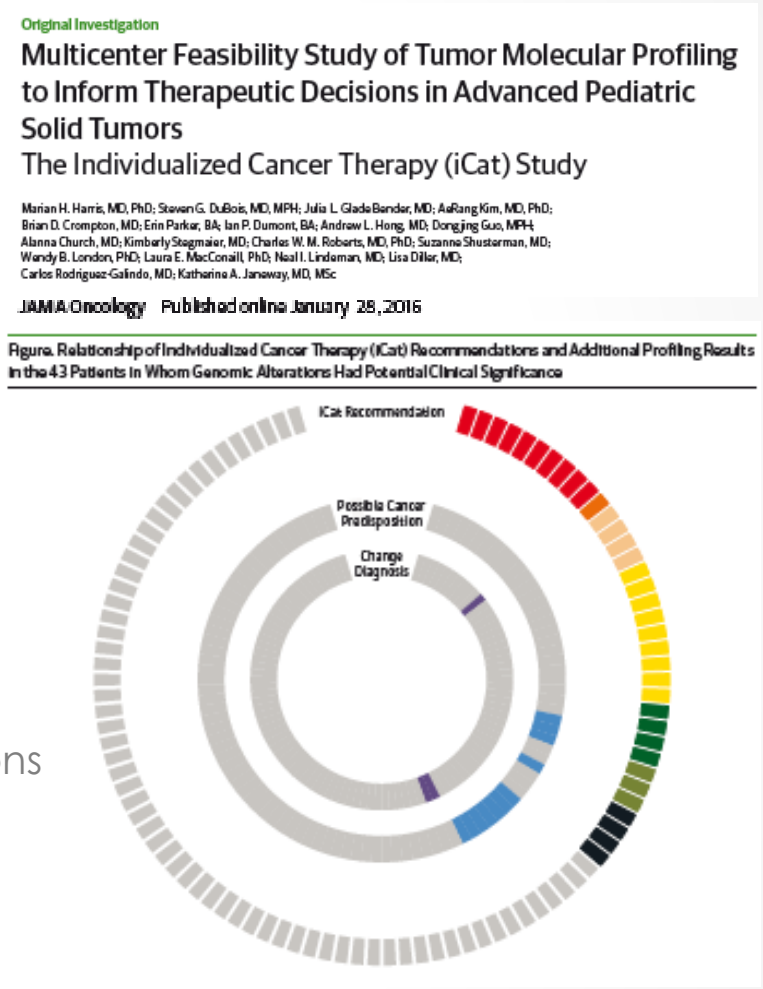
iCat recommendation

Expert Panel

The iCat1 Study, Results

- High degree of physician and patient engagement





Original Investigation

Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors

The Individualized Cancer Therapy (iCat) Study

Marian H. Harris, MD, PhD; Steven G. DuBois, MD, MPH; Julia L. Glade Bender, MD; AeRang Kim, MD, PhD; Brian D. Crompton, MD; Erin Parker, BA; Ian P. Dumont, BA; Andrew L. Hong, MD; Dongjing Guo, MPH; Alanna Church, MD; Kimberly Stegmaier, MD; Charles W. M. Roberts, MD, PhD; Suzanne Shusterman, MD; Wendy B. London, PhD; Laura E. MacConaill, PhD; Neal I. Lindeman, MD; Lisa Diller, MD; Carlos Rodriguez-Galindo, MD; Katherine A. Janeway, MD, MSc

JAMA Oncology Published online January 28, 2016

Figure. Relationship of Individualized Cancer Therapy (iCat) Recommendations and Additional Profiling Results in the 43 Patients in Whom Genomic Alterations Had Potential Clinical Significance

- Conducting a multi-institution study is feasible
  - 40% patients enrolled from 3 collaborating Institutions
- **30% of patients received an iCat recommendation**
- 40% had a result with implications for care
- >90% would participate again (Marron J,, PBC, 2016)

Harris M et al., JAMA Oncology 2016

The iCat1 Study, Results

- Actionable alterations identified highlight the drug classes where there is a high priority to develop early phase clinical trials with integrated genomic characterization in children with recurrent and refractory solid tumors

Drug class	Targeted genes altered in iCat enrolled pts	N pts with alteration
CDK4/6 inhibitor	*CDKN2A/B, CCND1, CDK4, CDK6*	11
BET bromodomain inhibitor	*MYC, MYCN*	6
BRAF / MEK / ERK inhibitor	*HRAS, NRAS, BRAF*	3
ALK inhibitor	*ALK*	3
PARP inhibitor	*ATM*	2
FGFR inhibitor	*FGFR2, FGFR4*	2
MDM2 inhibitor	*MDM2*	2
NTRK inhibitor	*NTRK3*	1
PI3K / mTOR inhibitor	*PIK3CA*	1

Unanswered Questions

1) Impact of receiving matched targeted therapy on outcome
2) Sequencing approach optimal
3) Full spectrum of actionable variants

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

G·A·I·N

Genomic Assessment Informs Novel Therapy

CONSORTIUM

- Boston Children's Hospital
- Children's Hospital at Montefiore
- Children's Hospital of Philadelphia
- Children's National Medical Center
- Columbia University Medical Center
- Dana-Farber Cancer Institute
- Huntsman Cancer Institute, University of Utah
- Nationwide Children's Hospital
- Seattle Children's Hospital
- UCSF Benioff Children's Hospital
- University of Chicago Comer Children's Hospital
- Children's Hospital Colorado
- UT Southwestern Medical Center

Extracranial solid tumors
800 patients

- Eligibility

All: T+N targeted NGS panel
Selected: WES and RNA Seq

- Tumor Profiling

Clinical Impact
Therapy Recommendation
Classify drug availability

- Curation
- Clinical interpretation

Vital Status
Treatment Response

- Follow-up

GAIN/iCat2 Primary Objectives

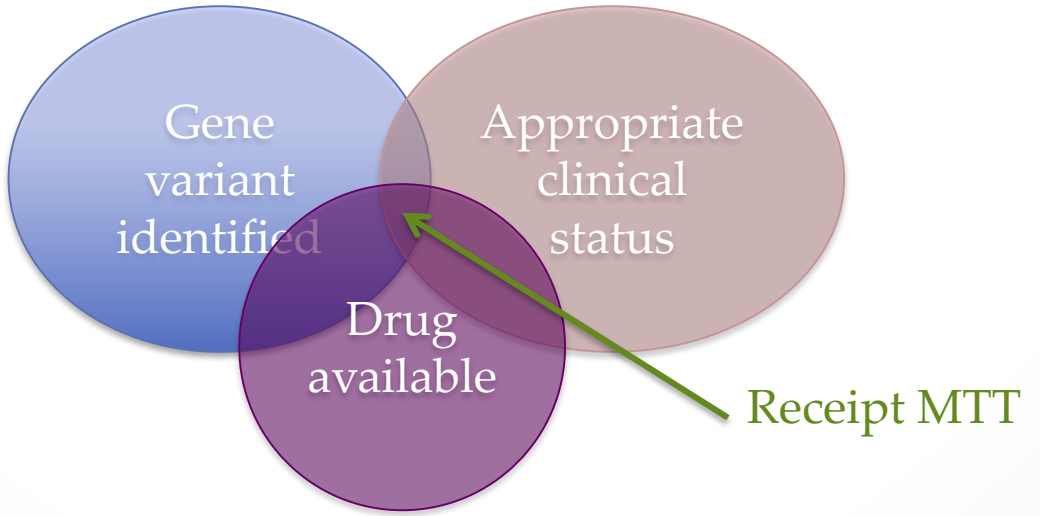
- Evaluable (recurrent) n=617
- No iCat n=401
- iCat, Unmatched therapy n=148
- iCat, Matched therapy n=68
- Extraordinary responder

- **Describe OS, PFS in each group**
- Identify factors associated with outcome
- Bank

HOWEVER

The iCat1 Study, Results

- 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



Targeted Agent and Profiling Utilization Registry (TAPUR) Study

February 21, 2017

Slides credit: **Pam Mangat, MS, ASCO**

TAPUR American Society of Clinical Oncology | Targeted Agent and Profiling Utilization Registry Study | ASCO

Problems

- Patient with advanced cancer; no standard treatment options
- Genomic profile test performed
- Potentially actionable aberration detected
- FDA-approved drug available for aberration

How to get the drug that might be beneficial?
How to learn from the treatment?

Overall Goals of TAPUR

- To learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target, or to predict sensitivity to a drug
- To educate oncologists about implementation of precision medicine in clinical practice

Who Benefits?

- **Patients** receive targeted agent matched to molecular profile – broader eligibility criteria
- **Physicians** receive interpretation of molecular test results, guidance in treatment recommendations, access to drugs, clinical data on off-label use
- **Industry** receives data on drug use and outcomes to inform R&D plans and life cycle management
- **Oncology Community** receives data on extent and outcomes of off label drug and test use and real world safety data

TAPUR Targeted Agent and Profiling Utilization Registry Study
American Society of Clinical Oncology | ASCO

Eligibility

- Patients with advanced solid tumors, multiple myeloma or B cell non-Hodgkin lymphoma for which standard treatment options are no longer available and acceptable performance status and organ function

TAPUR Study Primary Objective

- To describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs prescribed for treatment of patients whose tumors have a genomic variant known to be a drug target, or to predict sensitivity to a drug.

Study Endpoints and Analysis

- Primary endpoint: ORR or SD at 16 weeks per relevant response criteria
- Other endpoints: PFS, OS, time on treatment, grade 3-5 AEs per CTCAE, SAEs
- Each tumor type-variant-drug is a “group”
- **Enroll 10 patients/group. If 1 or fewer responses, stop**
- **If at least 2 responses, enroll additional 18**
- 7 or more responses/28, further study
- 85% power and an alpha error rate of 10%

How does TAPUR work?

A patient's treating physician has results of a genomic profile of the patient's tumor and determines that a study drug may benefit the patient.

The patient decides to participate in TAPUR and gives informed consent.

The Molecular Tumor Board —a group of experts convened by ASCO— is available for consult regarding the proposed treatment or to provide alternate treatment options.

A participating pharmaceutical company provides the study drug at no cost to the patient.

The patient is followed for standard toxicity and efficacy outcomes and data are collected for analysis.

The study's Data and Safety Monitoring Board reviews results and determines whether a treatment is promising for a particular cancer and genomic variant.

ASCO publishes study findings in peer reviewed journals to inform clinical practice and future research.

syapse

CardinalHealth™

TAPUR

American Society of Clinical Oncology

Targeted Agent and Profiling Utilization Registry Study

ASCO®

Key Milestones

- Seven companies currently committed to participate
  - **Providing free drug** (ongoing access for responders)
  - **Per-case payment**
  - **Infrastructure support**
- FDA reviewed and determined TAPUR Study IND-exempt *(08/31/15)*
- Chesapeake Institutional Review Board approval *(02/09/16)*
- **TAPUR Study Launch *(03/14/16)***
  - 317 participants registered as of 02/20/17
  - 175 patients on treatment as of 02/20/17

TAPUR Study Eligibility Criteria

- **Overall goal for TAPUR participants to be more representative of the overall patient population**
- Two sets of eligibility criteria:
  - **General study eligibility criteria**
    - Apply at outset
  - **Drug-specific eligibility criteria**
    - Specific to each drug & take precedence
    - Provided by the pharmaceutical companies

TAPUR Study: Other Considerations

- **Organ function**
- **No exclusion for prior malignancy**
- **Performance Status 0-2**
- **Pediatric Population:**
  - Current TAPUR study eligibility criteria requires that the patient is ≥ 18 years old
  - *Lowering minimum age to 12 years*
    - *Any drug with dosing information available*

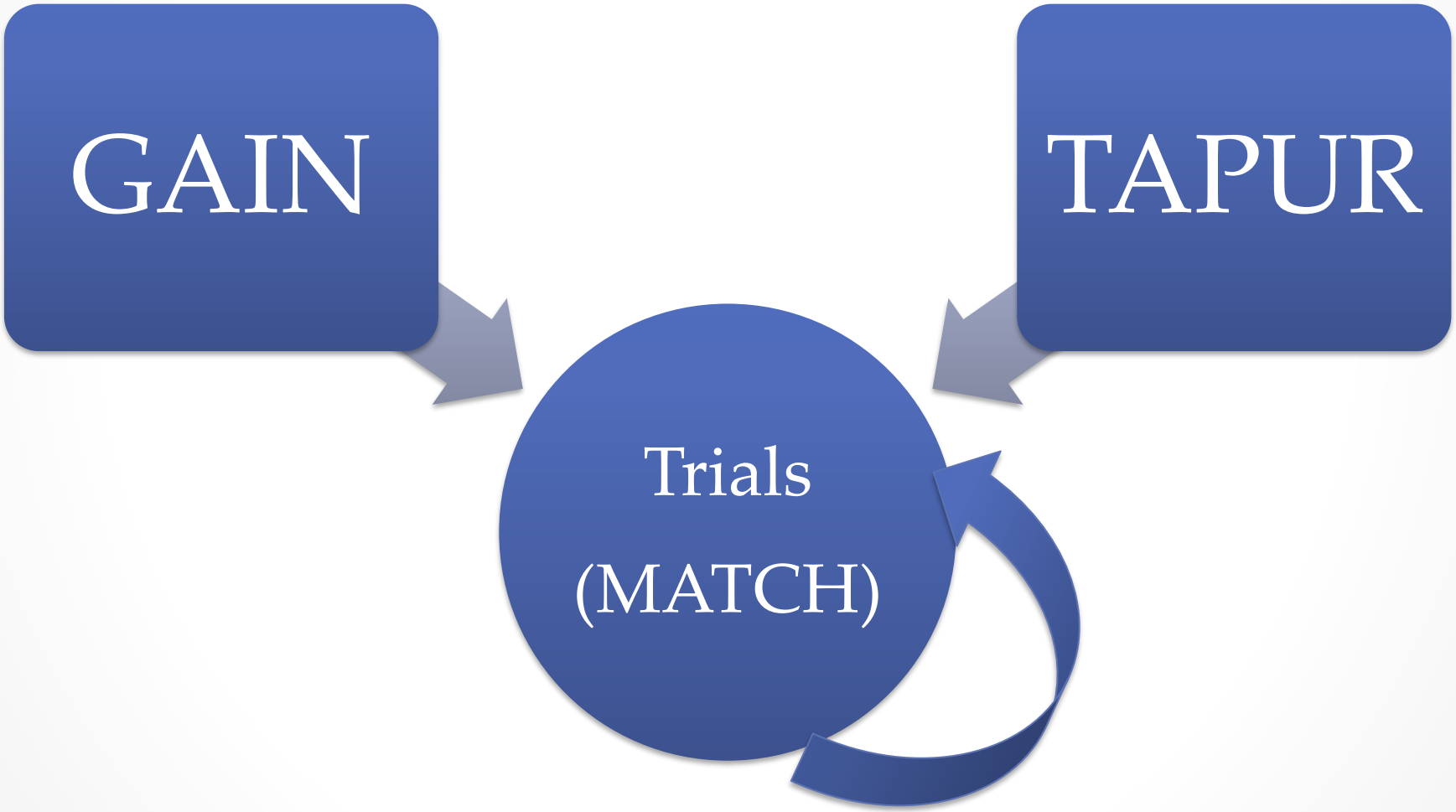
Clinical Sites:

TAPUR Targeted Agent and Profiling Utilization Registry Study
American Society of Clinical Oncology
ASCO

PCM Trials Pediatric Oncology

Trial Design	Summary	Pediatric Oncology Examples (USA)	Pros	Cons
Studies of Molecular Profiling Clinical Utility	-Frequency of alterations -Assess feasibility sequencing	-iCat1 -BASIC3 -MiOncoSeq	Foundation for subsequent studies	Does not assess impact on outcome
Longitudinal Cohort	-Collaborative -Prospective collection genomic, treatment and outcome data	-PROFILE -GAIN consortium/ iCat2 Study -G4K (Genomes for Kids)	-Provide access to profiling -Supplement pediatric sequencing databanks (recurrent samples) -Facilitate basket trial design -Assess impact MTT on outcome	Doesn't address access to MTT
Basket Trial	-Histology independent -Treatment arms defined by genotype -Typically phase II	Pediatric MATCH	Identifies histology-specific signals of activity → phase II/III	Significantly different activity by histology → risk missed signal of activity
Master-Protocol	-Single disease -Multiple treatment arms by genotype -Typically phase II	NEPENTHE	Increased likelihood patient receiving tailored therapy	Requires understanding genomic subtypes of disease

Adapted from Martine J. Piccart-Gebhart, D. Zardavas "Clinical Trials of Precision Medicine through Molecular Profiling", ASCO Ed Session, 2015


GAIN
TAPUR
Trials
(MATCH)

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Steven Dubois, MD, MS
Jon Marron, MD
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Former members: Carlos Rodriguez-Galindo, MD, Charlie Roberts, MD, PhD

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Eli VanAllen, MD, PhD
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TAPUR:
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Richard Schilsky, ASCO
Pam Mangat, ASCO

Brigham and Women's Hospital
Neal Lindeman, MD

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

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

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Master Protocols for Early Signal-Seeking: iMATRIX

Raphaël F. Rousseau, M.D., Ph.D.
Global Head, Pediatric Oncology (iPODD)
Genentech, a member of the Roche Group

Disclaimer

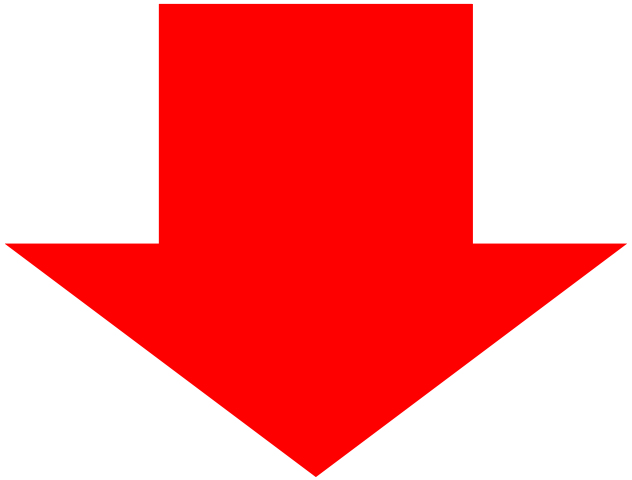
Some comments & views expressed in this presentation are endorsed by Roche, Genentech and affiliated parties but may not be by other pharmaceutical industry partners

Presentation Outline

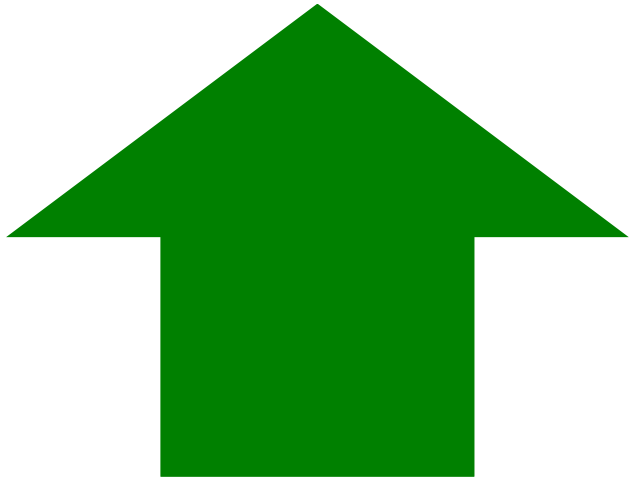
- Challenges in Pediatric Oncology Drug Development
- Mechanism-of-Action Based Drug Development in Pediatric Oncology
- The iMATRIX Trial Concept and Its Master Protocol
- Opportunities & Challenges

Children with cancer also need access to new and more efficacious therapeutic options

Challenges



- High **attrition rate in adult drug development** contributes to lack of early access to investigational drugs.
- Pediatric oncology drug development is largely based on adult drug development programs. The majority of **pediatric tumors are rare and distinct entities** from those seen in adults
- Multiple programs compete for **a limited patient pool** and for academic collaborators
- **Reactive obligatory** vs proactive approach based on patients' needs
- Limited market incentives



Opportunities

- Leverage **pediatric expertise**
- **Match and prioritize** molecules for pediatric cancers based on **target or mechanism of action** of the drug
- Identify **new targets** in pediatric cancer
- Increase efficiencies with **innovative trial designs**
- Greater multi-stakeholder **collaboration** and sharing of information

Mechanism of action or target-based drug development in pediatric oncology

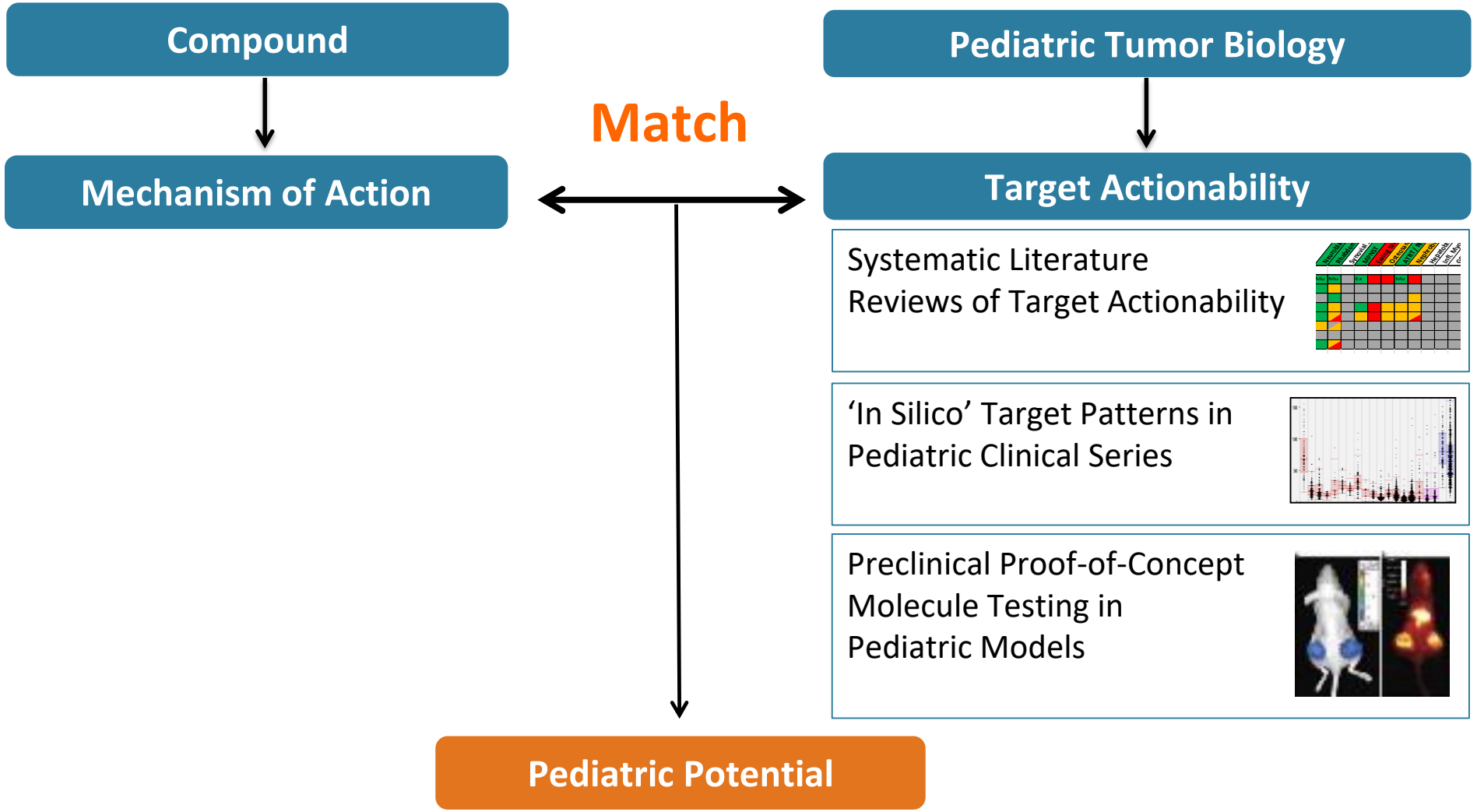
- Target-based drug development has largely benefited adult oncology patients. Drug development in children need to **keep pace with advances in science**
- **Adjust the focus of pediatric oncology drug development to the many pediatric diseases for which there are no adult counterparts**, rather than exclusively on the tumor types being investigated in adults
- Limit initial plan proposals to phase 1/2 clinical research, and defer discussion of pivotal trials until early-phase pediatric data is available
- Greater cooperation and collaboration between stake-holders to **prioritize new molecules based on mechanism of action or target of the drug**
- **Standardize** targeted approaches to ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability
- Ultimately, **preserve and match children with rare tumors to the most promising therapies**

:

G. Vassal et al., *New drugs for children and adolescents with cancer: the need for novel development pathways,* The Lancet Oncology 14 (3), e117-124 (March 2013) | doi:10.1016/S1470-2045(13)70013-5.

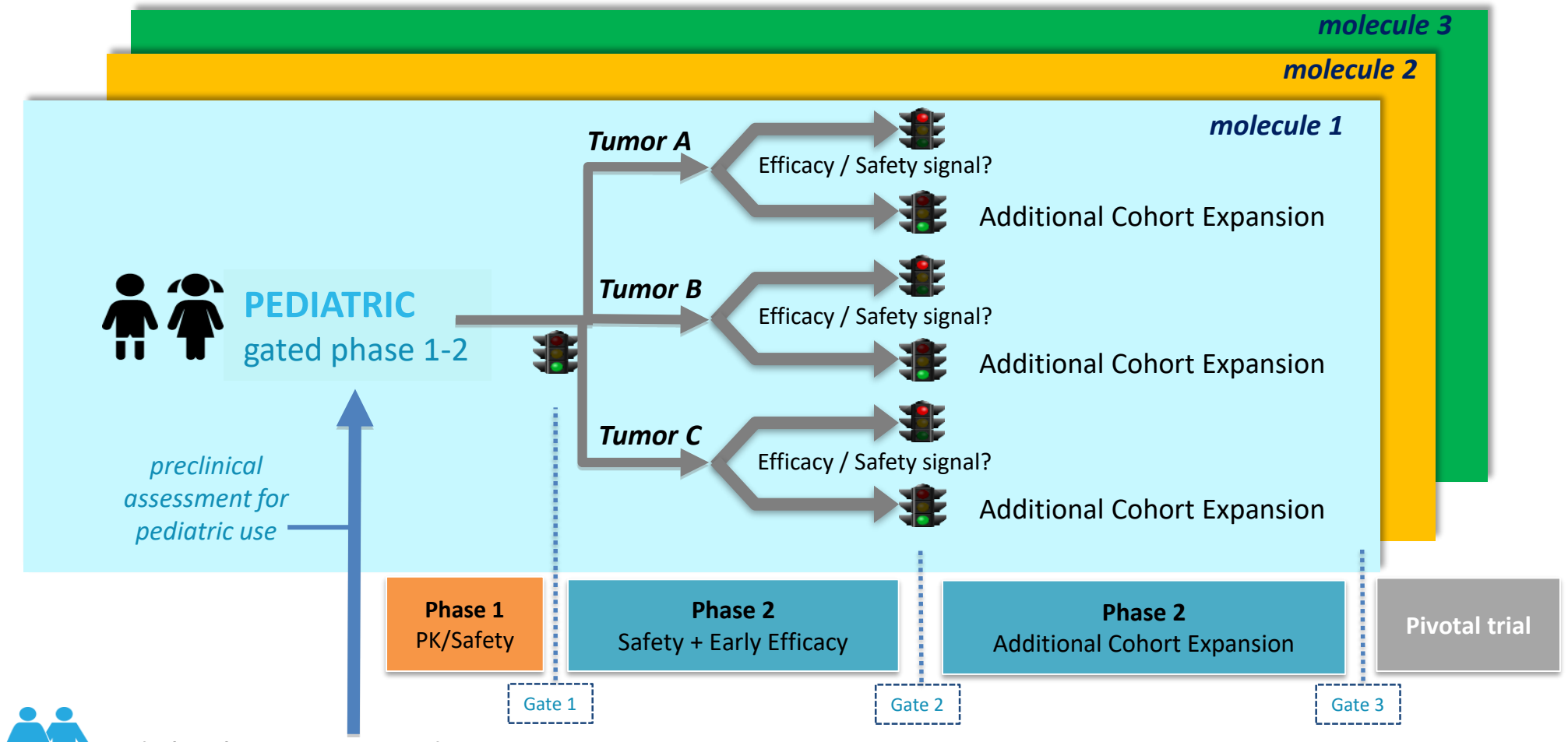
Robin Norris & Peter Adamson, *Challenges and opportunities in childhood cancer drug development,* Nature Reviews Cancer 12, 776-782 (November 2012) | doi:10.1038/nrc3370.

Preclinical pediatric prioritization by matching molecule MOA with pediatric tumor biology



The iMATRIX trial concept: preserve and match children with rare tumors to the most promising therapies

An innovative **pediatric** oncology clinical trial platform to **investigate several drugs in multiple tumor types**



The ultimate goal is to allow for molecule & disease prioritization within the regulatory framework

Disease	Molecule 1	2	3	4
A	√	√	x	√
B	x	√	x	x
C	N/A	x	x	x
D	x	x	x	√
E	√	x	N/A	x

Objective: one sponsored label-enabling study per molecule in the most relevant disease supported by clinical evidence and feasibility assessment (extensive consultation with Academic Community and HAs). Further label updates using additional data generated from supported research.

Advance to pivotal trial Available for supported research No further development

iMATRIX trial status update

rapid accrual across a number of pediatric tumor types

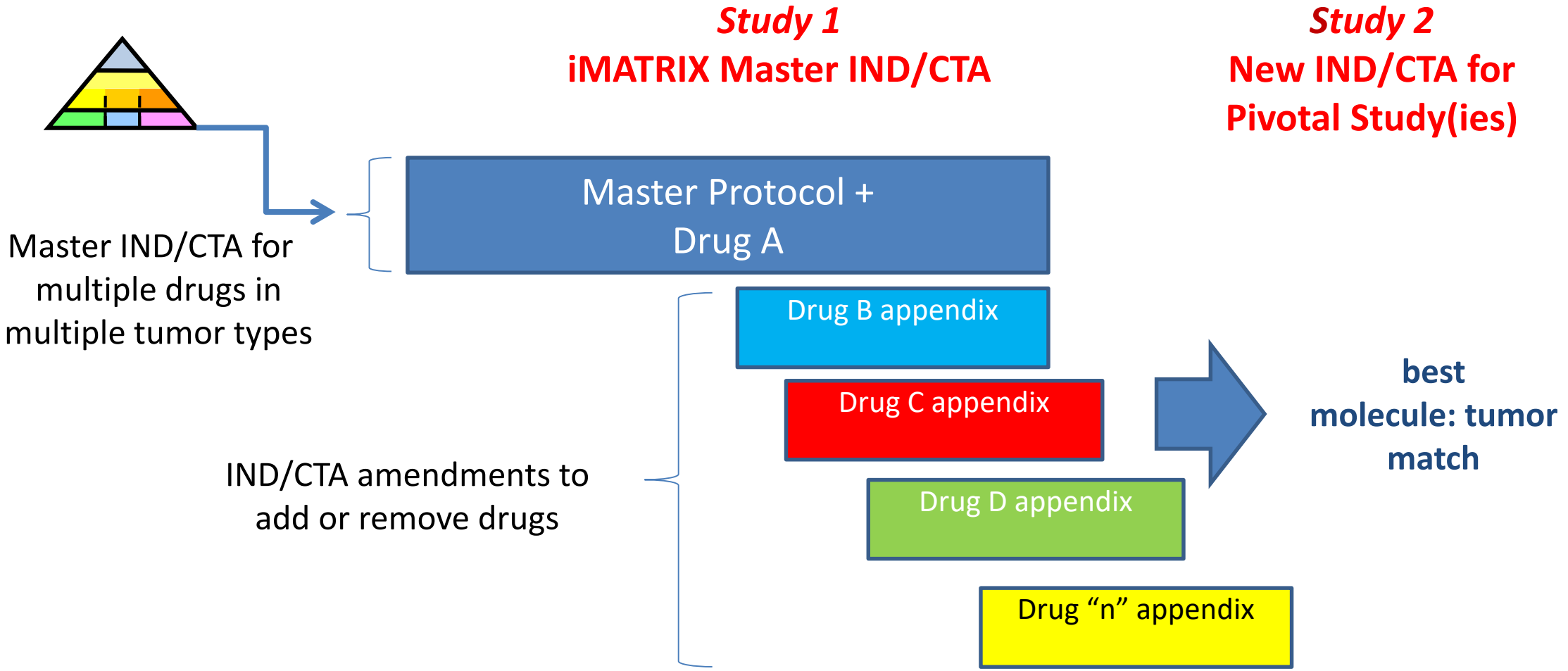
- **Single molecule clinical studies** for atezolizumab and cobimetinib in several pediatric cancer tumor types have been initiated

- **Master Trial proposal** has been evaluated by the FDA and EMA
  - Joint FDA and EMA *Parallel Scientific Advice* and EMA Qualification procedure meeting on 31st August, 2016
  - Endorsement from the agencies (subject to review) to continue with the iMATRIX Trial efforts

- **Outreach Efforts for future Multi-Sponsor Master Trial** collaborations to enable industry to fulfill its mission of addressing unmet need for children with cancer and to provide rare patients with the most promising therapies

iMATRIX Master Protocol

An open-label, multi-center, Phase I/II Study, to evaluate the PK, safety, tolerability and efficacy of drugs in the treatment of relapsed or refractory pediatric tumors with known or expected pathway involvement



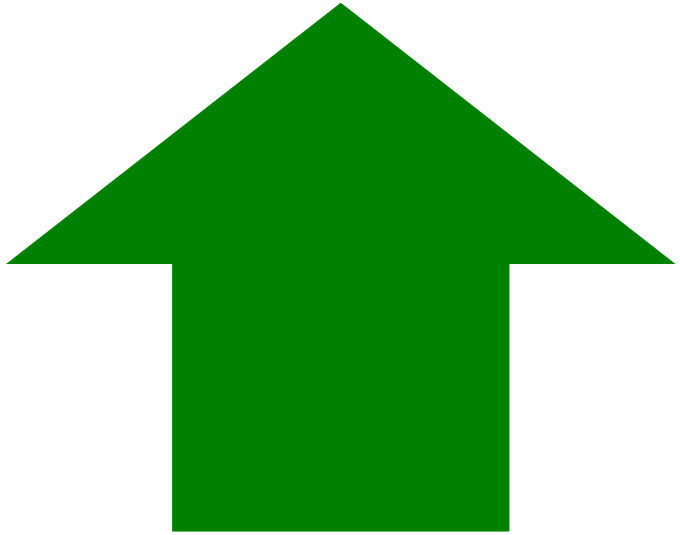
The iMATRIX trial and its master protocol

an ongoing experiment with obvious opportunities… and some remaining challenges

Challenges

- New concept for national HAs and IRBs, lack of centralized review process may impact **review timelines**
- Current **EU regulatory framework** is not able to accommodate a Master protocol under a single CTA
- **Combinations** may require separate IND/CTA
- Operational benefits may only be seen when **a critical number of molecules** are available on the iMATRIX
- Ultimately, **actionable molecular targets may be rarer in children** compared to adults, limiting the impact of predictive biomarkers

Opportunities



- Target true **unmet needs** in childhood cancer
- **Evidence-based** identification of optimal tumor type(s) for each molecule
- **Consistency** of data collection, analysis, and interpretation
- **Operational efficiency** of trial conduct: same sites, accelerated implementation, optimization of costs
- Ultimately, provide a **standardized framework** for **patient-centric** development that **preserves** study participants and **matches** children with rare cancer to the most promising therapies **across industry's portfolio**

Paradigm shifts are urgently needed in pediatric drug development

Isolated development		Harmonized across industry
Reactive, late		Proactive, early
“Stick and carrot”		Pediatric-centric
Molecule-based in disease context		Mechanistic, biomarker-bas disease and molecule contex

Doing Now What Patients Need Next

ACCELERATING PEDIATRIC DRUG DEVELOPMENT

A FRIENDS OF CANCER RESEARCH FORUM

SUPPORTED BY ST. BALDRICK'S FOUNDATION

ESMART and the European strategy

Gilles Vassal

Friends of Cancer Research

February 21st , 2017

An European academic consortium

created in 2003

- ITCC runs a **comprehensive clinical and biological early evaluation program of anticancer drugs** for children and adolescents.
- 52 investigating centers in 13 countries
  - Of which 20 centers qualified for FIC and early phase trials
- 4,500 new patients,yearly.
- 22 basic and translational research labs

The Innovative Therapies & PCM Programme

1

A tumor molecular and Immunology portrait at relapse

Molecular Matching Trials

WES, RNAseq, immuno

MATCH

2

Enriched Phase I and II Trials w single agents and combinations

Targeted and immune therapies

All patients are proposed access to new drugs

Innovative Therapies for Children with Cancer

ITCC European consortium

SIOPE SIOP Europe

MERGE

3

New Knowledge

Clinico-Biological Data

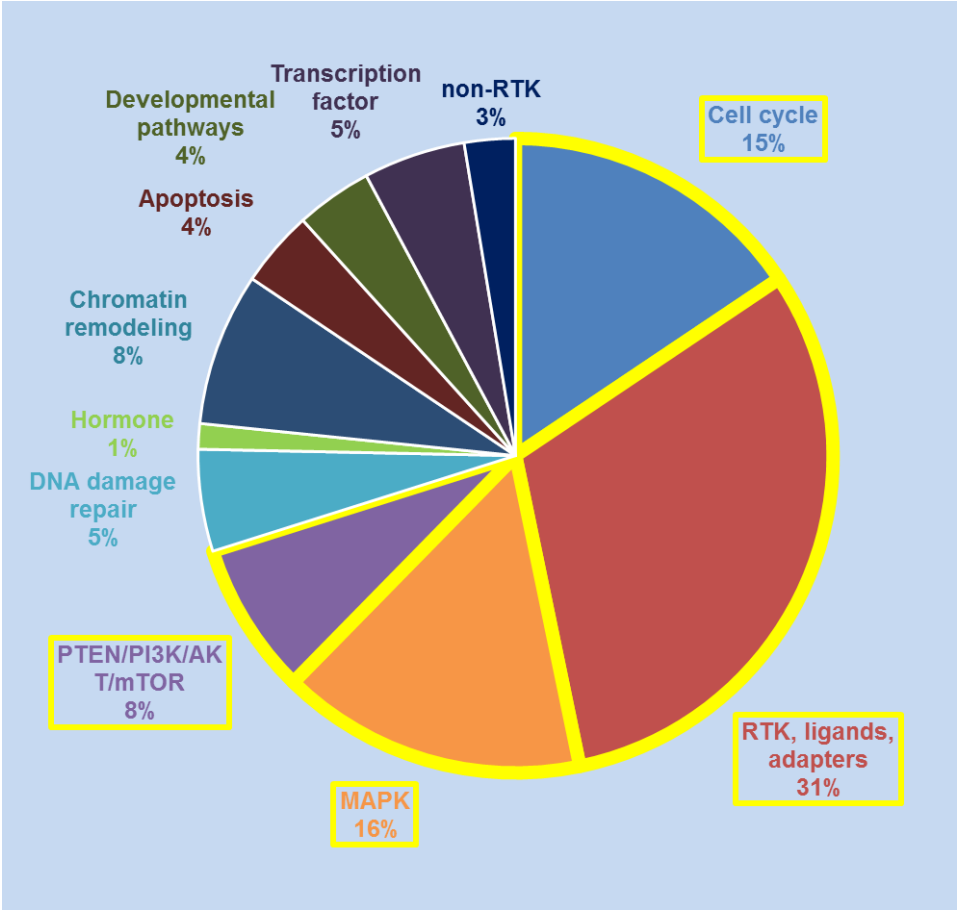
Specific Pediatric Drug Development

4

http://www.siope.eu/SIOPE_StrategicPlan2015/

MOlecular Screening for CAncer Treatment Optimization (MOSCATO-01)* NCT01566019

PI : Jean-Charles Soria, Birgit Geoerger



<u>Pediatric Cohort</u>:

73 patients with solid tumors

Median age 11y (0.8-24.3y)

Biopsy at relapse

NGS/CGHa – WES/RNAseq

Within 21 days

58%of patients had

at least 1 actionable target

of which

only 33% received

a matched treatment

Main reason :

drug not available

* 1036 patients in adult cohort

The ITCC Precision Cancer Medicine program

1. Generate molecular profiling for each patient

Molecular Matching Trials at relapse

WES, RNA seq, methylome immunophenotype

- **INFORM** (Germany) — dkfz. German Cancer Consortium
- **MAPPYACTS** (France, Spain, Denmark, Italy) — Institut National du Cancer; Fondation ARC pour la recherche sur le cancer; Gustave Roussy Cancer Campus Grand Paris
- **iTHER** (Netherland)
- **SM- PAED** (UK)

Platform, pipelines and data harmonization

Goal
1000 exomes
at relapse
By 2018

Innovative Therapies for Children with Cancer
European consortium

AcSé
INSTITUT NATIONAL DU CANCER

e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

IMAGINE FOR Margo
Children without CANCER

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Patient with tumor molecular profile at relapse (WES, RNAseq, Immuno)

MATCH

M A T CH

AcSé INSTITUT NATIONAL DU CANCER **eSMART** GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children (ESMART)

IST - phase I/II
single agent and combo

Goal >10 drugs from >3 Companies

A trial platform to be amended

launched august 2016

ITCC portfolio
Ongoing phase I II trials
single agent and combination

Trial	IMP
ITCC-022	Nilotinib
ITCC-032	Bevacizumab
ITCC-041	Ceritinib
ITCC-038	Abraxane
ITCC-043	Azacytidine
ITCC-047	Regorafenib
ITCC-049	Afatinib
ITCC-050	Lenvatinib
ITCC-053	Crizotinib
ITCC-054	Everolimus Dasatainib Erlotinib
ITCC-055	Comibetinib
ITCC-058	Atezolizumab
ITCC-059	Inotuzumab
ITCC-061	EPZ 6438
ITCC-065	Ibrutinib

Mainly first in child

AcSé INSTITUT NATIONAL DU CANCER

e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

Main Inclusion Criteria:

- Patients < 18 years with a relapsed or refractory malignancy (solid tumors, leukemias)
- Evaluable disease
- Lansky/Karnofsky ≥70%
- No toxicity ≥ G2
- Deep tumor molecular analysis available

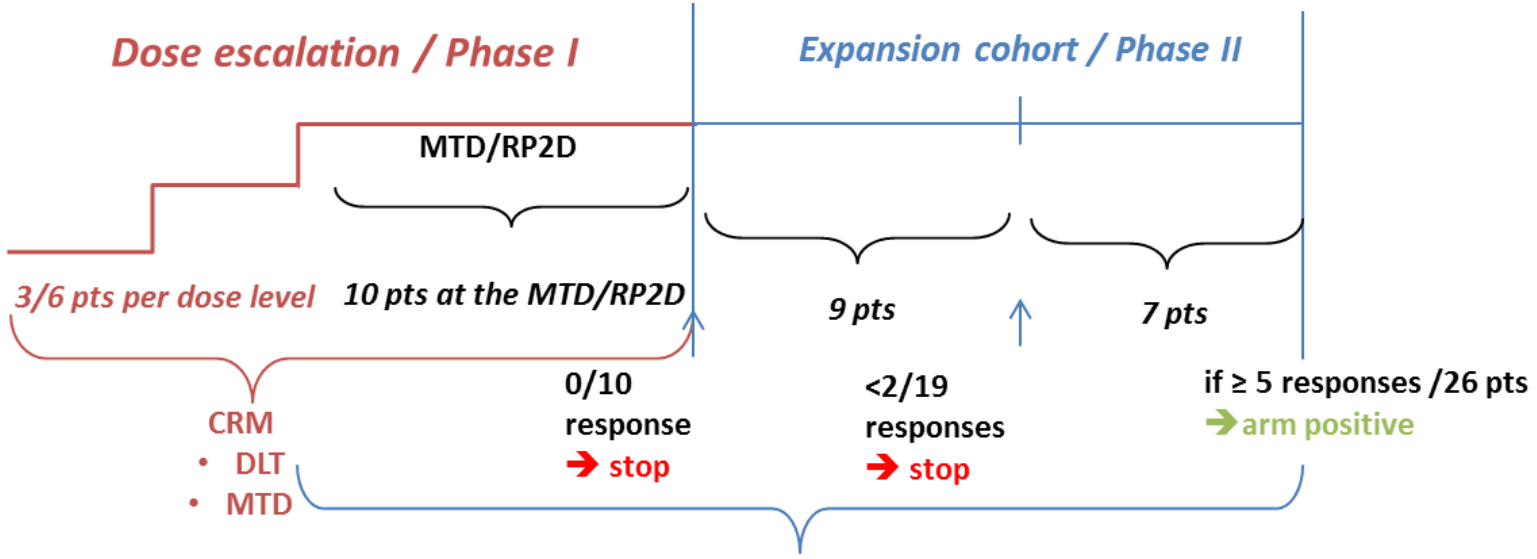
WAVE 1 of Treatments

ARM	Pathway	Target	Treatment	Enrichment	Pharma
Arm A	Cell Cycle	CDK4/6	Ribociclib + TOTEM*	50%	NOVARTIS
Arm B			Ribociclib + Everolimus	50%	
Arm C	DNA repair	WEE1	AZD1775 + Carboplatin	50%	AstraZeneca
Arm D		PARP	Olaparib + Irinotecan	50%	
Arm E	PI3K/AKT/mTOR	mTORC1/ TORC2	AZD2014	100%	
Arm F			AZD2014 + TOTEM*	50%	
Arm G	Immune checkpoints	PD1	Nivolumab + CyclophoP** +/-RT***	NA	Bristol-Myers Squibb

* topotecan + temozolomide; ** cyclophosphamide; ***radiotherapy

AcSé-ESMART statistical design

- Each arm is run independently (6-38 patients/arm)
- 2 parts : Phase I et Phase II
  - Evaluation of safety (DLT, MTD, RP2D) AND activity
  - 200 à 285 evaluable patients in 3 years
  - IDMC (1 pediatric oncologist, 1 medical oncologist, 1 pharmacovigilant, 1 stastitien)



As of February 2017:
31 patients enrolled in 6 months

The ITCC Precision Cancer Medicine program

1. Generate molecular profiling for each patient

Molecular Matching Trials at relapse

WES, RNA seq, methylome immunophenotype

- **INFORM** (Germany) — dkfz. German Cancer Consortium
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- **iTHER** (Netherland)
- **SM- PAED** (UK)

2. MATCH

3. Evaluate drugs and combinations

Phase 1 & 2 ITCC Trials
(sponsored by industry and ISTs)

MATRIX trial (Genentech/Roche)

eSMART trial
IST multi-agent from multi-company
AcSé; Gustave Roussy Cancer Campus Grand Paris; Imagine for Margo Children without CANCER; Institut National du Cancer; Fondation ARC pour la recherche sur le cancer

INFORM2 — dkfz. German Cancer Consortium

4. Create

European clinico – biological database

5. New knowledge

new druggable pathways
for specific pediatric drug development

1000 exomes in relapse

The ITCC strategy is aiming at :

- Speeding up access to innovation at relapse and frontline for children and adolescents with cancer
- Evaluating new agents and combinations in an enriched and well molecularly characterized population
- Signal searching for further developments (PIPs)
- Generating large data set and new knowledge

Thanks

- Patients and their Parents
- PIs, investigators and molecular profiling teams

- Pharmaceutical companies

ACCELERATING PEDIATRIC DRUG DEVELOPMENT

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Pediatric Cancer Drug Development: U.S. Regulatory Considerations

Gregory Reaman, M.D.
Associate Director, Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research
US FDA

FDA Advisory Committee Consensus Statement

- **Pediatric** oncology drug development should generally be **coordinated** with oncology drug development for **adults**, as part of an **overall drug development plan**

Priority Setting

- The evidence burden for initiating clinical studies in children with cancer should include **biological plausibility of the product having activity against a pediatric tumor** (which could be obtained from preclinical data), some expectation of potential benefit, a reasonable expectation of safety, and **sufficient information to choose an appropriate starting dose.**

MOA and RP2D

- Current practice would recommend that if a scientific rationale and a population of pediatric cancer patients with no available anti-cancer therapy exist, then **pediatric oncology clinical studies will be initiated, in most cases, immediately following adult Phase I studies.**

Timing

Challenges and Opportunities in Pediatric Oncology

Opportunities

- Scientific Discovery
  - Molecular drivers/validated targets
  - Available targeted therapies/immunotherapies
- Infrastructure
  - Clinical trial networks
  - Investigator/Patient/Family Engagement
  - Advocacy organizations
- Technology/Big Data
- **Evolving drug development paradigm**
- Emerging biomarkers
  - CTCs, ctDNA

Challenges

- Low Incidence
- Heterogeneity
  - Disease
  - Developmental
  - Genomic signature
- Formulation requirements
- Preclinical model/testing limitations
- Financial
- Combination drug development needed

- **Leveraging Adult Discovery**

Approaches to Pediatric Oncology Drug Development

- Use of current approaches continue but innovation, streamlining required
- New approaches needed: Evolving Drug Development Paradigm
  - increasing knowledge of genomic basis and heterogeneity of pediatric cancers
  - emergence of targeted therapies demonstrating large treatment effects in small subsets – “personalized medicine”
  - compressed drug development timelines in adults with innovative designs
  - limited patient, stakeholder resources

FDA Initiatives

- Increased role in promoting **collaborative** approach to **timely** pediatric drug development
- Optimizing regulatory authority
- **Proactive** identification of promising new treatments and engagement with industry/academia/advocacy groups to study these products earlier
- Harnessing regulatory science to meet drug development challenges

Leveraging Adult Discovery and Development: The Legislation

Pediatric Research Equity Act (PREA)

- Authorizes FDA to **require** pediatric assessments
- Triggered by NDA/BLA submission or a supplement with a new indication, active ingredient, dosage form, dose regimen or route of administration
- **Applies only to indication(s) included in the submission**
- **Drugs with Orphan Designation are exempted from PREA**
- FDA can grant full or partial waiver or deferral for pediatric studies if specific criteria are met
- **No relevance to Pediatric Cancer**

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf

Best Pharmaceuticals for Children Act (BPCA)

- Provides a financial incentive to companies to **voluntarily** conduct pediatric studies under a Pediatric **Written Request (WR)**
- A sponsor may request the FDA to issue a WR by submission of a Proposed Pediatric Study Request (PPSR) **or** FDA may issue WR without PPSR
- PPSR should contain rationale for studies, detailed study designs and plans for formulation development

PREA and BPCA Programs

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

BPCA: Written Request (WR)

- **Considerations when reviewing a PPSR for a potential WR**
  - What is the public health benefit?
  - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
  - Have all populations and conditions been addressed?
  - Are there other products already approved for the condition?
  - **WRs can be issued EARLY**
  - **WRs can be amended:** Emerging results may impact pediatric development plan

Selecting candidate therapies for WRs

- **Mechanism of action** suggests potential for activity
- Scientific rationale exists for the drug to be evaluated in pediatric cancers
- Activity in preclinical models of pediatric cancers
- Efficacy has been shown in a related adult cancer
- Evidence that the therapy will have similar efficacy and reduced toxicity compared to existing therapy
- Has potential to improve a clinical outcome for the pediatric patient

Shortening the timeline for development of drugs for pediatric cancers

- More efficient dose-finding studies (rolling six; continuous reassessment model) , modeling and allometric scaling
- Adult RP2D when no adult MTD
- Expanding FIP study sites- improved patient access
- Innovative trial designs/ development strategies
  - Embedding pediatric trials in adult studies
  - Adaptive design – with disease cohorts
  - Master protocols
  - Histology-agnostic development
- **Including pediatric cohort on select FIH trials**
- **Enrolling adolescents (children) on relevant disease-specific trials**

Characteristics of an Ideal Master Protocol

- One protocol
- Central governance structure
- Central IRB
- Central DMC
- Central Independent Review Committee
- Central repository of data and specimens

- Study multiple drugs
  - Targeting more than one marker/tumor
  - More than one drug for one marker/tumor
- Study multiple markers
  - Overlapping expression of markers
- Leverage common control group (s)
- Flexibility to add/remove agents (Adaptive)

Promoting expedited development of new drugs for pediatric cancers

- BPCA Pediatric Oncology Working Group holds quarterly meetings with representatives of the academic community to discuss **promising new agents for pediatric evaluation** through the WR mechanism
- OPT coordinates a monthly Pediatric Cluster meeting with international regulators for information exchange and discussion of specific product development, safety concerns and general scientific issues to assure alignment of pediatric development plans: PSPs, WRs and PIPs

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

- Forum where industry sponsors can obtain input from key academic and community opinion leaders regarding an ongoing or potential pediatric development program
  - gauge investigator interest in exploring pediatric development programs for products in various stages of adult development
  - select possible drug candidates for a Written Request
  - provide feedback to industry on trial design, pediatric regulations
  - Interactive discussion of a key topic in designing trials for pediatric patients with cancer

- Ideal to come early in drug development timeline even prior to NDA submissions

- Sponsors are encouraged to seek an invitation if there are questions regarding or interest in a pediatric development program

Expanding the Authority of PREA

- Indication-based trigger to MOA-based
- Requiring pediatric studies based on known molecular mechanism of action could significantly increase the number of pediatric studies under PREA
- Proposed PREA amendment to require that certain drugs (including biologic agents) developed for adult cancer indications be evaluated for a pediatric cancer indication when there is evidence that the drug affects specific molecular targets and/or molecular mechanisms that are common to both adult and pediatric tumors

Addressing the Challenge of New Drug Development when No Adult Indication Exists

- No current legislative fix
- Meaningful and early incentives to industry require evaluation
- Continued success of current special initiatives (Pediatric Rare Disease Priority Review Vouchers) – subject to dilution of benefit and competing priority review mechanisms/"early" development incentive lacking – reauthorization uncertainties
- Public/Private Partnerships – Role of NCI and other funding bodies
- **Orphan Drug Act**

Orphan Drug Act 1983

- Promote development of products for rare diseases (<200,000 persons in US)
- Designation: Prevalence/Promising clinical efficacy
- Financial incentives
  - PDUFA exemption ($2.4 M FY'16)
  - 50% tax credit for clinical study costs
  - Orphan grant program eligibility $14M/yr
  - 7 years marketing exclusivity
- 1/3 of all NMEs and 2/3 of all BLAs have designation
- 37% of Oncology products 2015- 2017.
- Same approval standards for safety and effectiveness, but regulatory flexibility and "scientific judgment"
- Substantial clinical trial design diversity

Future Direction

- **Maximize Regulatory Authority**
  - Aid in Legislative amendments when warranted
  - Expand opportunities for evaluating Precision Medicine approaches
  - Paradigm shifts in study design,conduct, initiation, and F/U
  - Optimize Orphan Drug Product Act opportunities
  - Rational science-based strategy for prioritizing which/when new products to test in what diseases; successful integration with “standard” therapy
  - Expanded collaboration. Patients/families- Investigators – Industry – Regulatory Agencies

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Real World Experience from the Trenches

Raymond Rodriguez-Torres

Live Like Bella Childhood Cancer Foundation

15 Minute Break

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A FRIENDS OF CANCER RESEARCH FORUM

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Session 2: Considerations for Pediatric Master Protocols

Moderator: Peter Adamson, Children's Hospital of Philadelphia

Trial Design and Molecular Prioritization Criteria in Multi-Sponsor Trials

Discussants: Bouchra Benettaib (Celgene), Kenan Onel (Northwell Health), Eric Rubin (Merck)

Role of a Multi-Stakeholder Decision-Making Body and Governance

Discussants: Shakuntala Malik (NCI), Pam Mangat (ASCO)

Logistical and Operational Considerations/Challenges

Discussants: Kenneth Cohen (Johns Hopkins), Giles Robinson (St. Jude)

Fulfilling Regional Pediatric Drug Regulations and Addressing Globalization Challenges

Discussants: Martha Donoghue (FDA), Tahira Khan (Genentech), Gilles Vassal (Gustave Roussy)

Closing Remarks

Jeff Allen

President and CEO, Friends of Cancer Research

FRIENDS of CANCER RESEARCH

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