Childhood Cancer Data Initiative Symposium

NIH NATIONAL CANCER INSTITUTE

March 24, 2023

Welcome and Overview of CCDI Progress

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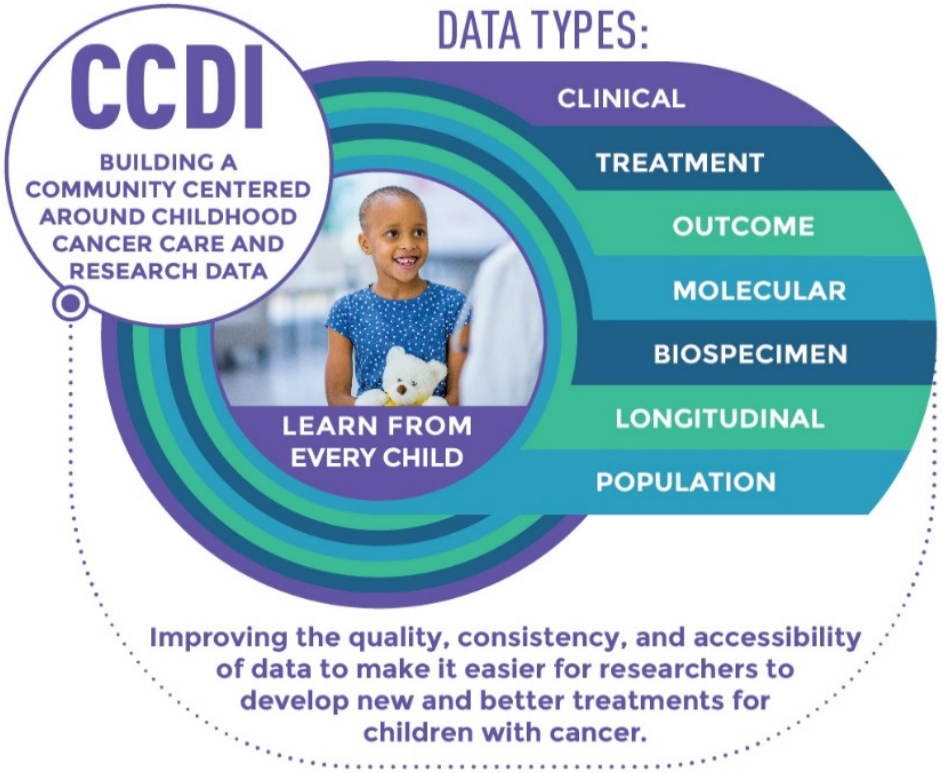
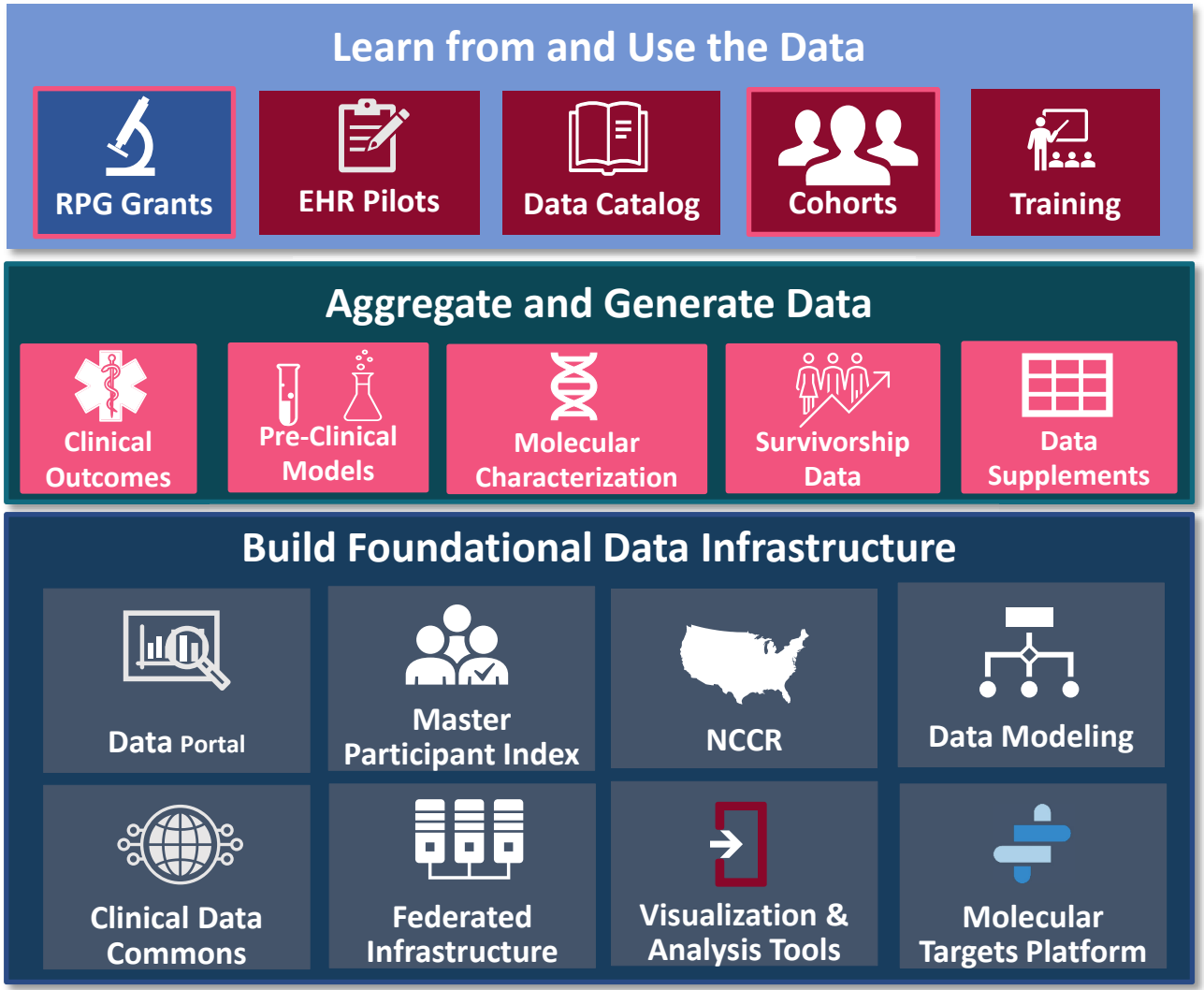
March 24, 2023

Foundational Goals for CCDI

- Gather data from every child, adolescent, and young adult diagnosed with a childhood cancer, regardless of where they receive their care
- Create a national strategy of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of childhood cancers
- Develop a platform and tools to bring together clinical care and research data that will improve preventive measures, treatment, quality of life, and survivorship for childhood cancers





Program Vision: The Three Pillars of CCDI

All funded projects fit within one of these three pillars.

CCDI is highly collaborative and informed by community needs, so we must be strategic about:

- Funding priorities
- Project planning
- Tracking, reporting, and collecting information

Reporting on the sum total of CCDI's accomplishments—not simply individual projects—is critical for advancing the initiative and keeping the community up-to-date.

Next Steps

Building Data Infrastructure

Expand the Data Ecosystem with more tools and a portal for access and broad use

Aggregate and Generate Data

Establish CCDI Rare Tumor Protocol that includes comprehensive clinical and molecular characterization, collected over time

Learn from and Use the Data

Develop consortia/network opportunities to oversee and explore a series of EHR extraction feasibility studies to support all types of research

Foundational Phase of CCDI (2020 – 2022) – Develop a framework of critical activities that will fill major areas of need in the pediatric research community and support future efforts

Discovery and Expansion phases of CCDI (2023 – 2026….2029) – Establish opportunities to expand foundational efforts to make them work well together and create feasibility studies in the wider community

CCDI High Priorities - Confirmed Across Working Groups

Priority	What CCDI Has Funded To Date (In progress)	Future CCDI Plans
Patient Identifiers: Required to connect patients across repositories for research, while preserving patients' privacy	• **CCDI Participant Index** • National Childhood Cancer Registry PPRL	• Incorporate patient-specific IDs for CCDI • Work with COG on alignment with COG identifiers
Data Models and Standards: Required to enable data federation & interoperability (API)	• Childhood Cancer Clinical Data Commons(C3DC) • Data harmonization effort across data sets	• Incorporate harmonized data model into CCDI supported projects • Work to define standards across ecosystem • **Expand EHR extraction**
Consent: Consent patients early, and to recontact or to opt-out at age of majority; power in the hands of the patients and families	• Updated for **Molecular Characterization Initiative (MCI)**	• **Develop computable consent**, with consistent language that allows for research use • Incorporate consents for clinical and research use into CCDI protocols
Baseline Data Collection: Collect more clinical data early, and identify high-value data elements for research (cohorts)	• Collection of additional data elements in CCDI data sets (MCI, others)	• **Working group to identify key data elements** • Collect these data as part of CCDI studies **(Rare Tumor Initiative and Protocol)** • **Identify additional cohorts**

CCDI Symposium Breakout Sessions: Stakeholder Input to Move Forward

- Molecular Characterization Initiative and the potential for additional cohort studies
- Patient and family perspectives on computable consent and the CCDI Participant Index
- Electronic Health Records data extraction: current status and continuing challenges
- CCDI Data Ecosystem resources for constructing external controls for pediatric cancer clinical trials
- Collaborations and transformative research opportunities using data available through the CCDI Data Ecosystem
- Observational studies and novel interventional approaches for rare pediatric cancers

CCDI: Harnessing the Power of Data to Learn From Every Child

Jaime M. Guidry Auvil, Ph.D.
Director, NCI Office of Data Sharing

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learn from every child

Critical Importance of Pediatric Cancer Data

Even our most effective treatments don't work for all patients

Improve understanding of why some cancers develop resistance or don't respond to treatment

Virtually no progress for some cancer types

Generate new ideas for interventions

Short- and long-term adverse effects of cancer and its treatment

Identify less toxic treatments and strategies for management

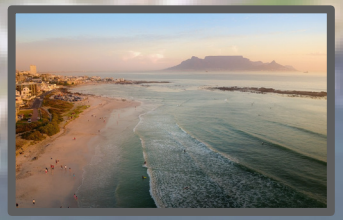
How do we “see” data?

What Are We Going to Study?







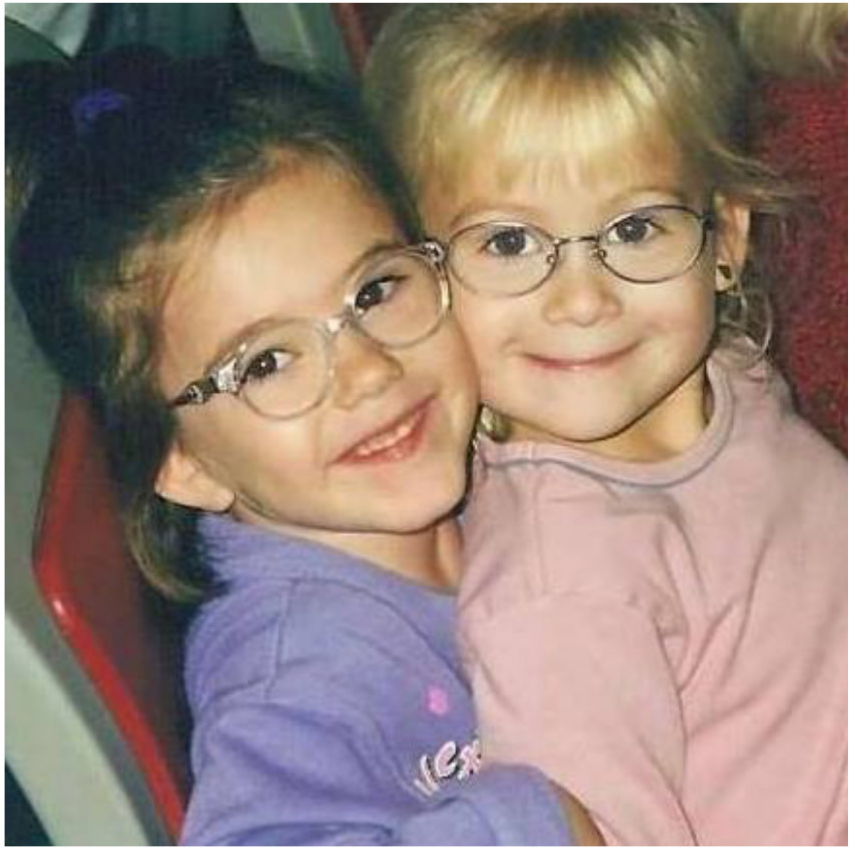



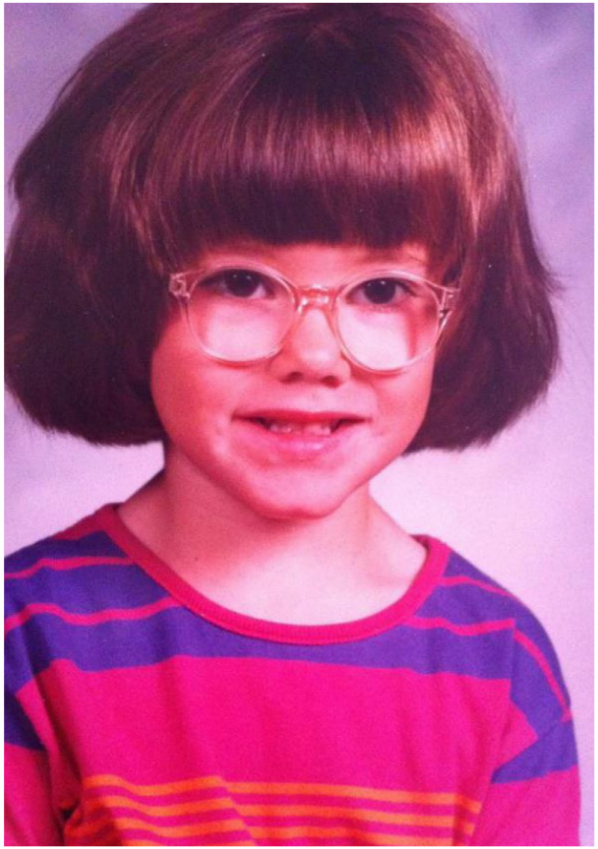

Hanna Jorgenson

Connect with me!

hanna.jorgenson

www.hannajorgenson.com



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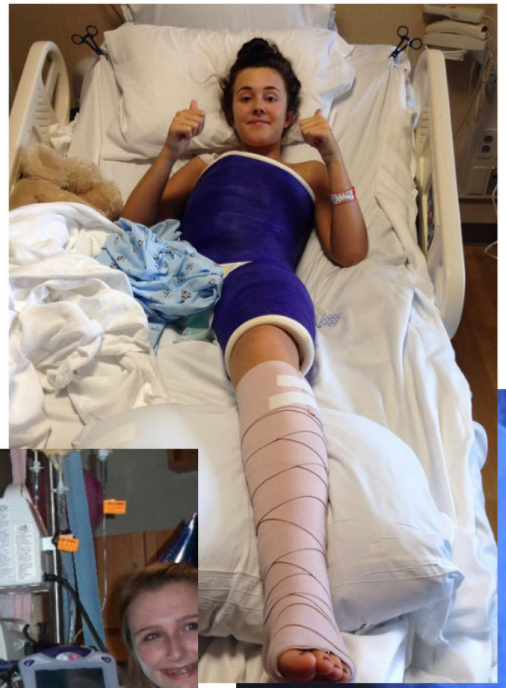


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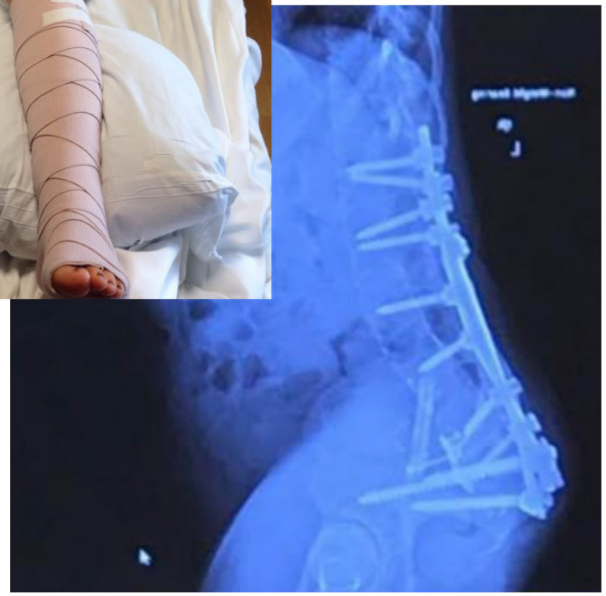

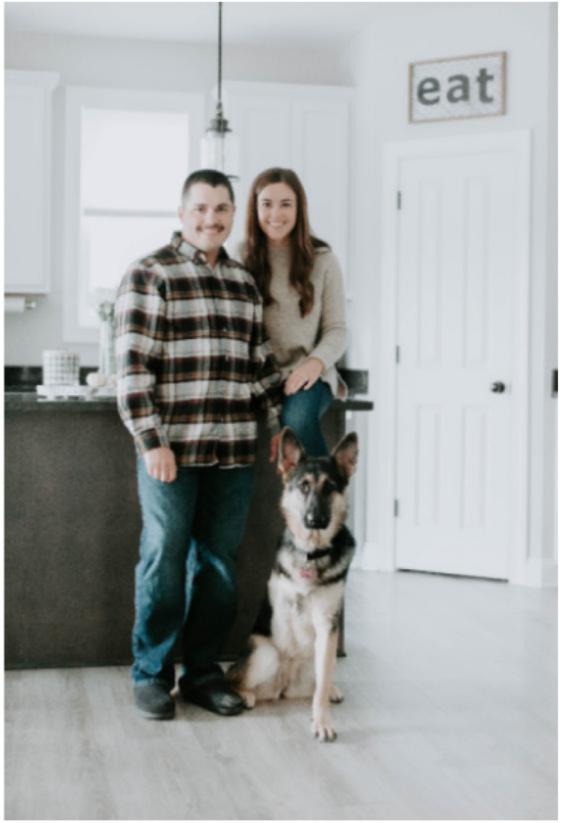
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The Molecular Characterization Initiative

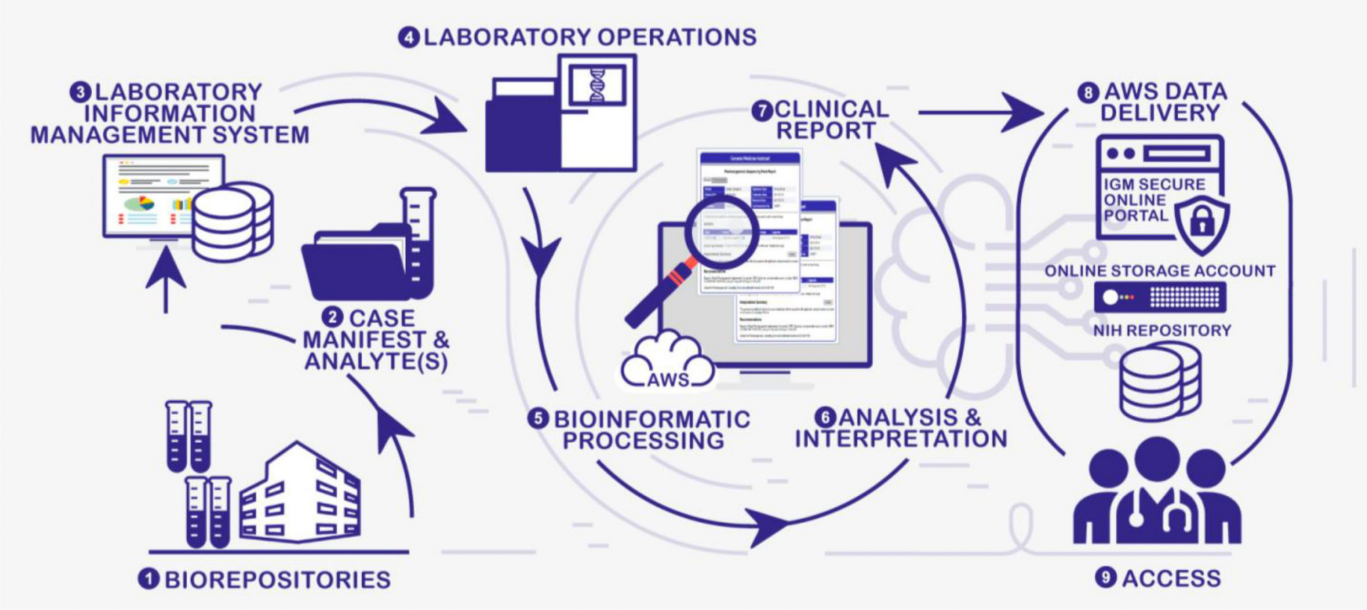
Fueling Precision Pediatric Cancer Diagnosis and Perpetuating Discovery

Elaine R. Mardis, PhD
Nationwide Children's Hospital

NIH NATIONAL CANCER INSTITUTE

15 March 2023

MCI: Pediatric Cancer Molecular Profiling



- NCI has contracted our clinical laboratory to perform molecular characterization of pediatric solid tissue malignancies for NCI-supported pediatric cancer cooperative groups, starting with the Children's Oncology Group (COG)
- Clinical testing (T/N exome, Archer FusionPlex, methylation arrays) and sign-out/return of results (**14d TAT**)
- **Data deposition** to CCDI public data repository within 90 days of test results
- To-date, we have studied patients with brain cancers, sarcomas and rare cancers

MCI Assays and Analytics

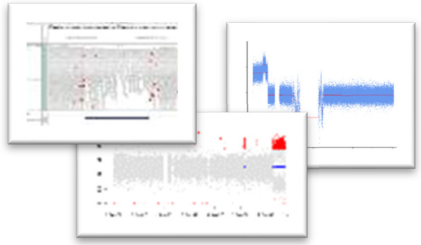
ASSAY | **ANALYTICS** | **CLINICAL REPORTS**** | **RESULT TYPE**

Tumor + Normal DNA

enhanced WES

250x

Churchill alignment to GRch38
IGMseq Pipeline Analysis in AWS

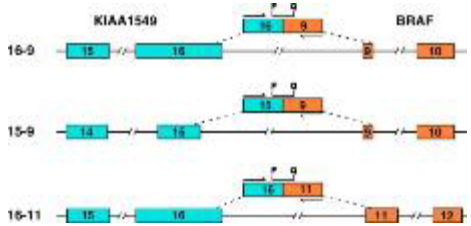


Germline + Somatic SNVs, INDELs, CNV & LOH

Tumor RNA

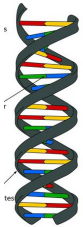
Archer Dx Pan-Solid FusionPlex

Archer Analysis v. 6.0 in AWS



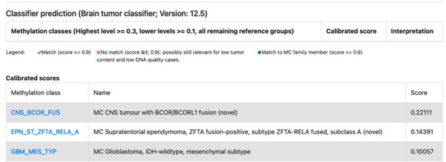
Fusion/ITD Detection

Tumor DNA



Illumina 850K EPIC methyl array

DKFZ Classifier v. 12.5

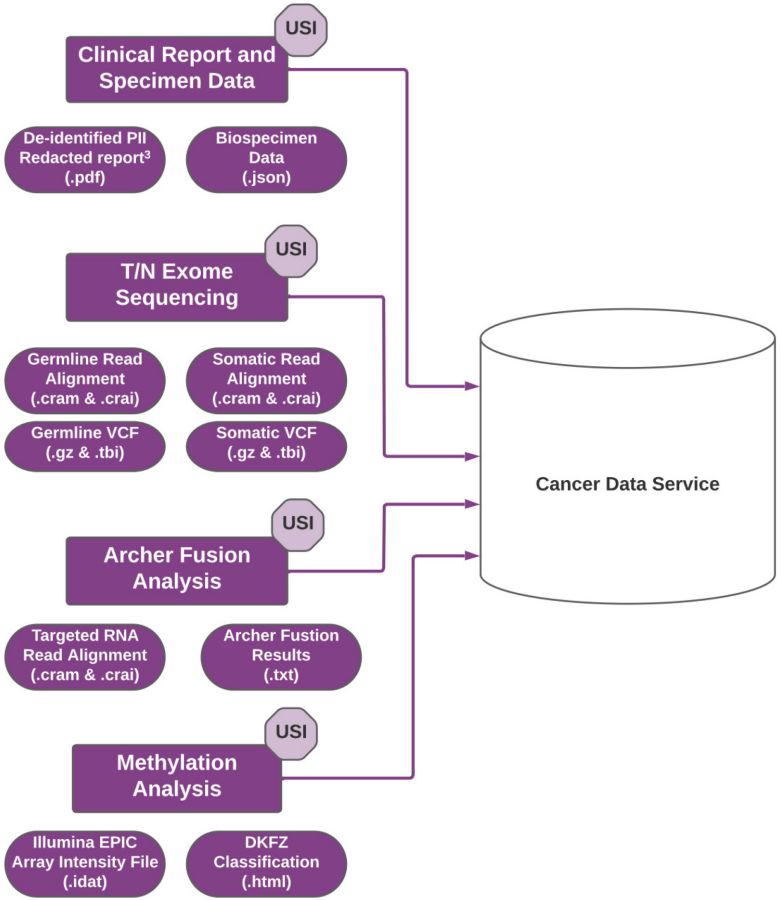


Disease classification

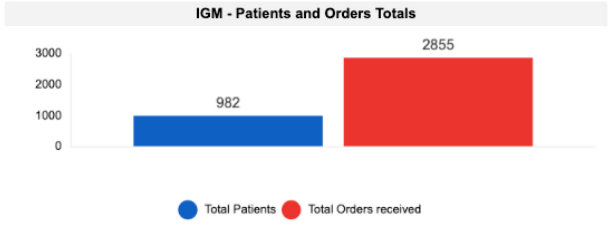
**All assays validated by CAP and NYSDOH

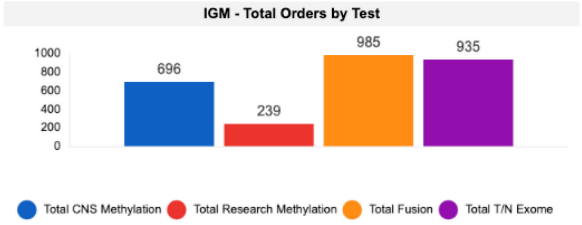
MCI Data Transfer to CCD

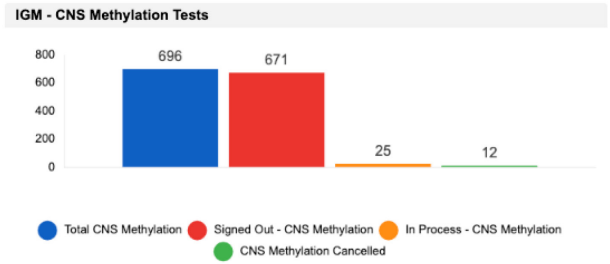
- Data transfer occurs once corresponding clinical report is signed out
- In addition to VCF from T/N exome, we transfer JSON format files of clinically relevant copy number altered and LOH regions for germline and somatic tissues
- Subsequent release of data into CCD by the NCI team occurs at an established cadence

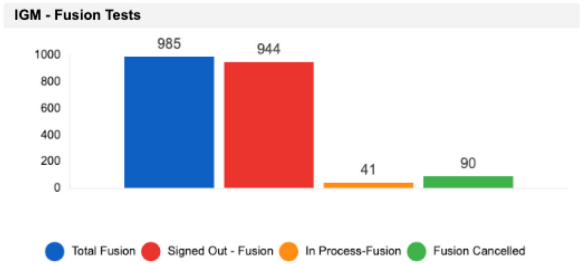


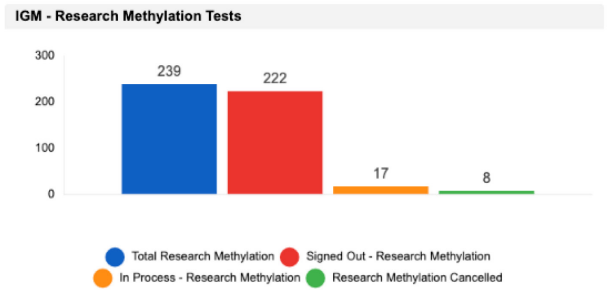
Keeping Track of MCI Clinical Testing

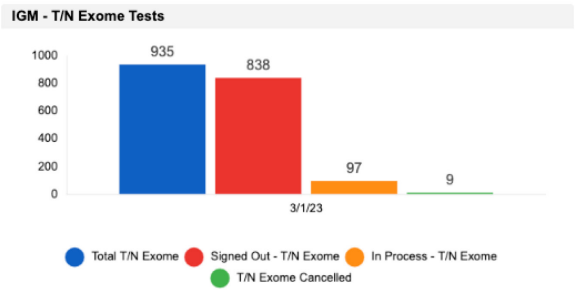








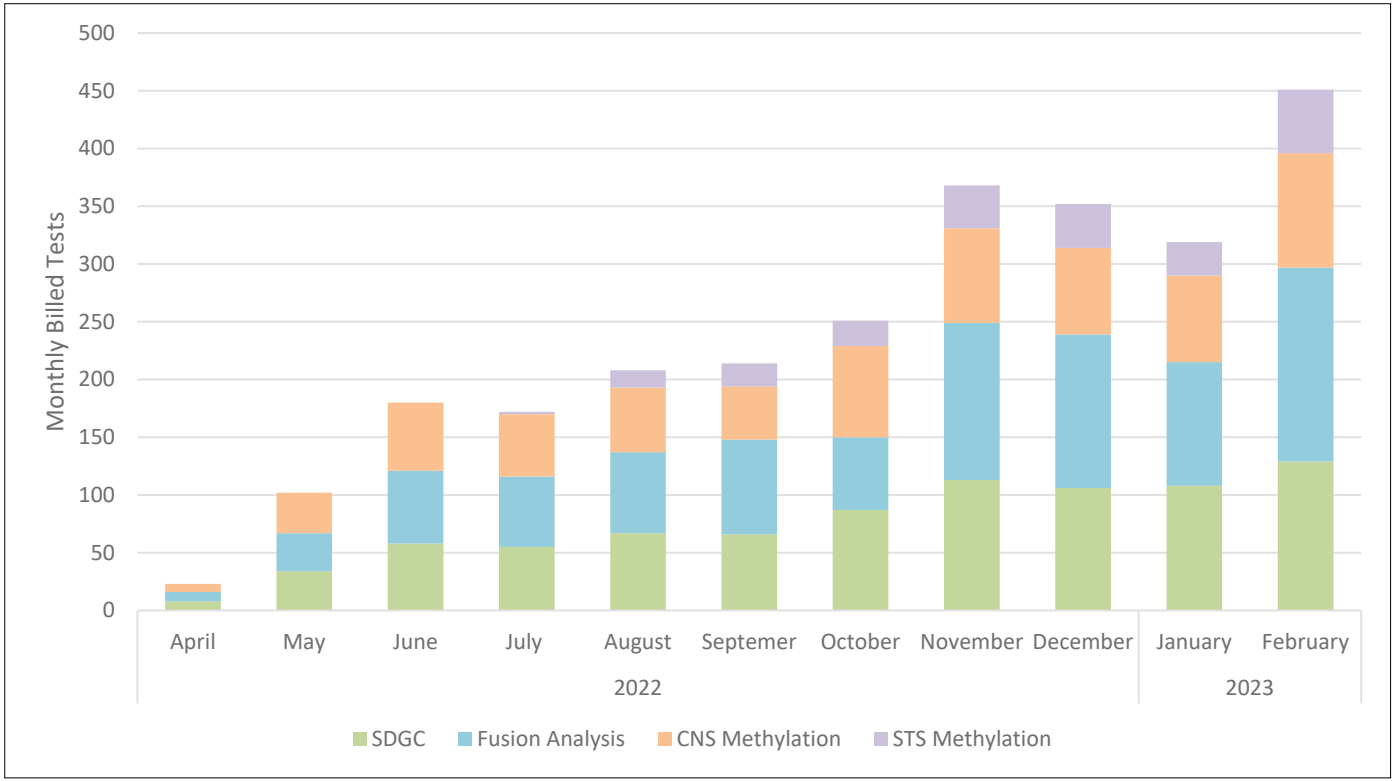




- To-date, **1072 cases** with tumor and normal samples received at BPC
- 92% of submitted samples yielded adequate nucleic acids for testing

Current as of 3/01/2023

MCI Testing Ramp-Up



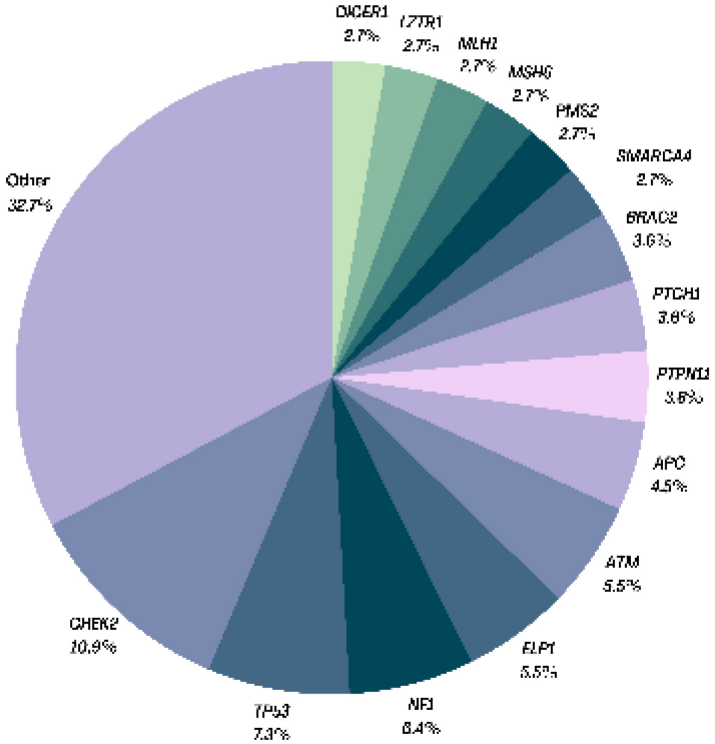
Data from LabVantage monthly sign-outs

Return of Germline Susceptibility Results in MCI

- Only pathogenic or likely pathogenic findings in genes that may be contributory to the underlying reason for studying cancer in the proband will be returned from a consensus list of germline cancer susceptibility genes
- Variants of Uncertain Significance in genes with clear association to the cancer type under study are reportable
- TP53 germline variants are interpreted using the ClinGen specific guidelines
- Reportable germline copy number variation includes gain, loss, biallelic loss or amplification reported in association with cancer predisposition (ACMG/CGC guidelines)
- We are not reporting typical secondary carrier findings such as those informing reproductive risk, nor will we return incidental findings
- The clinical report returning germline susceptibility results is sent electronically to the enrolling physician, who will coordinate a referral for local genetic counseling for patient and family, and offer familial cascade testing (where appropriate)

https://cogmembers.org/prot/apec14b1/APEC14B1FACTs_MCI.pdf

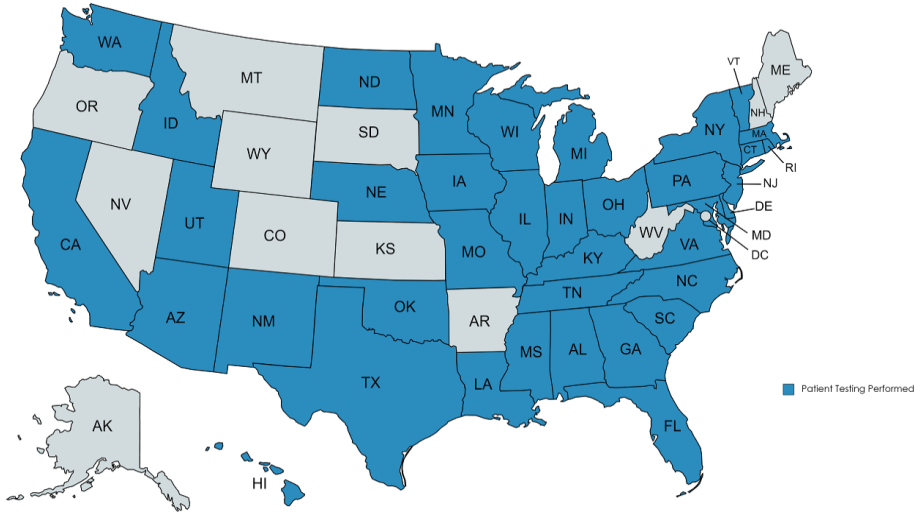
MCI: Germline Findings



Molecular Characterization Initiative

In 2022…

- **693 patients enrolled & consented**
- **2,008 orders received** (~7% cancelled)
- **Testing Completed**
  - **627 Methylation** (~5% cancelled)
  - **649 Fusion** (~8% cancelled)
  - **594 Exome** (~5% cancelled)
- **1,544 orders (77%) signed out within 14d TAT**
- **Patients from 38 states**
- **160 tests performed for international patients (Canada, Australia, New Zealand)**

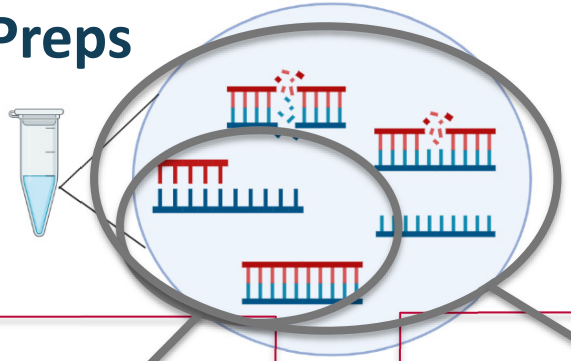


1st case received March 31st

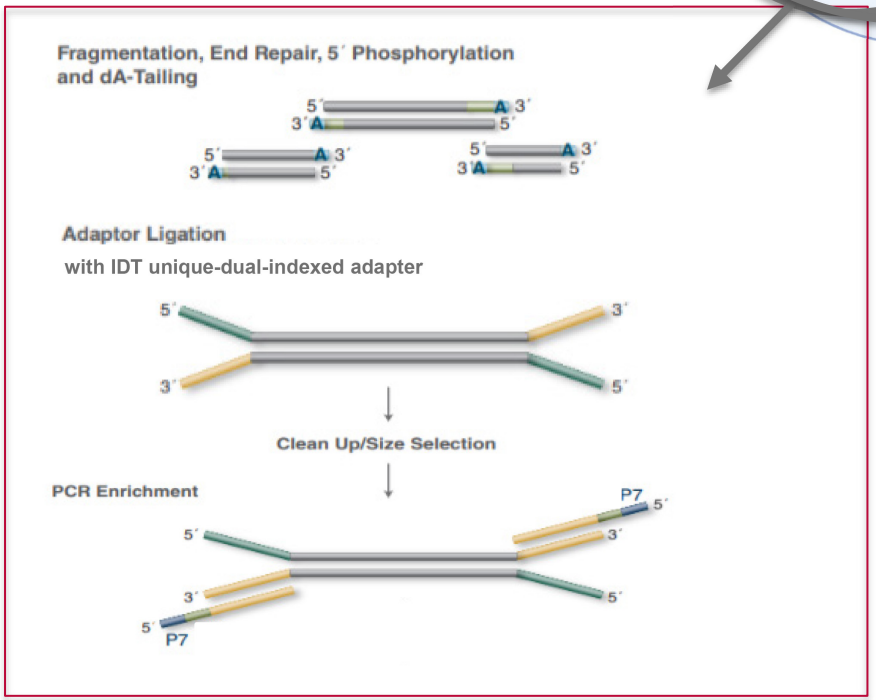
Challenges to 14d TAT

TAT challenges scale with the complexity of the assay	• Wet lab, computational, analytical, sign-out • Methylation<Archer<T/N exome
Scale of operations in wet lab is rate-limiting based on manual pipetting	• Automated pipetting robots will facilitate these protocols and enable higher throughput per tech
NGS instrumentation failures and loading optimization per flow cell	• Planned transition to Illumina NovaSeq X platform to replace NS6000 and verifying the NextSeq2000s
DNA input, data quality and coverage challenges of FFPE-derived tumor DNA for T/N exome assay	• New NGS library kit evaluation from Claret Biosciences in validation
IGMseq scalability is being challenged by increased volumes	• Planning is ongoing for a new NGS Workflow Manager, designed for this scale of operations, including automated sample sheets

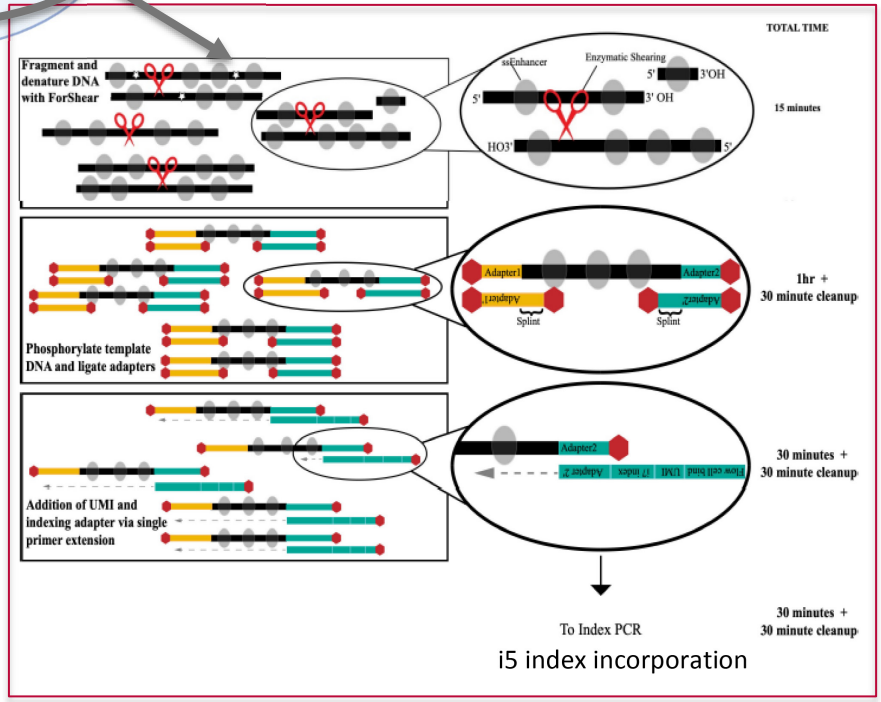
Comparing Library Preps



NEBNext Ultra II FS



Claret SRSLY



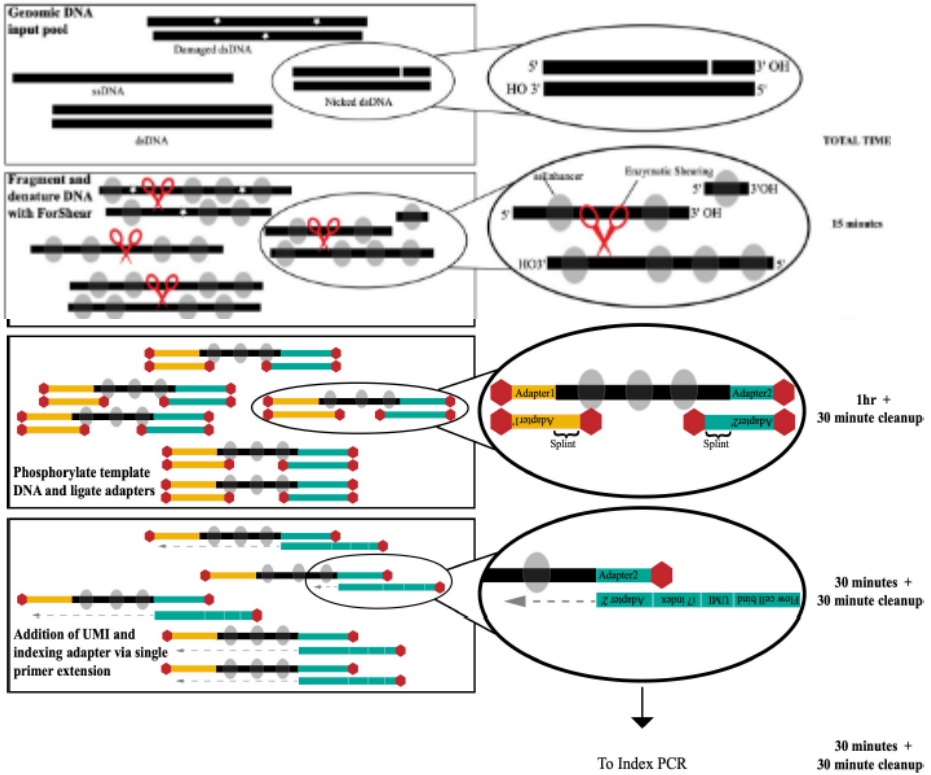
i5 index incorporation

Claret SRSLY chemistry

Single **R**eaction **S**ingle-stranded **L**ibrar**Y**

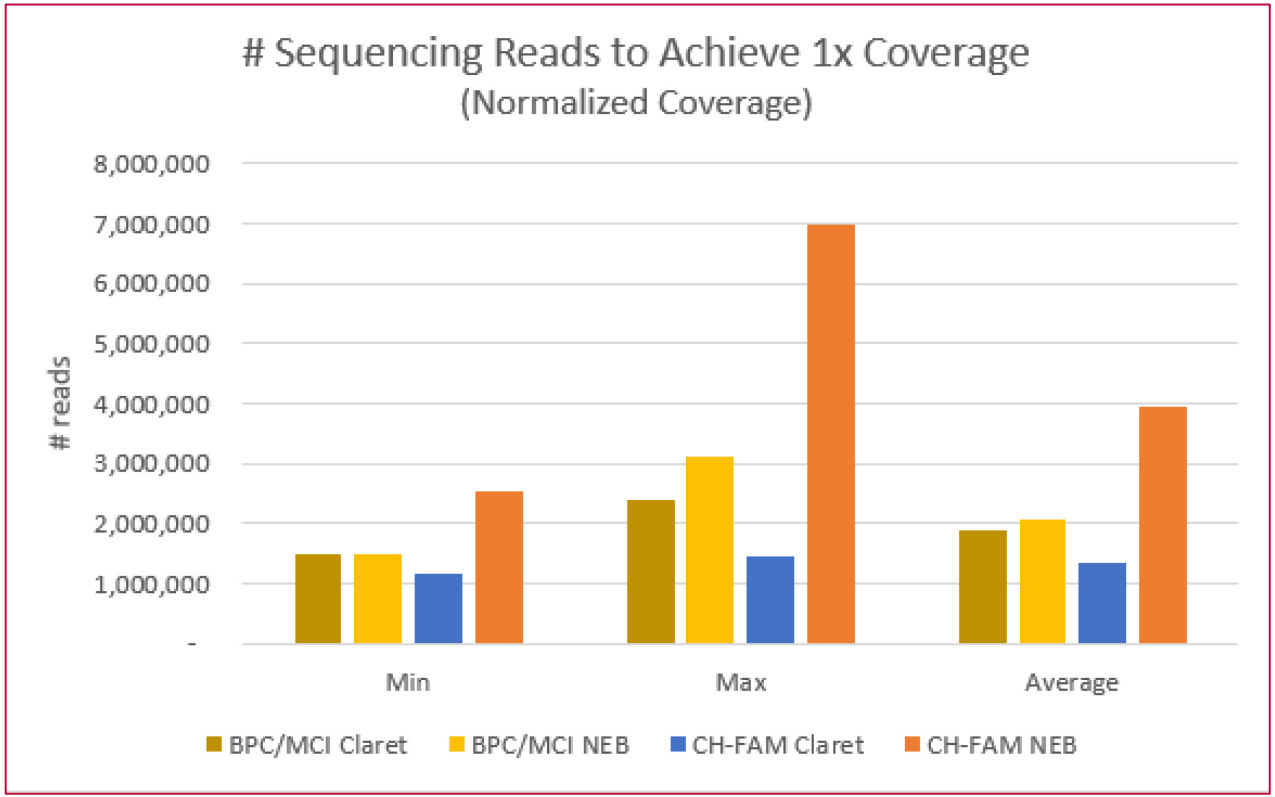
- SRSLY formula:
- 10ng – 50ng input of gDNA

- Current protocol with NEBNext Ultra II FS
- 250-500ng input of FFPE gDNA
- 100ng FF gDNA



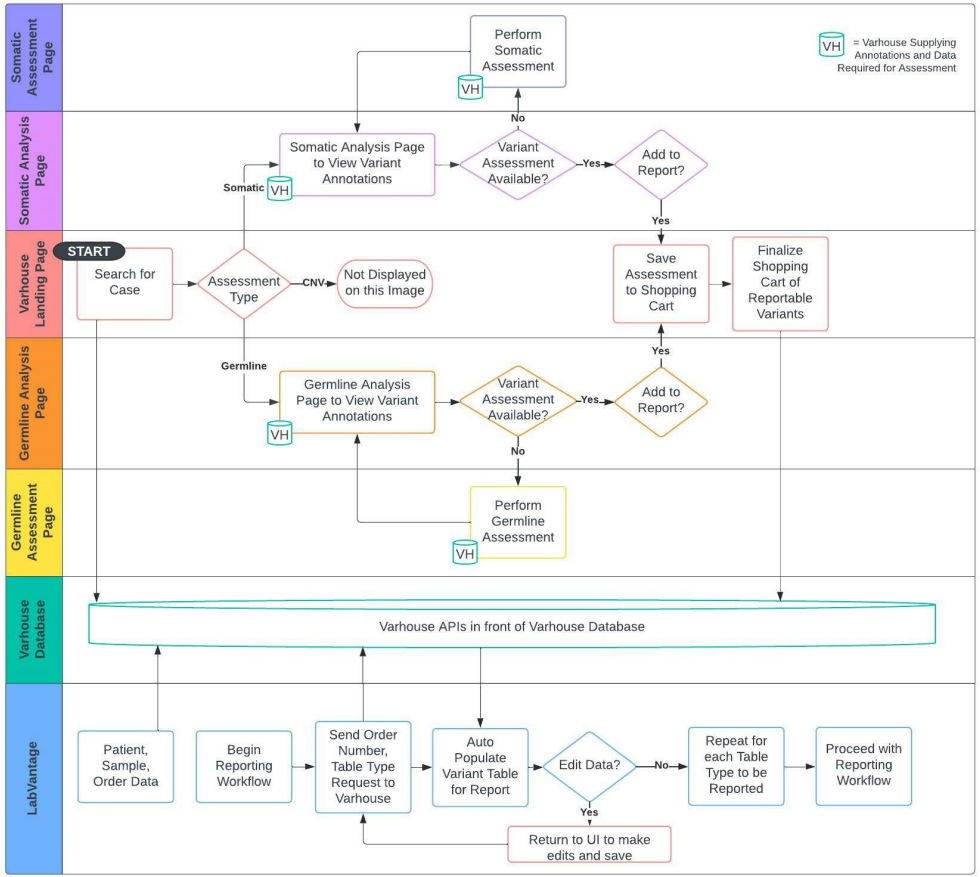
i5 index incorporation

Reads Needed to Achieve 1X Coverage



- Initial testing of the Claret NGS library utilized in-house DNA from FFPE-preserved cancer samples (CH-FAM) and MCI samples (BPC/MCI) in comparison to their clinical results from NEB libraries.
- This comparison evaluates the number of reads needed to achieve 1X coverage on the exome .bed file

Automated Variant Annotation (AVA) Project



- The overarching goal of this multi-month development program is to facilitate the annotation of detected variants (germline and somatic) in the sign-out of tumor/normal exome assay results
- Varhouse is the IGM data lake that warehouses our variant annotations and the additional data required for assessment
- The indicated workflow permits clinical directors to assess both germline and somatic variants of all types prior to adding to report via “shopping cart”, used to auto-populate the variant table according to regulatory guidelines (ASCO/AMP/CAP or ACMG/CGC)

Acknowledgements

IGM Clinical NGS and Microarray teams

IGM Technology Development

IGM Computational Analysis
Ben Kelly (and CGG teams)
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Clinical Lab Directors
Mariam Mathew, PhD
Marco Leung, PhD
Katie Schieffer, PhD
Melanie Babcock, PhD
Claire Hou, PhD
Yassmine Akkari, PhD
Shalini Reshmi, PhD
Catherine Cottrell, PhD

IGM Leadership and Pis
Alex Wagner, PhD
Peter White, PhD
Richard Wilson, PhD

CCDI Data Ecosystem: Connecting Resources

Status Update

NIH NATIONAL CANCER INSTITUTE

Tony Kerlavage, Ph.D.
CCDI Symposium,
3/24/2023

Outline

CCDI Data Ecosystem Objectives

Foundational Infrastructure

- Data Input, Processing, and Access

CCDI Components

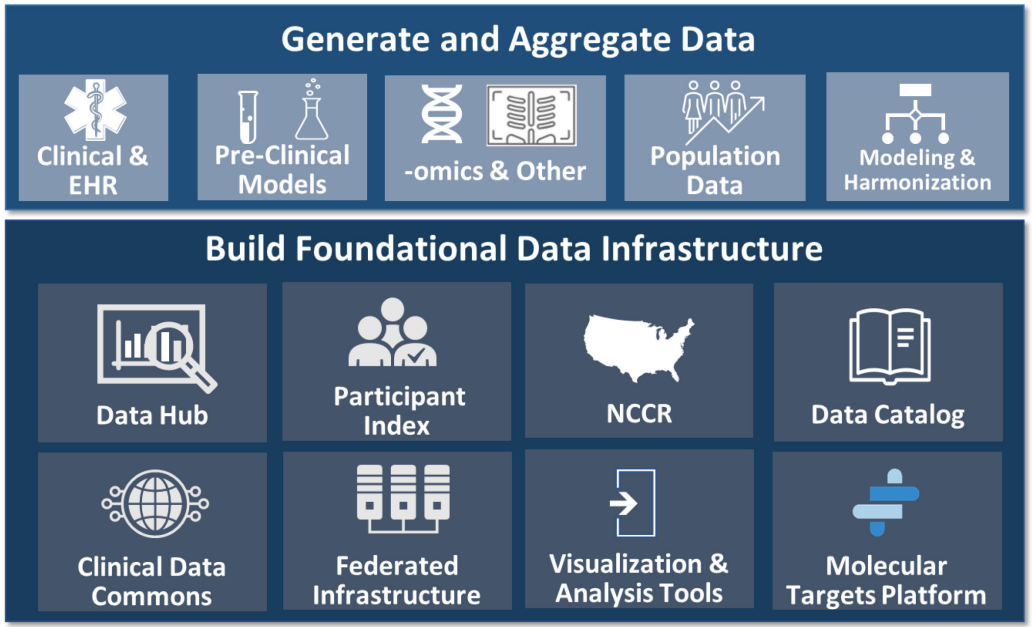
- Deeper Dive

CCDI Objectives

CCDI Data Ecosystem: Objectives

Create a platform that:

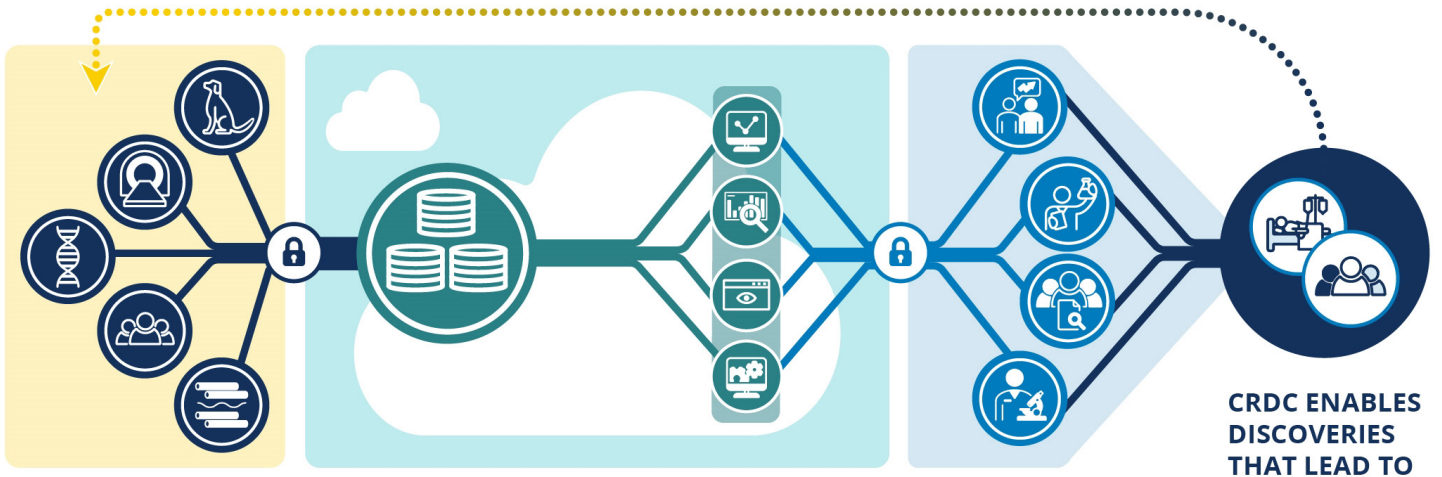
- Supports broad sharing of deidentified individual-level data
- Supports interoperability among existing and new data resources
- Enables the collection, query, visualization, and analysis of longitudinal patient data
- Offers a central Hub to facilitate discovery and analysis



Foundational Infrastructure

Data Input, Processing, and Access

NCI Cancer Research Data Commons:
Empowering Discovery



CCDI Data Ecosystem Components: Connecting the Data

Primary databases

- Childhood Cancer Clinical Data Commons
- Cancer Research Data Commons
- National Childhood Cancer Registry
- CCDI Data Federation

Data processing & harmonization

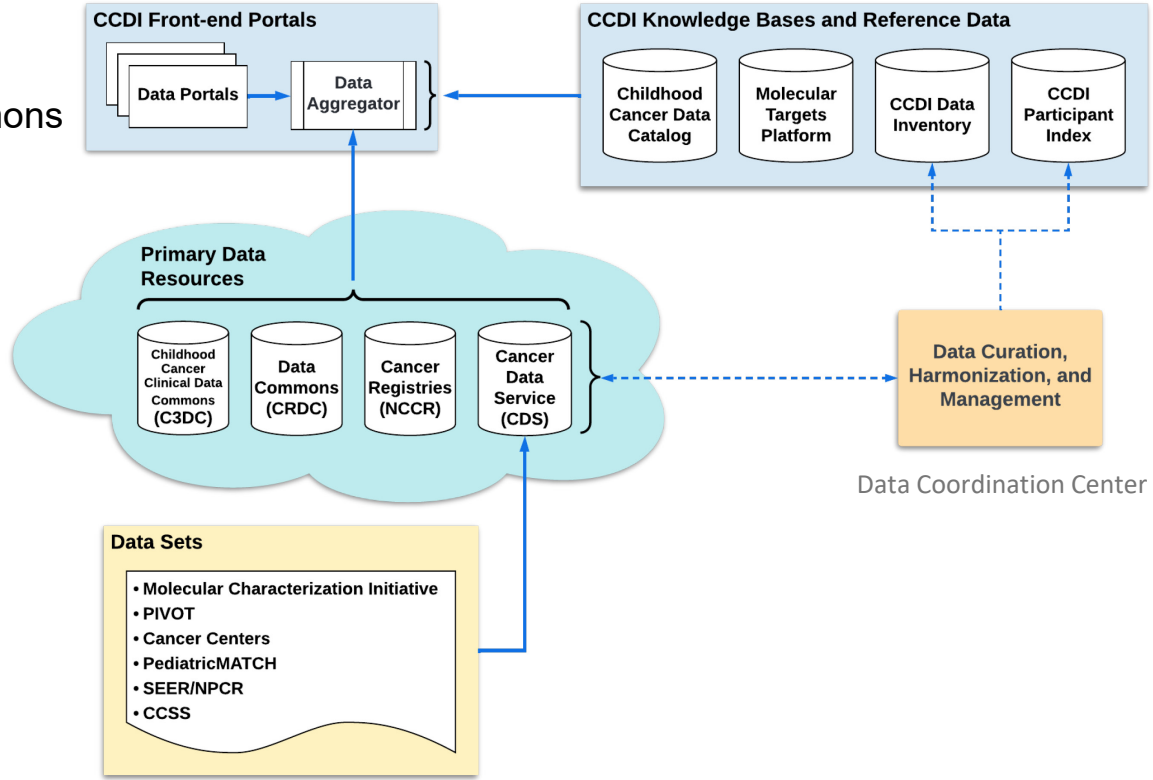
- Data Coordination Center

Reference databases

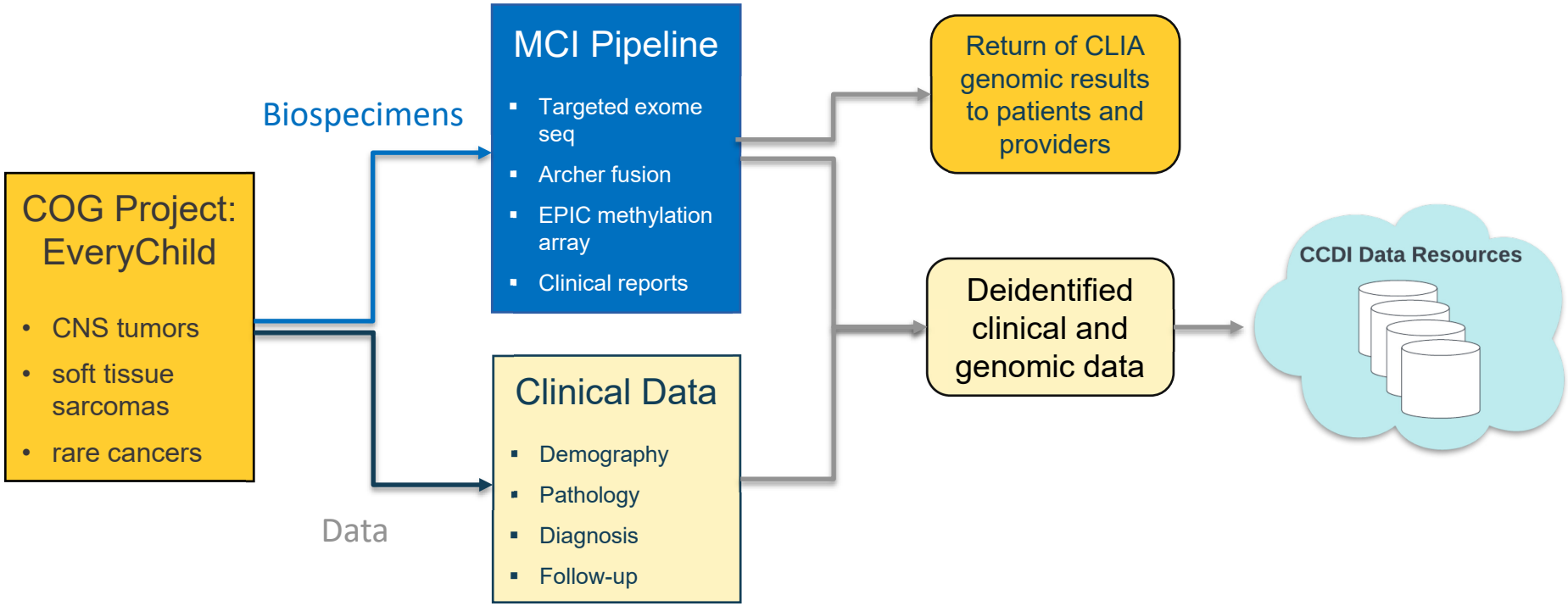
- Data Catalog
- Molecular Targets Platform
- Data Inventory
- Participant Index

Data access

- Various portals



Molecular Characterization Initiative Process



Phs002790: Genomic data: 880 patients; Clinical data: 978 patients

CCDI Data Access

Study-level directories

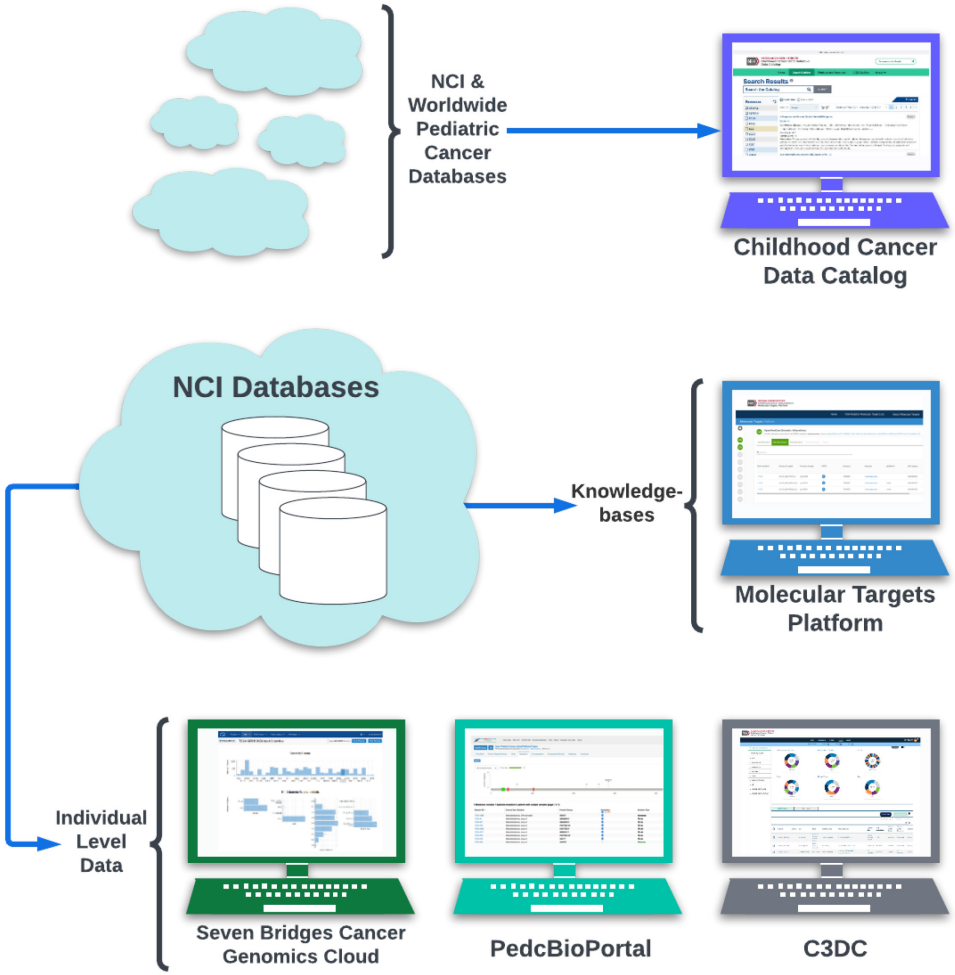
- Childhood Cancer Data Catalog

Aggregations and knowledge bases

- Molecular Targets Platform

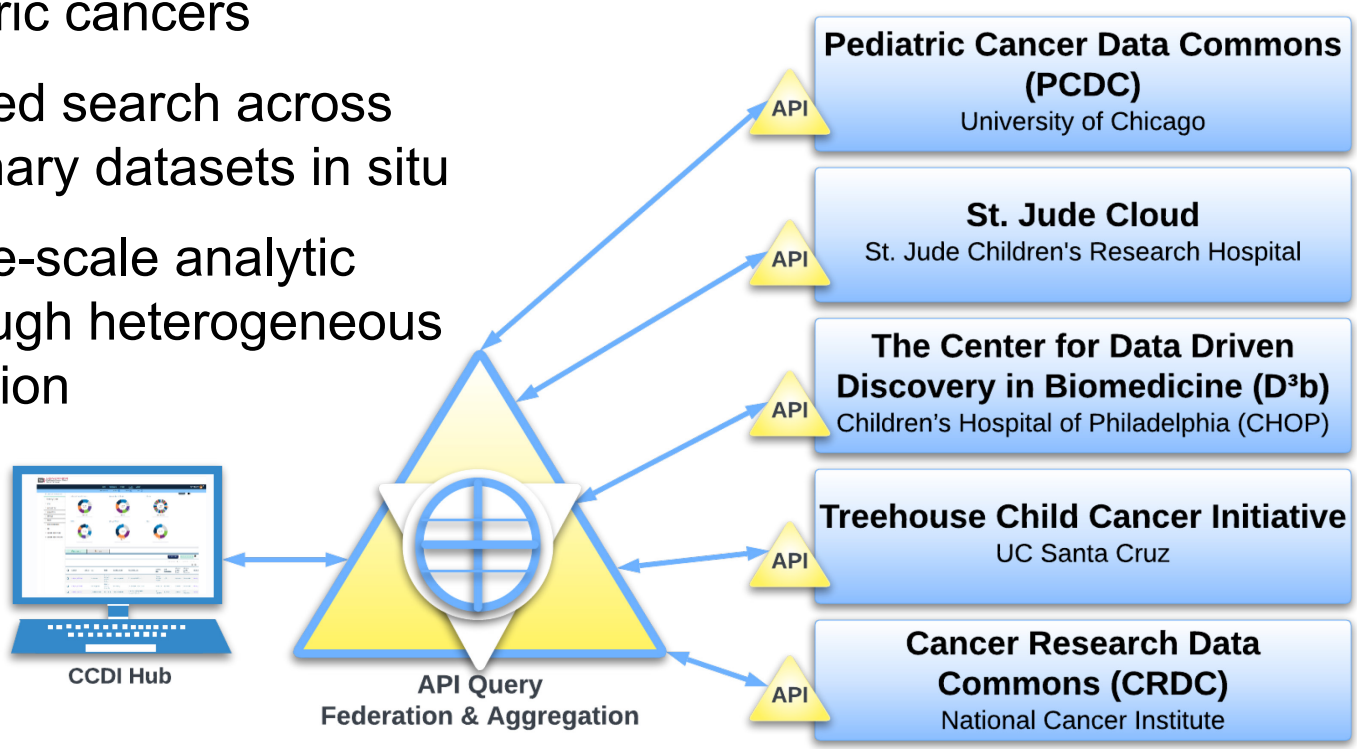
Individual-level data

- Clinical: C3DC
- Genomics: PedcBioPortal
- Custom analyses: Cancer Genomics Cloud



Data Federation Demonstration Project

- Aggregate clinical and research data of pediatric cancers
- Support faceted search across cross-disciplinary datasets in situ
- Facilitate large-scale analytic research through heterogeneous data aggregation
- Tentative MVP release in Q3, 2023



CCDI Components

A Deeper Dive

National Childhood Cancer Registry

Approximately 16,000 childhood cancer patients are diagnosed in the United States annually, compared with 1.8 million new cancer cases among all ages

Initial Registry Participation = ~70% of US population

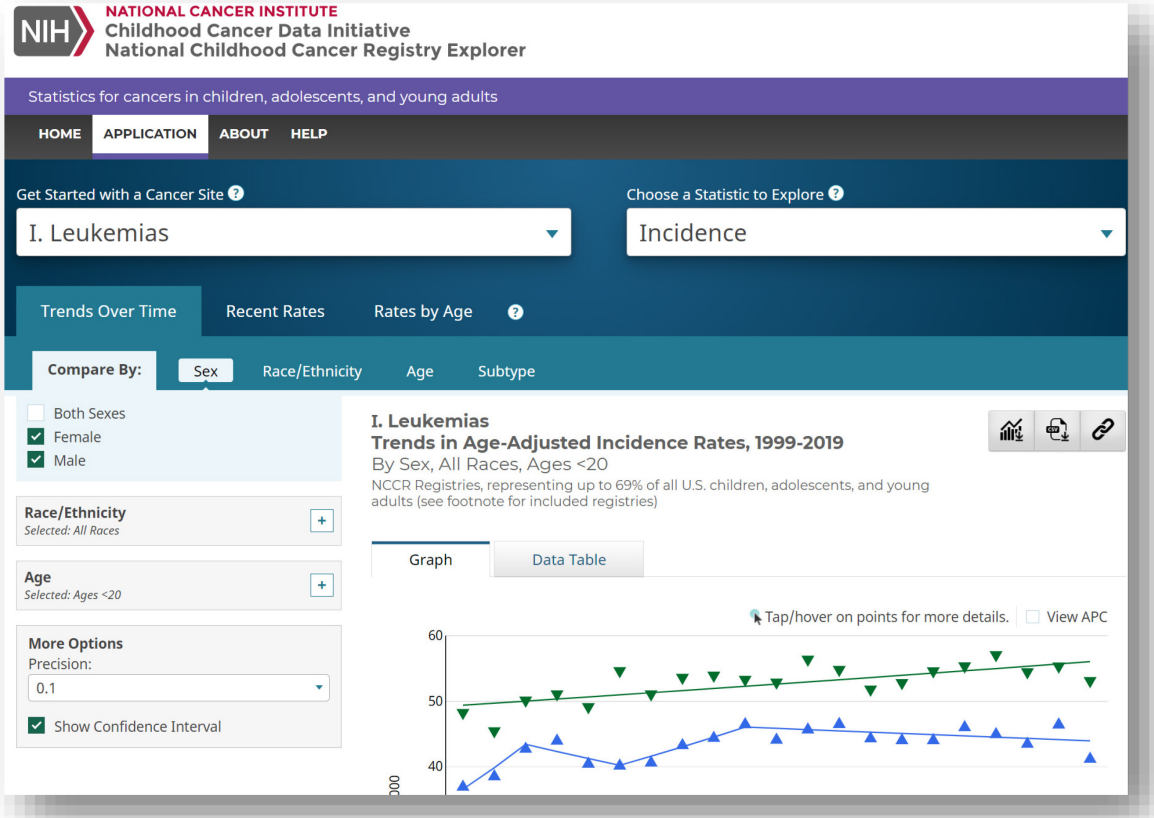
All childhood cases from registries (<40 at diagnosis; 1995+)

Consolidate and standardize data in a single infrastructure

Analyze and share data, in a controlled access environment, to gain insight

Data Domains:

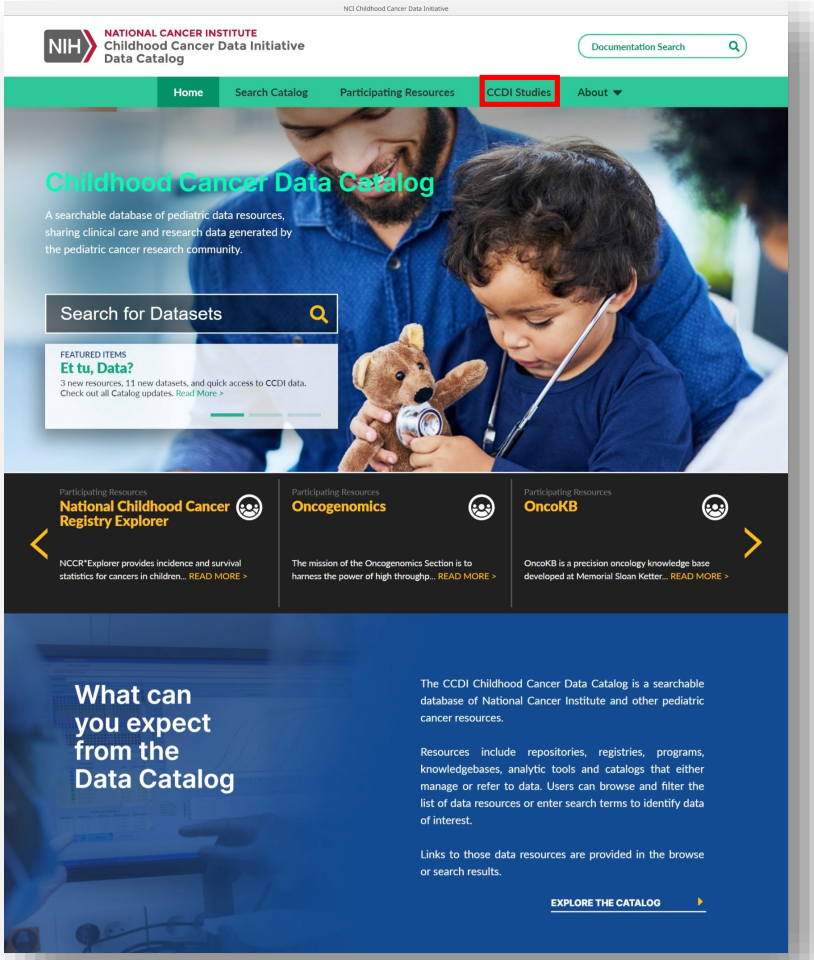
- Longitudinal Treatment, Procedures, Outcomes
  (including pharmacy data, radiation oncology, claims, radiology, vital status)
- Social Determinants of Health
  (including financial toxicity, residential history)
- Clinical Trials and Survivorship Studies
- Germline Molecular Characterization



https://nccrexplorer.ccdi.cancer.gov/about/nccr.html

Childhood Cancer Data Catalog

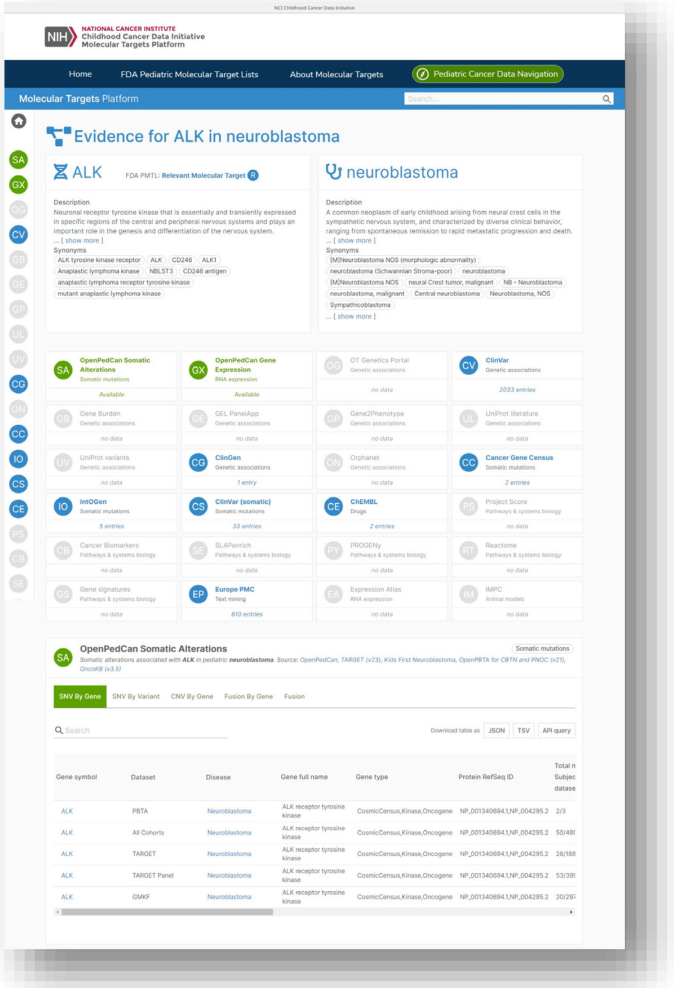
- An inventory of pediatric oncology data resources
  - repositories, registries, knowledgebases, and catalogs
- 41 Resources, 203 Datasets
- Launched in April 2022
  - seven functional & data updates



https://datacatalog.ccdi.cancer.gov/

Molecular Targets Platform (MTP)

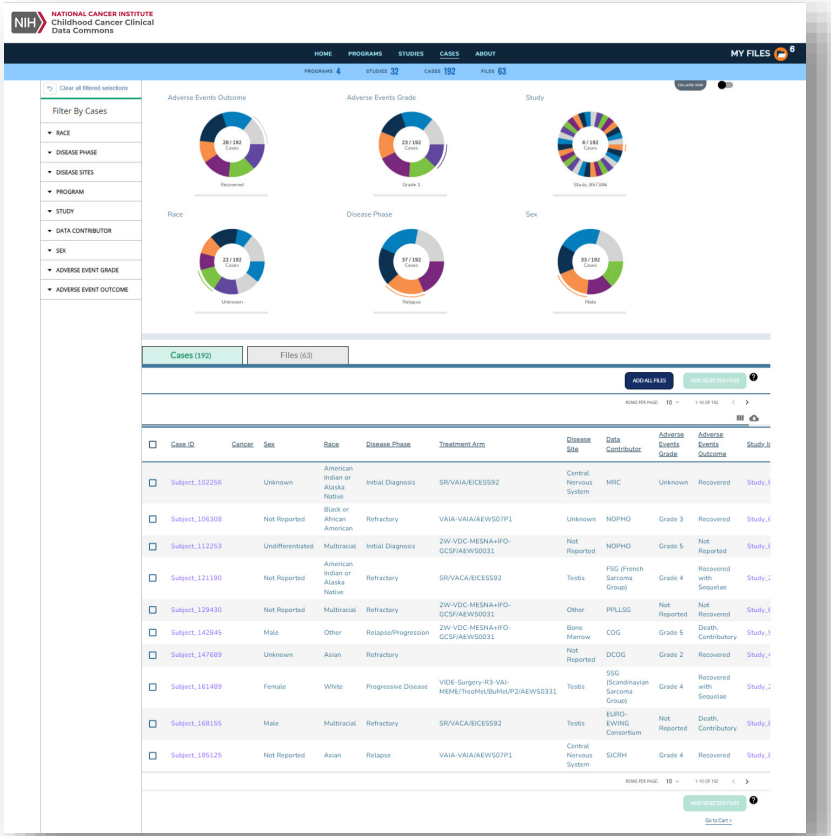
- Open Targets Platform with a focus on pediatric cancer data.
- Browse and identify associations between molecular targets, diseases, and drugs.
- Includes 215 from FDA Pediatric Molecular Target Lists
- 40,929 molecular targets and 63 diseases
- Launched August 2022



https://moleculartargets.ccdi.cancer.gov/

Childhood Cancer Clinical Data Commons (C3DC)

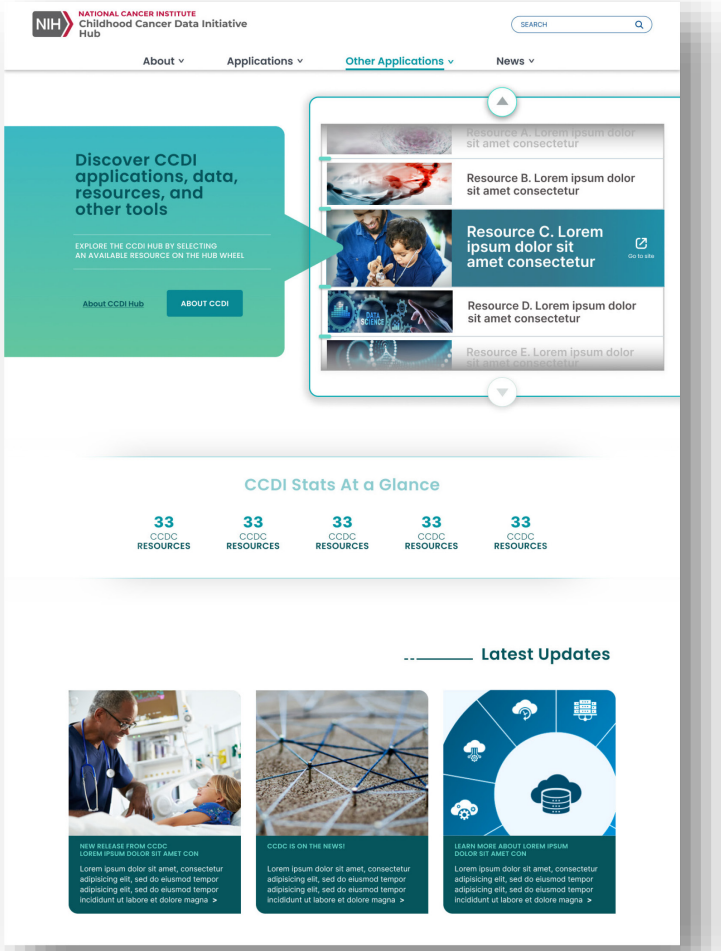
- Allows researchers to search for participant-level data collected from multiple studies
- Facilitates longitudinal data collection and analysis
- Created C3DC data model in GitHub
- Tentative MVP release Q3 of 2023



https://github.com/CBIIT/c3dc-model

CCDI Hub

- CCDI Hub is an entry point for researchers, data scientists, and citizen scientists looking to use and connect with CCDI
- Facilitates exploration of CCDI applications, data, tools, and other resources
- MVP will be released in April 2023



Contact Information

- Ask questions through CCDI Mailbox: NCIChildhoodCancerDataInitiative@mail.nih.gov
- Learn more on the CCDI Website: https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative
- Subscribe to CCDI's RSS feed: https://public.govdelivery.com/accounts/USNIHNCI/subscriber/new?topic_id=USNIHNCI_223

A National Initiative for Rare Cancers in Children, Adolescents, and Young Adults

Mary Frances Wedekind, DO

POB/CCR/NCI/NIH

NIH NATIONAL CANCER INSTITUTE

Pediatric ONCOLOGY BRANCH

March 24, 2023

Background: Rare Pediatric and AYA Cancer

- Rare cancer: Less than 150 cases per million per year
  - Very rare pediatric cancer:
    - Less than 2 cases per million per year (11% of all pediatric cancers)
- Challenges:
  - Accurate and timely diagnosis
  - Poor understanding of natural history and biology
  - Lack of standard therapy & treatment trials
  - Identification of centers with treatment expertise
- Substantial progress for select cancers, but
  - Siloed
  - Focus on few cancers
  - Insufficient patient numbers for most cancers
  - Data collection not standardized/structured

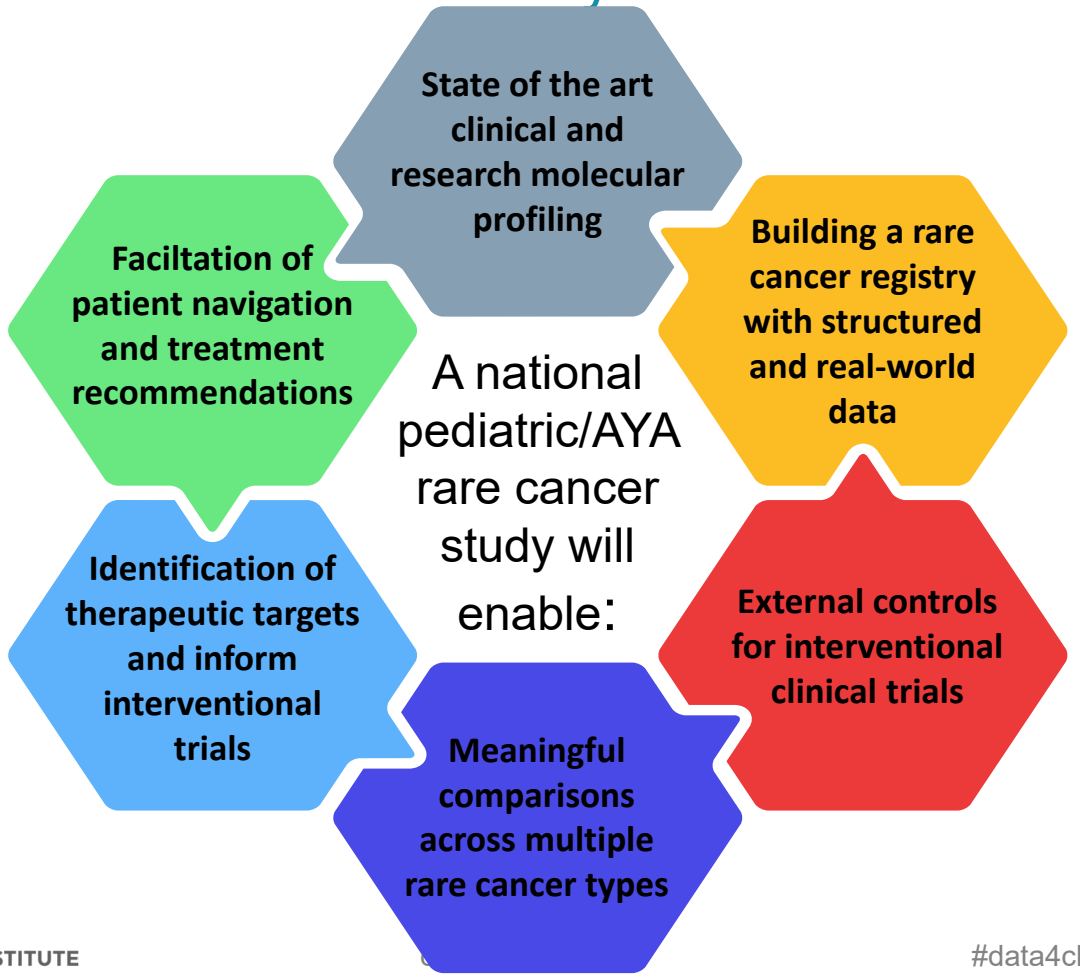
Successful Pediatric/AYA Efforts

- PPB/DICER1 Registry
- My Pediatric and Adult Rare Tumor Network (MyPART)
- International pediatric ACC tumor registry
- ExPERT/PARTNER Consortium
- GlobalREACH – International Rb data commons
- Numerous disease specific clinical trials:
  - ARET0321 – Metastatic retinoblastoma
  - ARAR0331 – Nasopharyngeal carcinoma
  - ARAR0332 – Adrenocortical carcinoma
  - Larotrectinib in NTRK fusion tumors

Lessons Learned: Rare Pediatric and AYA Cancer Efforts

- Despite ongoing efforts there remains a large unmet need
- Successful efforts have:
  - Advocacy, patient engagement, and disease champions
- Conducting registry/natural history studies first facilitates clinical trials
- Achieving meaningful cohorts is time efficient
- Partnership and integration with consortia / COG / PBTC / PNOC / CBTN / disease specific initiatives / community hospitals / advocacy and national experts is critical to accelerate rare tumor efforts
- A national effort will allow enrolling adequate numbers of participants to more rapidly, efficiently, and consistently study multiple rare cancers

CCDI Coordinated National Study of Pediatric/AYA Rare Cancers



CCDI Coordinated National Study of Pediatric/AYA Rare Cancers

- Key elements of the proposed national rare cancer study will be synergistic with CCDI and other rare tumor efforts:
  - CCDI:
    - Conduct of longitudinal epidemiological cohort studies
      - Genetic tumor predisposition
    - Collect core clinical information on the Molecular Characterization Initiative (MCI)
  - Other efforts:
    - Support data collection and connection
    - Patient navigation
    - Portable patient owned medical record
    - Ability to follow patients longitudinally and facilitate data for survivorship studies

Objectives & Eligibility

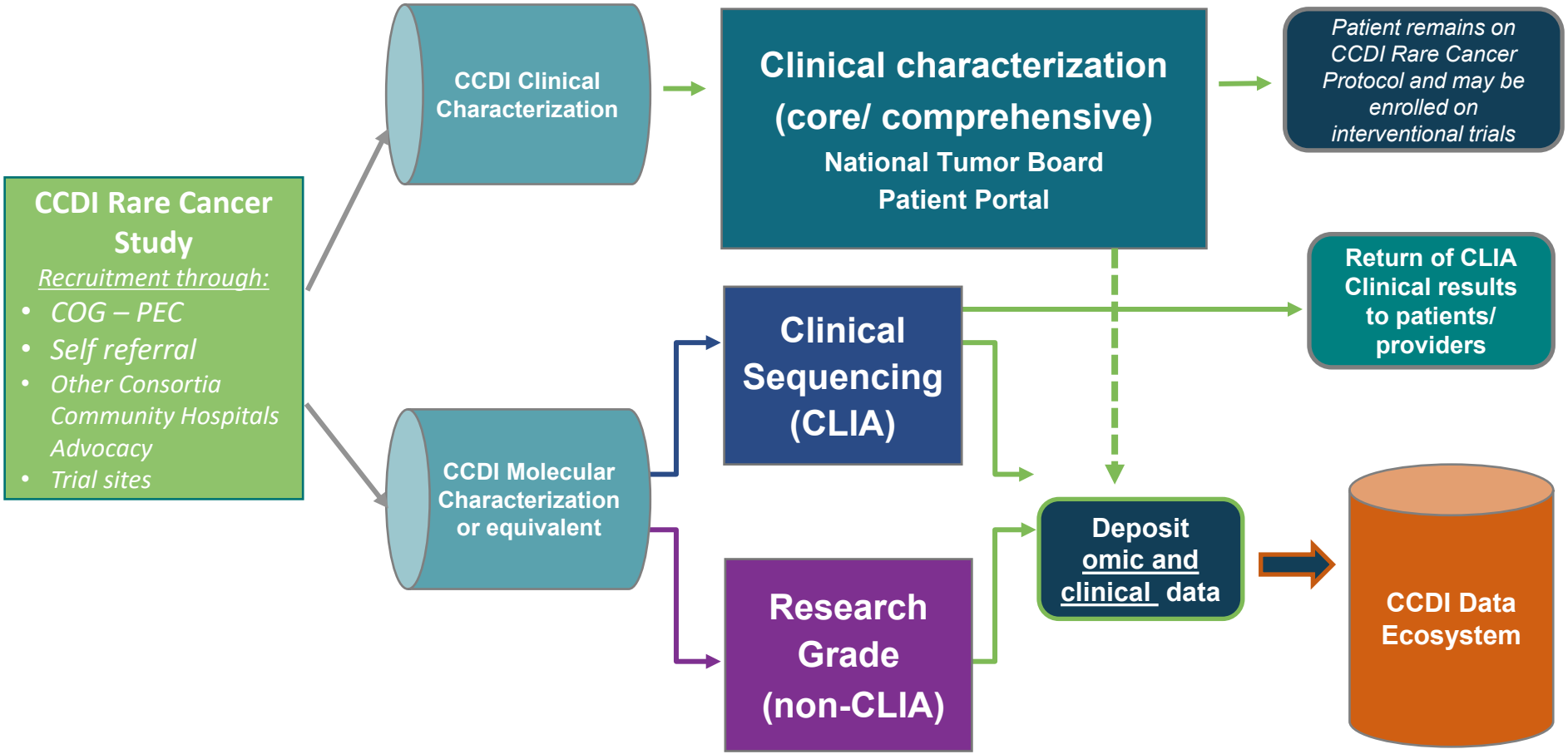
Objectives:

- Determine feasibility of a national observational protocol for very rare pediatric and AYA solid cancers and hematologic malignancies
- Comprehensively and longitudinally evaluate the disease course of participants with rare cancers
- Collect clinical and research molecular characterization
- Determine feasibility of national molecular/clinical tumor boards for rare cancers

Eligibility:

- Pediatric and young adult patients with rare solid tumors or hematologic malignancies

CCDI-Coordinated Rare Pediatric/AYA Cancer Study



Recruitment

- Self-referral
- All clinical care and research centers involved in the diagnosis and management of cancer in children and young adults
  - Initially, COG's Project Every Child (PEC) and CCDI's Molecular Characterization Initiative (MCI)
    - Will be utilized to identify patients for rare cancer study
  - Other consortia, such as PBTC, CBTN, CONNECT, PNOC, TACL etc. will be engaged
- Community hospitals/physician/advocacy

Study Design

- Coordination:
  - CCDI coordinated national collaboration
  - Overall Study PIs
  - Rare cancer cohort PIs (rare tumor experts/champions)
- Self referral from anywhere
- Trial sites:
  - Potential to open at other sites
  - Not limited to COG sites (maximize ability to enroll patients who may not have access to COG site)
- Enrollment:
  - At participating sites for comprehensive, longitudinal evaluations
  - Remotely (electronic/phone consent) for collection of core data

Study Design

- Data collection:
  - Core data set (remote patients)
  - Comprehensive data set (selected rare cancers)
  - Biospecimen analysis offered through the CCDI MCI for clinical molecular characterization
  - Research molecular characterization TBD
  - Data for patients enrolled through PEC-MCI, will be accessible to the national rare cancer study
  - Data sharing with other rare cancer registries to not duplicate efforts
- Data platform: TBD
- Patient portal: TBD
  - Entry of patient reported outcomes and patient information
  - Access to results/information

Disease Specific National Molecular/Clinical Tumor Boards

Tumor board composition:

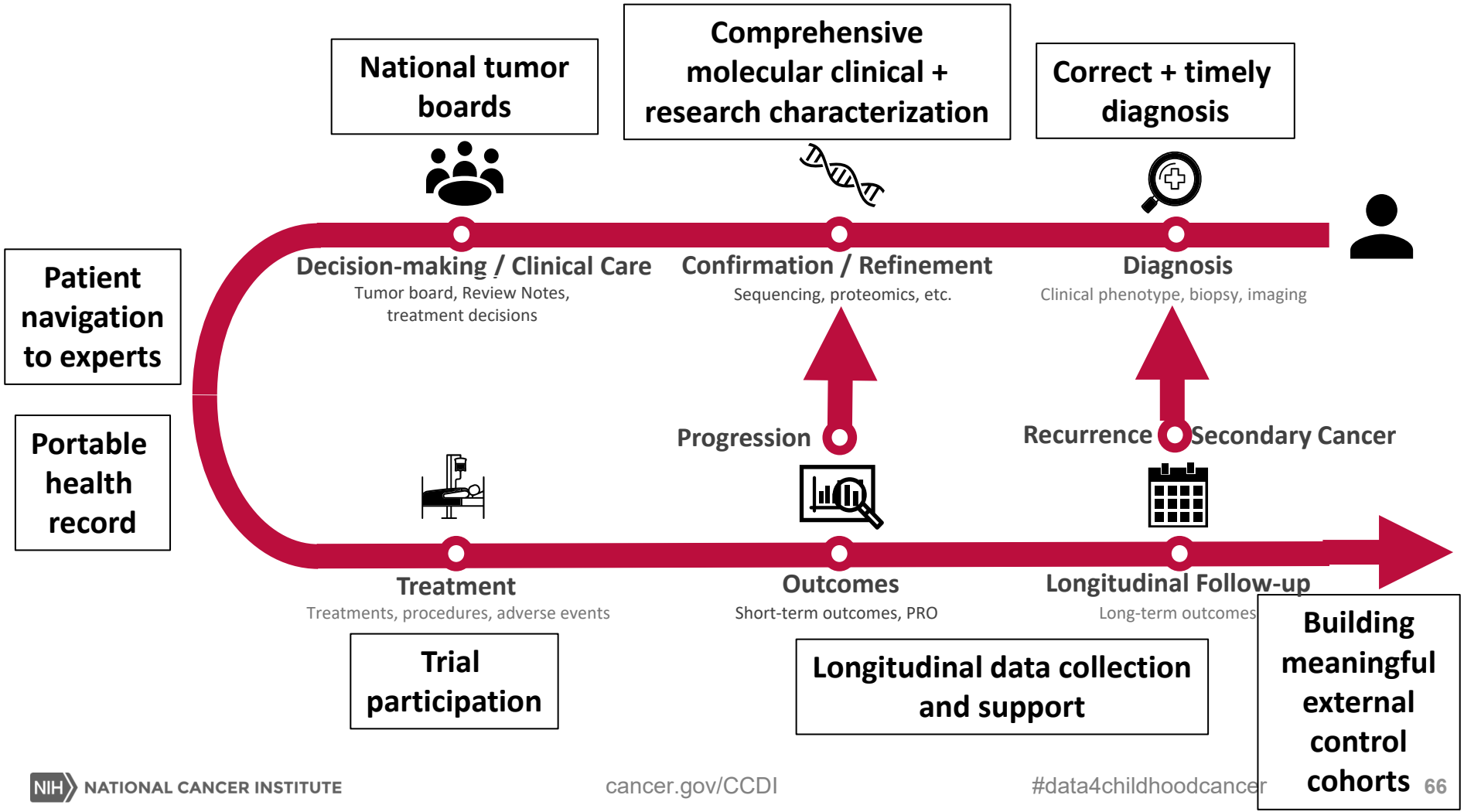
- Clinicians and researchers with specific interest and experience in the rare cancer presented
- Genetic counselor to provide treatment recommendations for patients and build upon the collective knowledge base of treating clinicians
- Learn from and collaborate with already established molecular and clinical tumor boards
- Assemble experts from within and outside COG representing all expertise required to provide the very unique benefit of an expert opinion to patients with very rare cancers

NIH Rare Tumor Clinics:

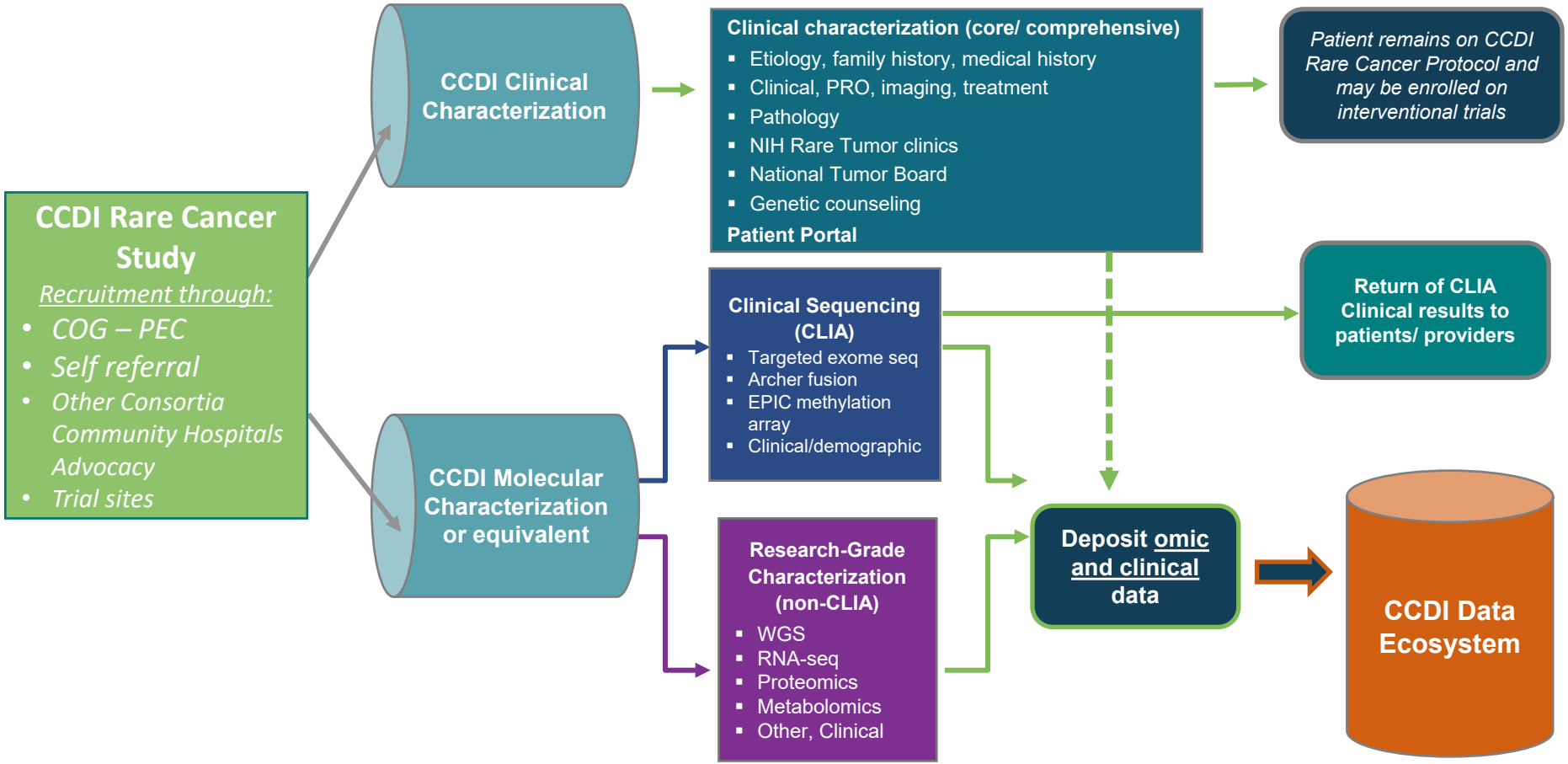
- Can complement this effort and allow for focus groups

NIH Rare Tumor Clinics: wt-GIST, MTC, Chordoma

- Rare tumor clinics bring 8-10 patients with select very rare tumors to the NIH CC
  - Disease experts (intra- and extramural) and advocates
  - Detailed clinical evaluations
  - Patient reported outcome, focus groups
  - Patients meet with experts and receive “expert opinion”
- Current Specialty Clinics:
  - Wt-GIST
  - MTC
  - Chordoma
- Benefits:
  - Experts discuss experiences and approaches
  - Patients receive valuable recommendations
  - Trends and similarities more easily identified
  - Patients get to meet others with the same disease


National tumor boards
Comprehensive molecular clinical + research characterization
Correct + timely diagnosis
Patient navigation to experts
Portable health record
Decision-making / Clinical Care
Tumor board, Review Notes, treatment decisions
Confirmation / Refinement
Sequencing, proteomics, etc.
Diagnosis
Clinical phenotype, biopsy, imaging
Progression
Recurrence
Secondary Cancer
Treatment
Treatments, procedures, adverse events
Outcomes
Short-term outcomes, PRO
Longitudinal Follow-up
Long-term outcomes
Trial participation
Longitudinal data collection and support
Building meaningful external control cohorts

CCDI-Coordinated Rare Pediatric/AYA Cancer Study



Acknowledgments for helpful discussions and support

- CCDI/NCI
  - Jim Doroshow, Warren Kibbe, Jaime Guidry-Auvil, Tony Kerlavage, Anne Lubenow
  - Greg Reaman
  - Malcolm Smith, Nita Seibel, Meg Mooney
  - Engagement Committee
- MyPART
  - Brigitte Widemann, Karlyne Reilly, Jack Shern
  - Abby Sandler, Christina Vivelo
  - Advocacy partners
- COG
  - Doug Hawkins, Ted Laetsch, Philip Lupo
- CBTN
  - Adam Resnick
- **And so many more!**

Extra thank you to the patients and families!

Panel Discussion: CCDI Work in Progress

Samuel Volchenboum, MD, PhD

Hanna Jorgenson

Anthony R. Kerlavage, PhD

Javed Khan, MD

Elaine Mardis, PhD

Troy McEachron, PhD

Mary Frances Wedekind, DO

Rationale for Cohort Studies

Smita Bhatia, MD, MPH

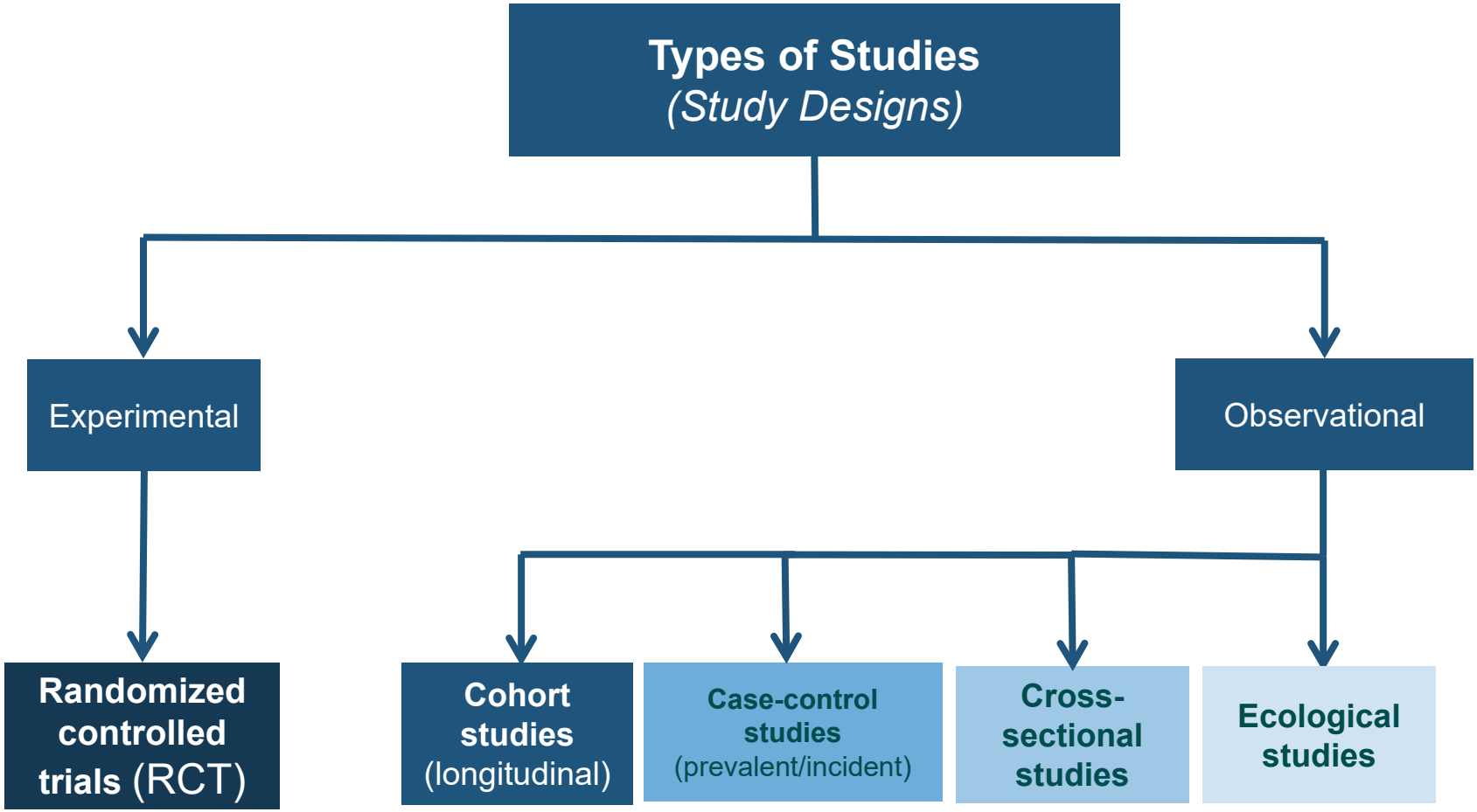
Hypothesis-driven study question

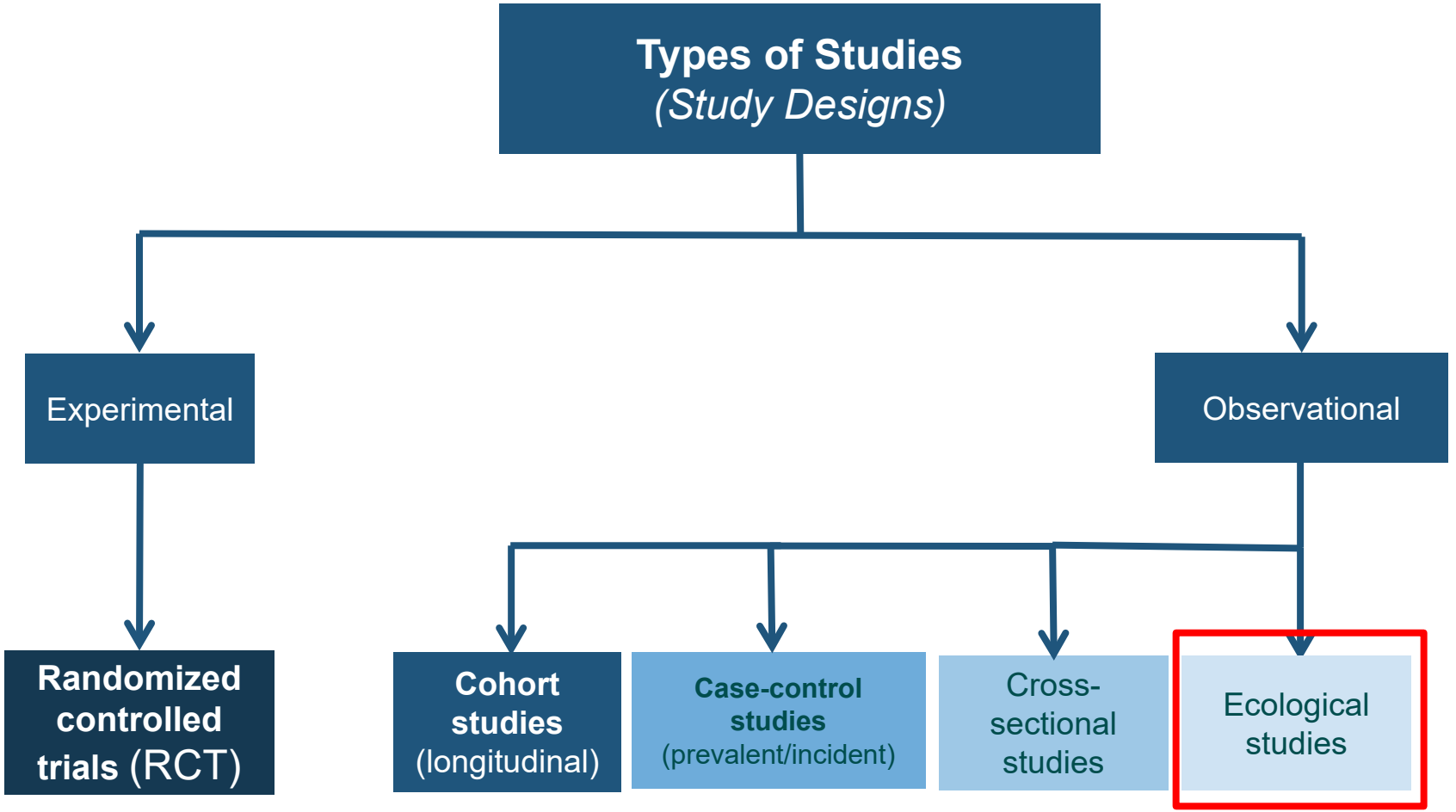
Determine outcome(s) of interest

- *Prevalence*
- *Latency from exposure*

Identify study population

Use appropriate study design


Types of Studies
(Study Designs)
Experimental
Observational
Randomized controlled trials (RCT)
Cohort studies (longitudinal)
Case-control studies (prevalent/incident)
Cross-sectional studies
Ecological studies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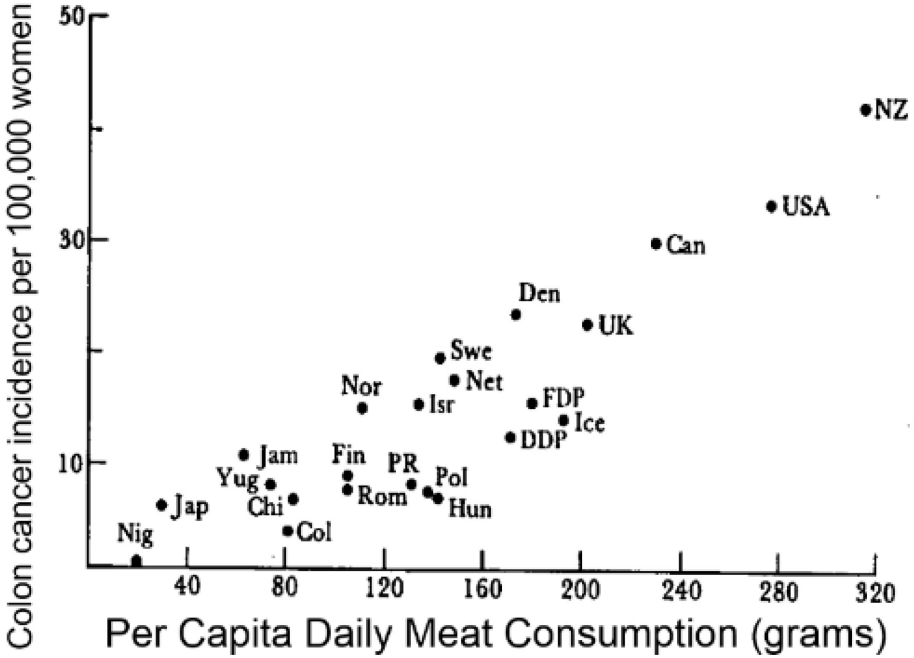
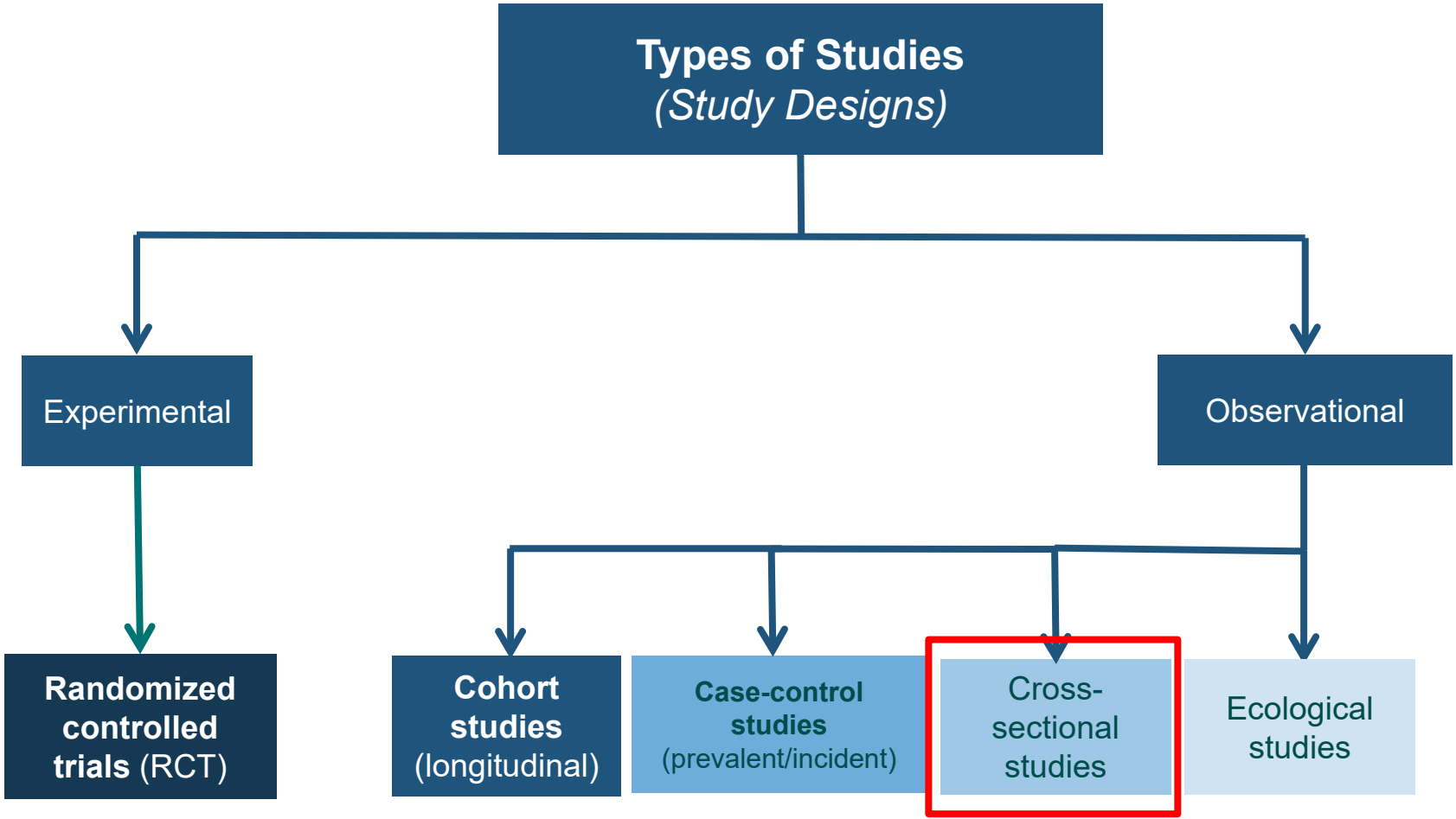
Ecological studies

Ecological Study

- Compares large groups of people instead of individuals



Subject to ecological fallacy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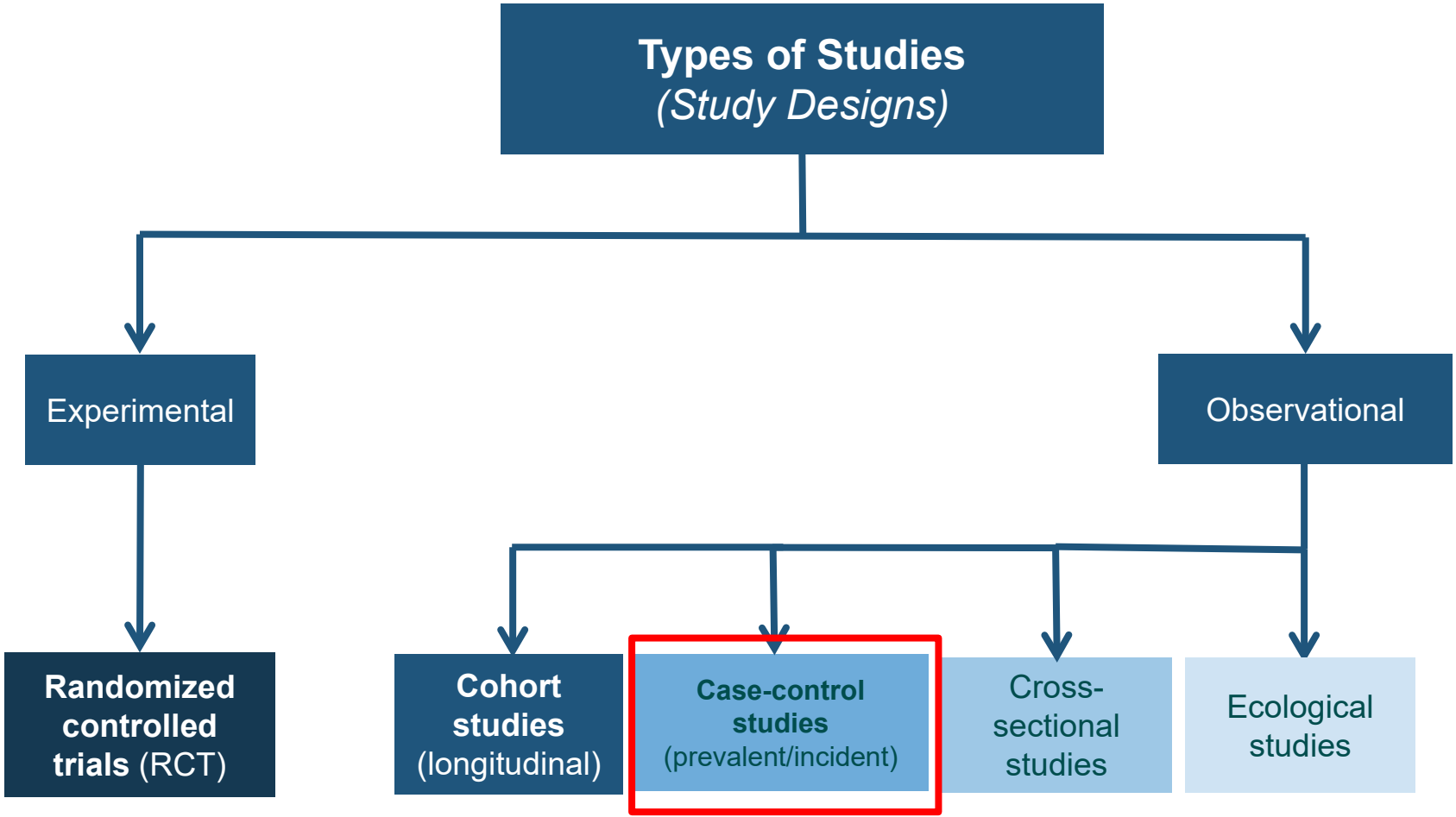
Ecological studies

Cross-sectional study

- Looks at data at a **single time point**
- **Outcome is present or absent** in a cross-sectional sample of patients
- Temporal relation between exposures and outcome is not possible
- **Cannot ascribe causality**
- BUT
  - Inexpensive and fast
  - Hypothesis-generating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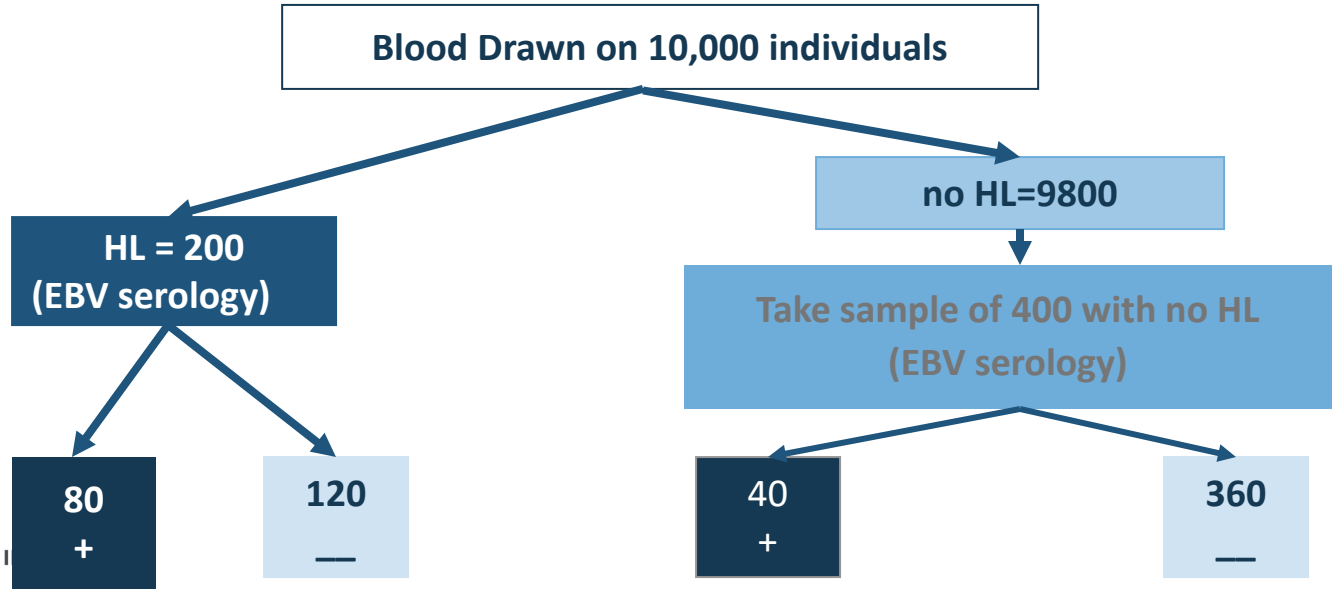
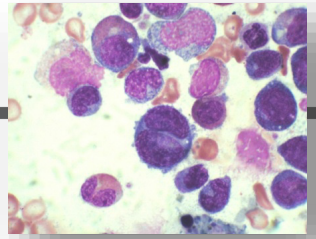
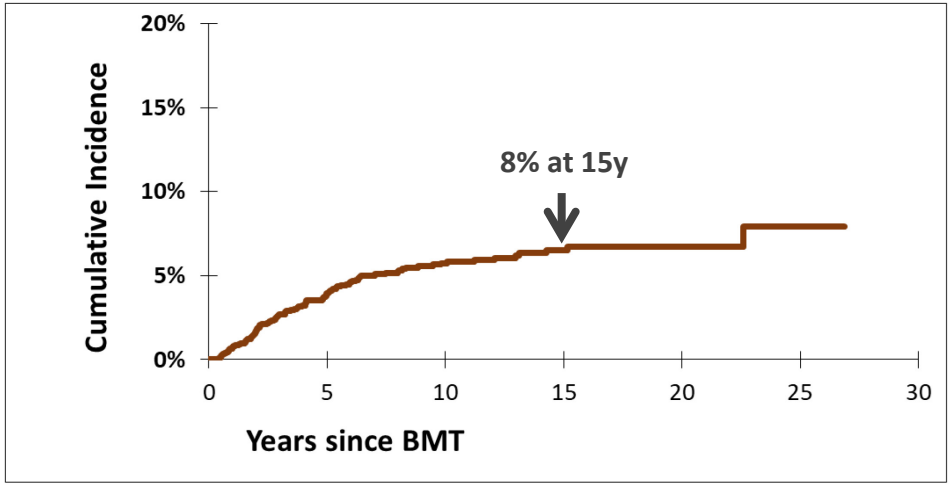
Nested case-control studies

- Case-control study nested within a cohort study
- Useful when exposure is expensive to measure and can be assessed at a later time in cases and matched controls (from within the cohort)



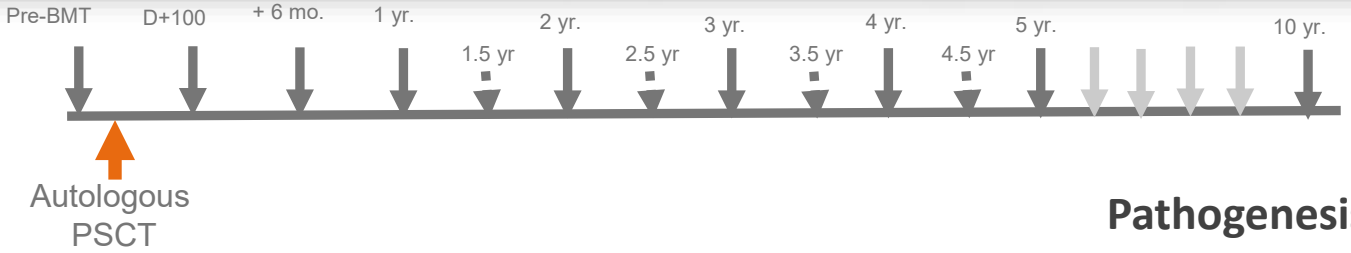
Therapy-related Leukemia





High fatality

Prospective, longitudinal study in patients undergoing autologous BMT for HL/NHL



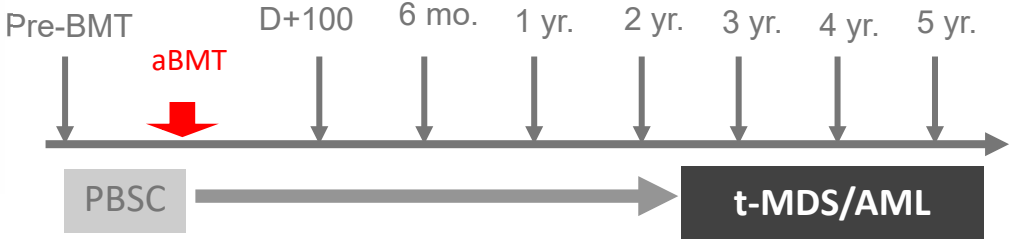
Pathogenesis and Prediction

Gene Expression Changes in CD34+ Cells in patients undergoing Autologous BMT for HL or NHL

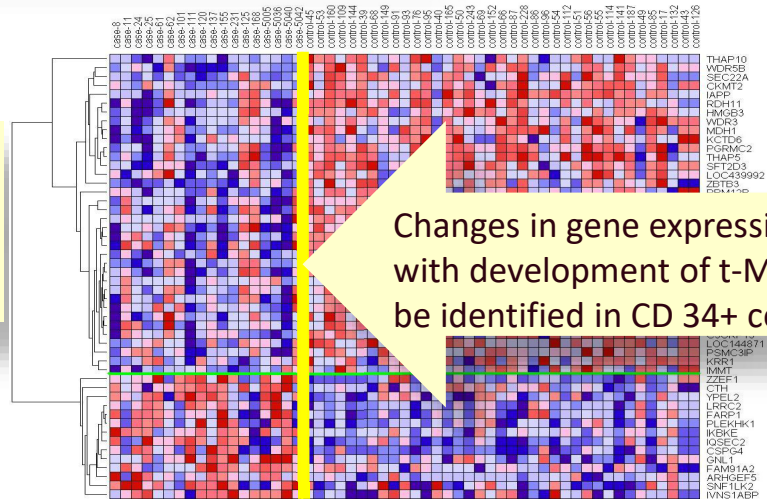
An optimal 38-gene **PBSC gene signature** accurately distinguished patients prior to aBMT at high risk of developing t-MDS/AML

Specificity: 95% Sensitivity: 87.5%

Cancer Cell, *2011; 20:591-605*



Differential gene expression in CD 34+ cells from **PBSC**

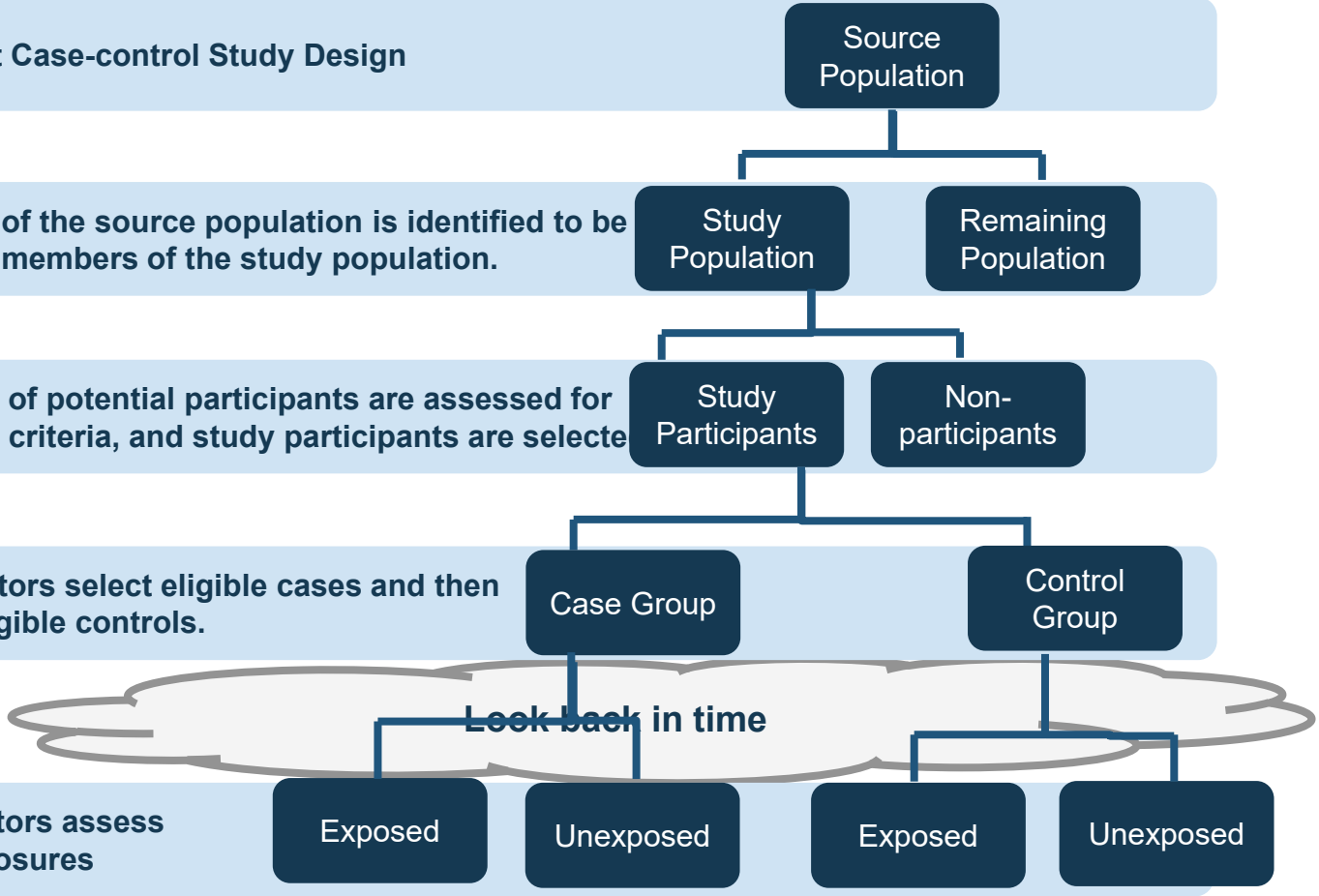


Changes in gene expression associated with development of t-MDS/AML can be identified in CD 34+ cells from PBSC

Case

Control

Prevalent Case-control Study Design



Study Design

Eligibility - Cases

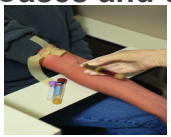
1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. Subsequent development of a key adverse event

Matching Criteria
Primary cancer diagnosis
Year of diagnosis (±5y)
Race/ethnicity
Time since primary cancer

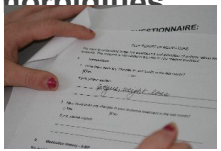
Eligibility - Controls

1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. No evidence of key adverse events

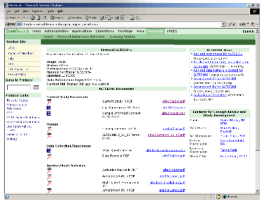
Collect DNA from **Cases and controls**



Self-report of **comorbidities**



Summarize therapeutic exposures for cases and **controls**



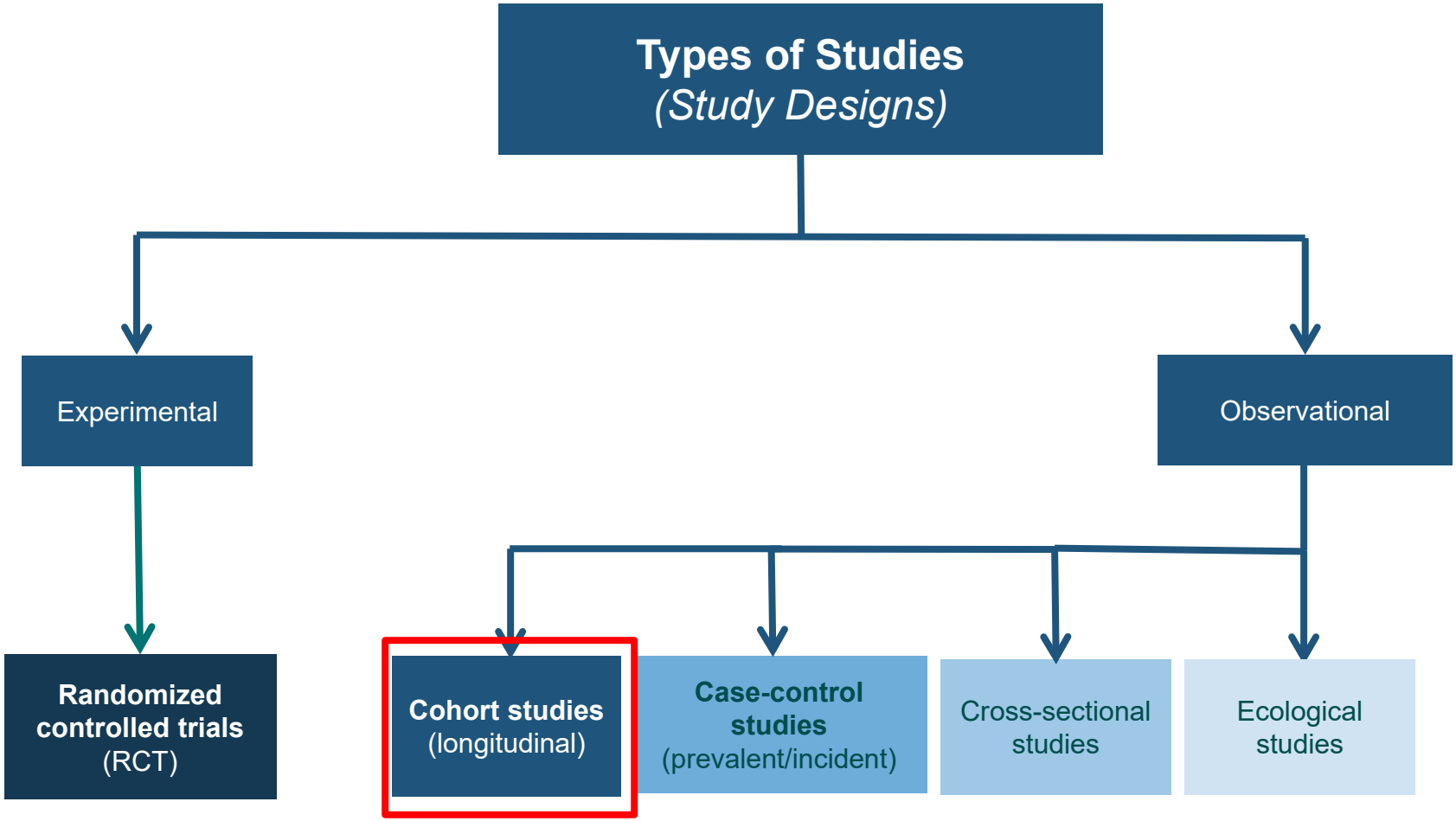
Source documentation (Cases only)

Osteonecrosis *(diagnostic radiology)*

Cardiomyopathy *(echocardiogram report)*

Subsequent malignancies *(pathology report)*

Stroke *(diagnostic radiology)*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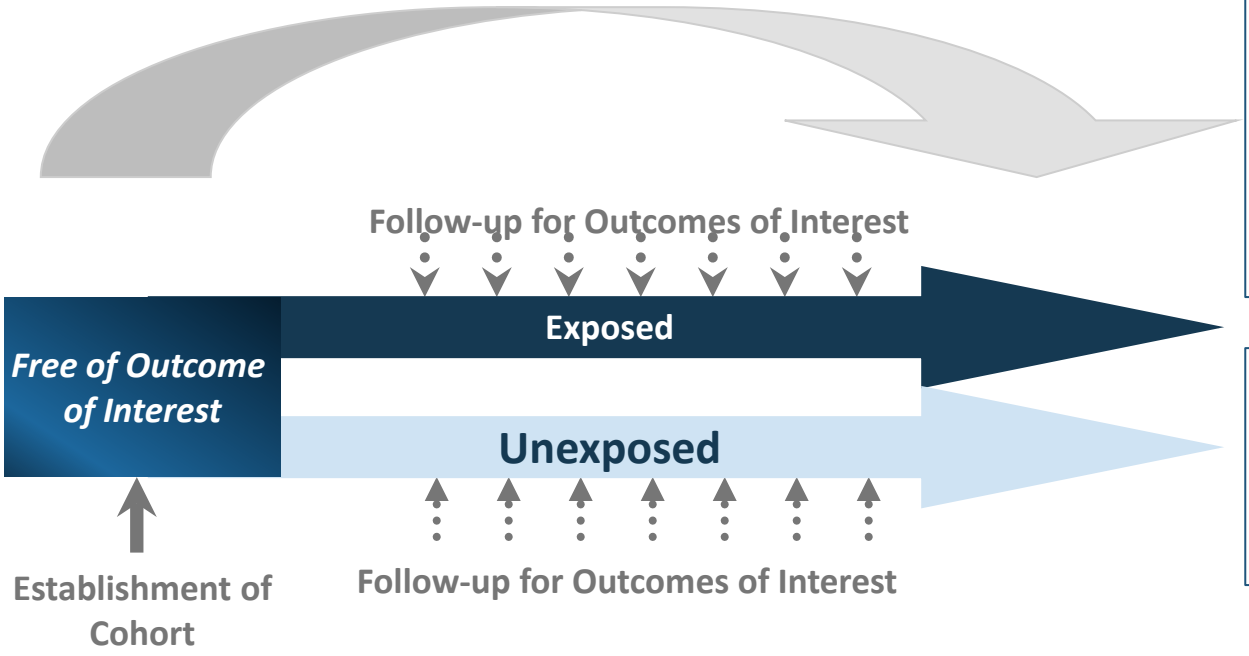
Prospective Cohort Studies



Multiple outcomes can be studied

Collection of all possible variables needed for study

Ability to assess outcomes in real time – as they develop or at pre-determined time points – thus temporal relation can be established

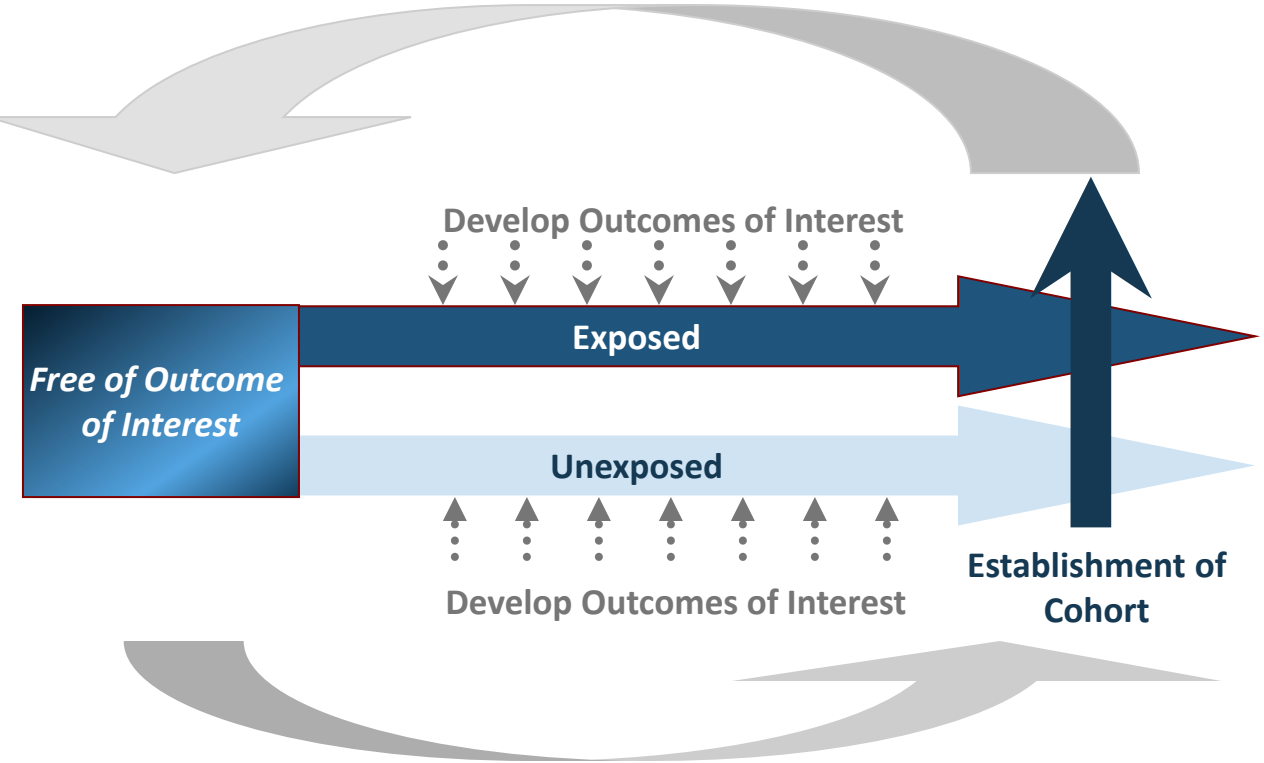
Outcomes can be validated or objectively measured

Large sample size

Long and complete follow-up of cohort members

High cost

Retrospective Cohort Studies



Advantages

Can be **completed in a more timely fashion** than prospective cohort studies

Less expensive

If a cohort exposed 30y ago can be identified, then the appropriate latent period will already have passed and the epidemiologic questions of interest can be addressed solely on the basis of historical information.

One need not wait for decades to observe the eventual effects of the suspected carcinogen, as would be necessary in a prospective cohort.

Measuring Exposure

- **Questionnaires**
  - smoking history, alcohol consumption, occupation
- **Physical examination**
  - Blood pressure, height, weight
- **Laboratory tests**
  - Blood levels of specific exposures
- **Medical Records**
  - Therapeutic exposures
- **Biospecimens**
  - Omic exposures
- **Neighborhood exposures**
  - SDOH

Measurement of exposure

- **Measurement may be difficult, when exposure takes place many years before initiation of study**
  - Errors of measurement are likely to bias the apparent magnitude of association
- **Where extensive information on exposure happens to have been collected, the quality of the data may rival that which would be collected in a prospective cohort study**

Measuring Outcomes

Measurement of Disease

- **Procedures for disease identification should be identical for exposed and unexposed**
  - Population-based disease/ death registries
  - Questionnaires
  - Physician records
  - Physical examinations and lab tests

Diagnostic Criteria

- **Diagnostic Criteria should be established before the study begins**
  - Pathology reports
  - Echocardiograms/ PFTs
  - Radiologic reports
  - Questionnaire reports

Measurement of vital status

- **National Death Index (NDI) Plus**
  - Date of death, cause of death

Non-participants – Selection bias

- **Non-participants will almost always differ from participants**
  - Selection bias
- **Affects generalizability of results**
  - Prevalence of exposures or incidence of disease may be lower or higher than in entire group
- **Affects measures of association**
  - Depends on size of group omitted from the study
  - Specific characteristics of the group omitted
- **Imperative that everything possible be done to include nearly everyone into the study**

Characteristics of Participants vs. non-participants

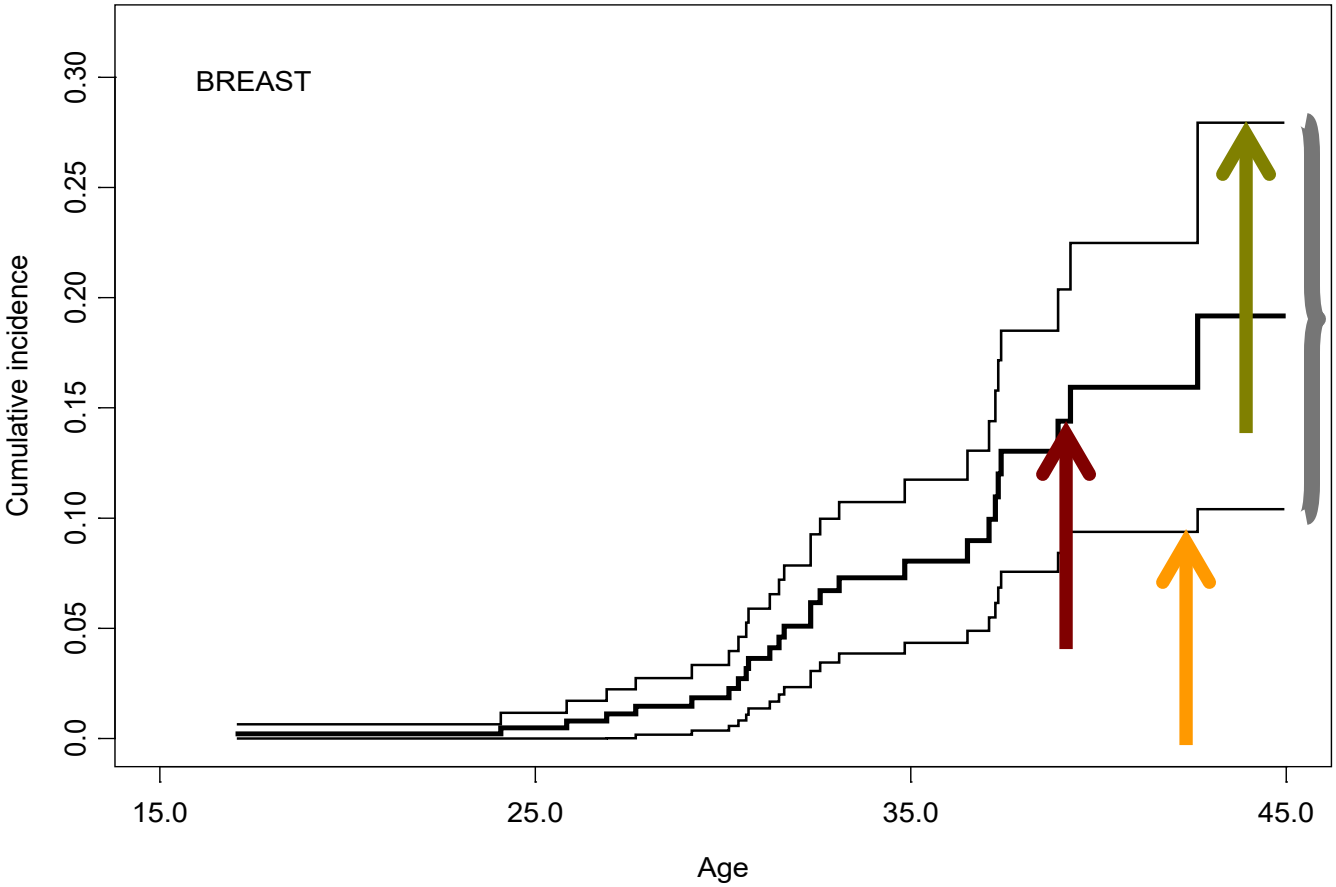
Participation rate:	71%
Participants more likely to be	
– Females	78% vs. 62%
– non-Hispanic white	77 % vs. 67 %
– Older	
➢ at study	median 46.3 vs. 44.1y
– Shorter length of follow-up	median 6.5 vs. 7.6y
No difference in participation rates by	
– Initial cancer diagnosis	
– Participating site	

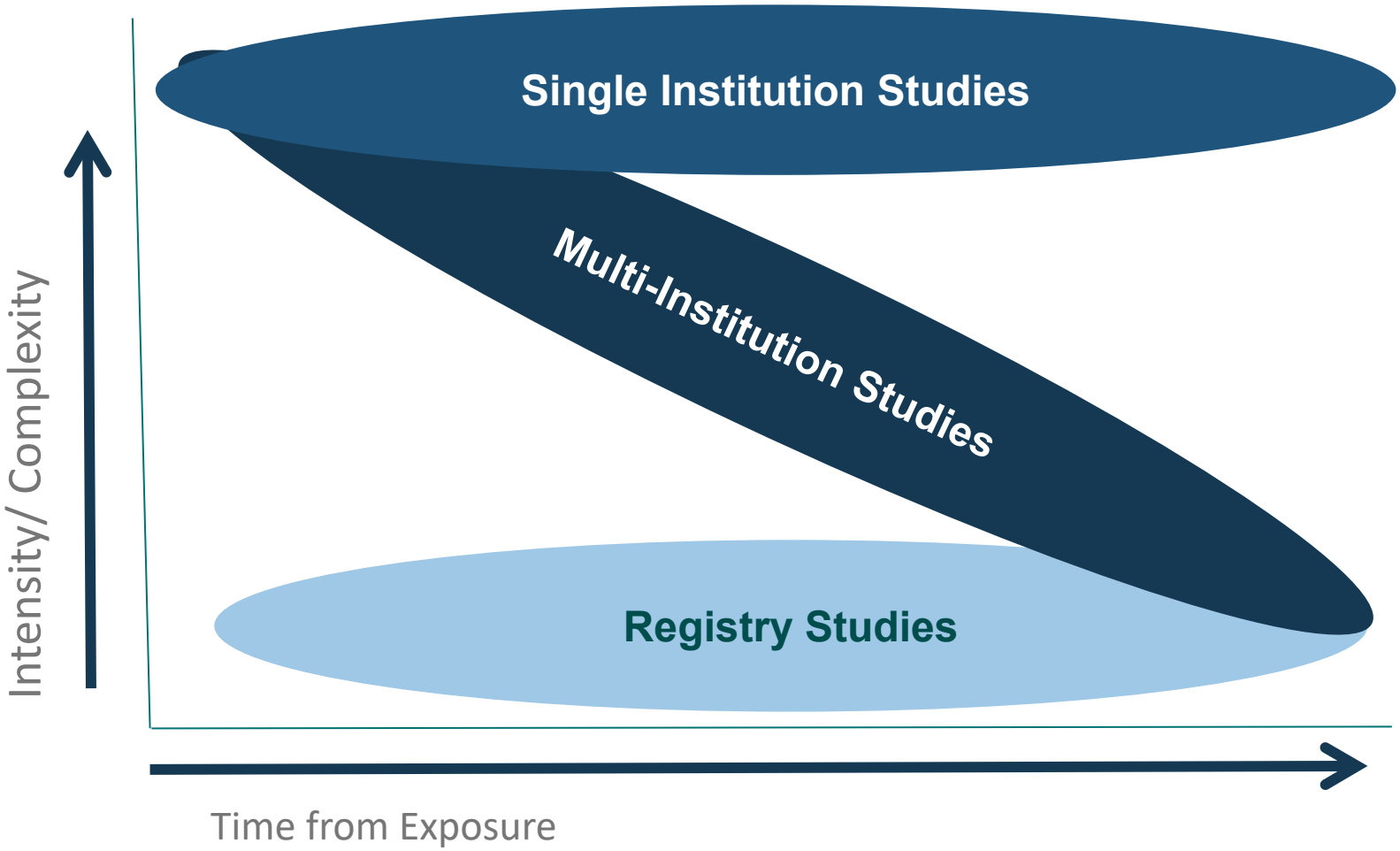
Methods for tracing

- **Keeping track of large populations in the highly mobile US culture is a challenge**
  - Large amount of energy needed for follow-up and track
- **Follow-up requires individualized tracing efforts**
  - Ensure that differential losses to follow-up do not bias results
  - Hold losses to an absolute minimum
- **Tracing Resources**
  - Accurint databases or other person-locating service (web-based)
  - Medicare/Medicaid databases
  - National Death Index
  - National Change of Address database from USPS
  - Population-based cancer registries
  - Others

Loss to Follow-up

- Selection bias
  - Precision of the outcomes – long-term
    - Population-based studies
      - Magnitude of risk
    - Clinical trials
      - overall/ event-free survival


BREAST
Cumulative incidence
0.0
0.05
0.10
0.15
0.20
0.25
0.30
15.0
25.0
35.0
45.0
Age


Single Institution Studies
Multi-Institution Studies
Registry Studies
Intensity/ Complexity
Time from Exposure

Registry-based studies

Strengths

- Availability of very large numbers of patients
- Good for studying rare conditions or diseases
- Good for studying diseases with long latency
- Possible to address prevalence/incidence within specific parameters
- Control groups or ‘matching’ can be performed
- Allows examination of multiple risk factors
- Useful first step in establishing an association

Limitations

- Loss to follow-up
  - Variability across sites
- Lack of many pre-existing disease or sociodemographic factors or health risk behaviors
- Dependence on participating sites in providing data
  - Variability in data points collected by site/ over time
- Lack of associated biospecimens
- Difficulty assigning ‘causative’ associations

Single institution vs. multi-institutional vs. registry

	Single Institution	Multi-institution consortia	Registry
Patient numbers	+	+++	+++++++++
Diversity of population/ exposures	+	+++	++++++++
Rare conditions	+	++	+++++
Long latency	+++	+++	+++++
Control/matching	+++	+++	+++
Multiple risk factors	+++	+++	+++++++
Long term follow up (intensive)	++++++	++++	+++
Pre-diagnosis exposures	++++++	++++	++
Consistency in data points over time	+++++	+++	++
Associated biospecimens	++++++	++++	++

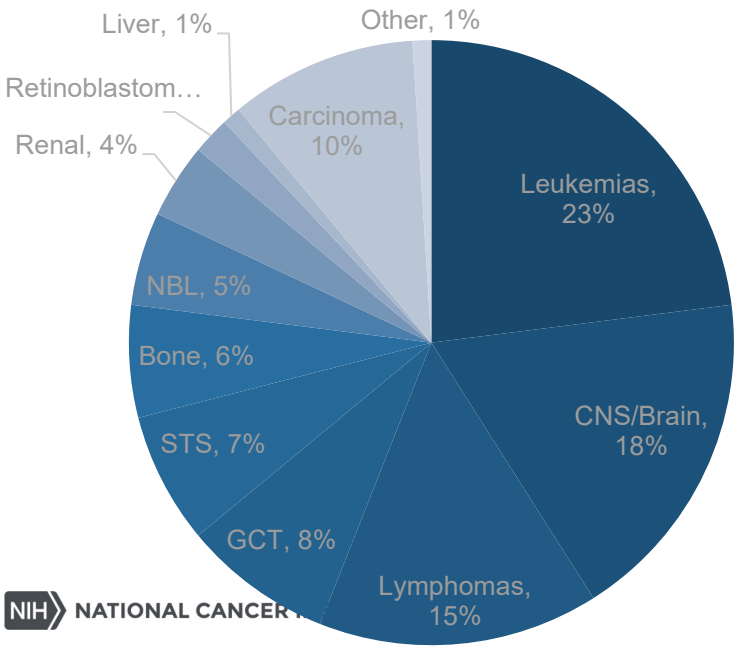
Challenges with Pediatric Oncology Cohort studies

Childhood cancer

15,000 cases of childhood cancer diagnosed each year

In comparison – 229,000 lung cancers diagnosed each year

Not a single cancer



Five year survival rates can range from almost 0% for cancers such as DIPG, to as high as 90% for ALL

Current cohorts

- **CCSS**
  - Multi-institutional
  - Therapeutic exposures (medical records)
  - Radiation dosimetry
  - Large sample
  - Available sequencing data for a sub-cohort
  - Diagnosed 1970-1999
  - Self-report of outcomes
  - 5y survivors

- **SJLIFE**
  - Single institutional
  - Therapeutic exposures (medical records)
  - Radiation dosimetry
  - Large sample
  - Available sequencing data for a sub-cohort
  - Diagnosed 1962-2012
  - Clinically measured cohorts
  - 5y survivors

Challenges with current cohort studies

- Selection bias
- Differential attrition
- Survival bias (sp. applicable to biospecimens)
- Self-report of outcomes
- Unable to evaluate early events
- Not able to harness the study questions asked in randomized clinical trials

ALTE05N1
Specific Aims

1. To **maintain regular, lifetime contact** with patients to obtain current contact information and self-reported health status.

2. To **locate patients who are lost-to-follow-up** for select protocols closed prior to creation of the LTFC.

3. To **provide current contact information/ health status back to the SDC**, which is accessible to the treating COG member institutions.

ALTE05N1
Eligibility

- Enrollment on **active frontline COG therapeutic trial** for a primary malignancy OR
- History of enrollment on pre-identified **COG (or legacy group) therapeutic or non-therapeutic protocol** targeted for long-term follow-up.

ALTE05N1

LTFC – Contact Information (at registration)

- Patient's full name
- Patient's date of birth

- Patient's address, telephone number, and e-mail address
- Patient's gender
- Patient's race/ethnicity
- Patient's place of birth

- Patient's language preference
- Patient's father's and mother's full name, address, telephone number, social security number (optional), date of birth, language preference, email address
- Name, address, telephone number, and e-mail address of a family member (preferably grandparent) or close friend who can be contacted when patient contact is not successful

Legacy Protocols

1. ALTE15N2 - LEAHRN
2. ALTE16C1 – chemotherapy and spermatogenesis
3. CCG 5942 – HL – with or without chest radiation
4. POG 9425/ 9426 – HL – with or without cardioprotectant
5. POG 9404 – T cell ALL and lymphoblastic NHL – cardioprotectant
6. POG 9754 – osteosarcoma - cardioprotectant
7. COG AHOD0331 – HL – dose-intensive treatment
8. CCG A9961 – average risk medulloblastoma – RT with randomization to CCNU/CPM

If epidemiologic studies are
well designed and conducted,
and if data are
properly analyzed and interpreted,
they can provide
strong and reliable evidence
on which to base policy and
ultimately decisions affecting
the health of the general public.

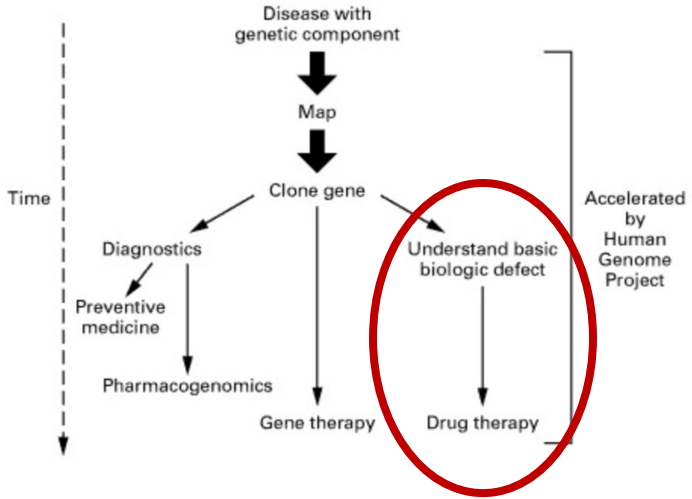
Options for new cohorts: Building on the MCI

Sarah E. S. Leary, MD, MS

Professor of Pediatrics, Seattle Children's

March 24, 2023

If we could only understand cancer biology….



nature
International journal of science

Article | Open Access | Published: 25 July 2012

Subgroup-specific structural variation across 1,000 medulloblastoma genomes

Paul A. Northcott, David J. H. Shih […] Michael D. Taylor

Nature **488**, 49–56 (02 August 2012) | Download Citation

nature genetics

Article | Published: 14 April 2013

Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas

the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project

Nature Genetics **45**, 602–612 (2013)

Cancer Cell Log in

ARTICLE | VOLUME 32, ISSUE 4, P520-537.E5, OCTOBER 09, 2017

Integrated Molecular Meta-Analysis of 1,000 Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma

Alan Mackay • Anna Burford • Diana Carvalho • ... Michael Baudis • Adam Resnick • Chris Jones 44

Show all authors • Show footnotes

Open Access • Published: September 28, 2017 • DOI: https://doi.org/10.1016/j.ccell.2017.08.017 • Check for updates

Figure 1. Steps Involved in the Genetic Revolution in Medicine. 1999 Francis Collins *NEJM*

Roles and Perspectives:

- Children's Oncology Group CNS committee Vice-Chair
- Children's Brain Tumor Network, Clinical Data Working Group Lead
- INSPiRE, Executive Committee Co-Chair

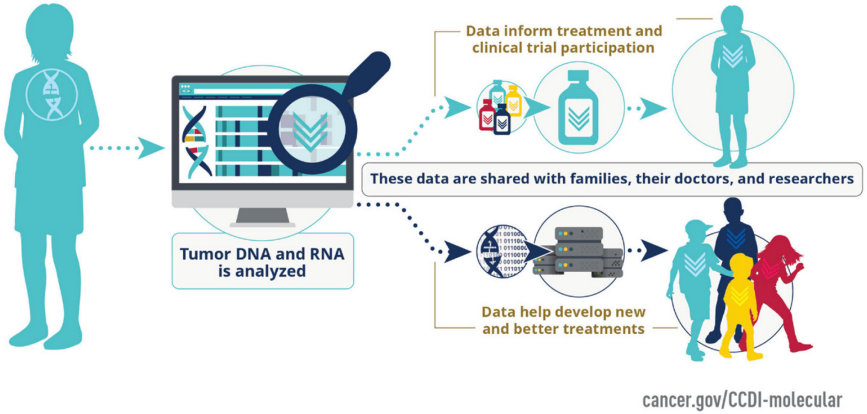
CHILDREN'S ONCOLOGY GROUP

Children's Brain Tumor Network
Until every child is cured

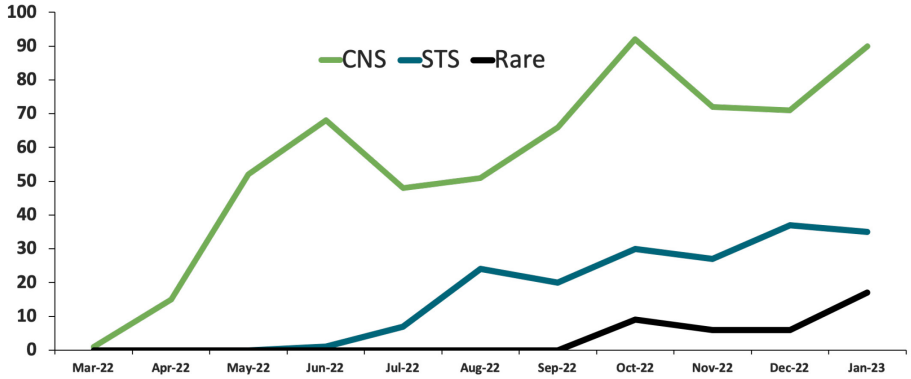
The INSPiRE consortium, established in September 2021, brings together all types of central nervous system tumors in a comprehensive data resource. Researchers involved in INSPiRE represent the following groups: the Children's Oncology Group (COG), the Pacific Pediatric Neuro-Oncology Consortium (PNOC), the International DIPG/DMG Registry (IDIPGR), the European Society for Pediatric Oncology (SIOPE), the Rare Brain Tumor Consortium (RBTC) and the Children's Brain Tumor Network (CBTN).

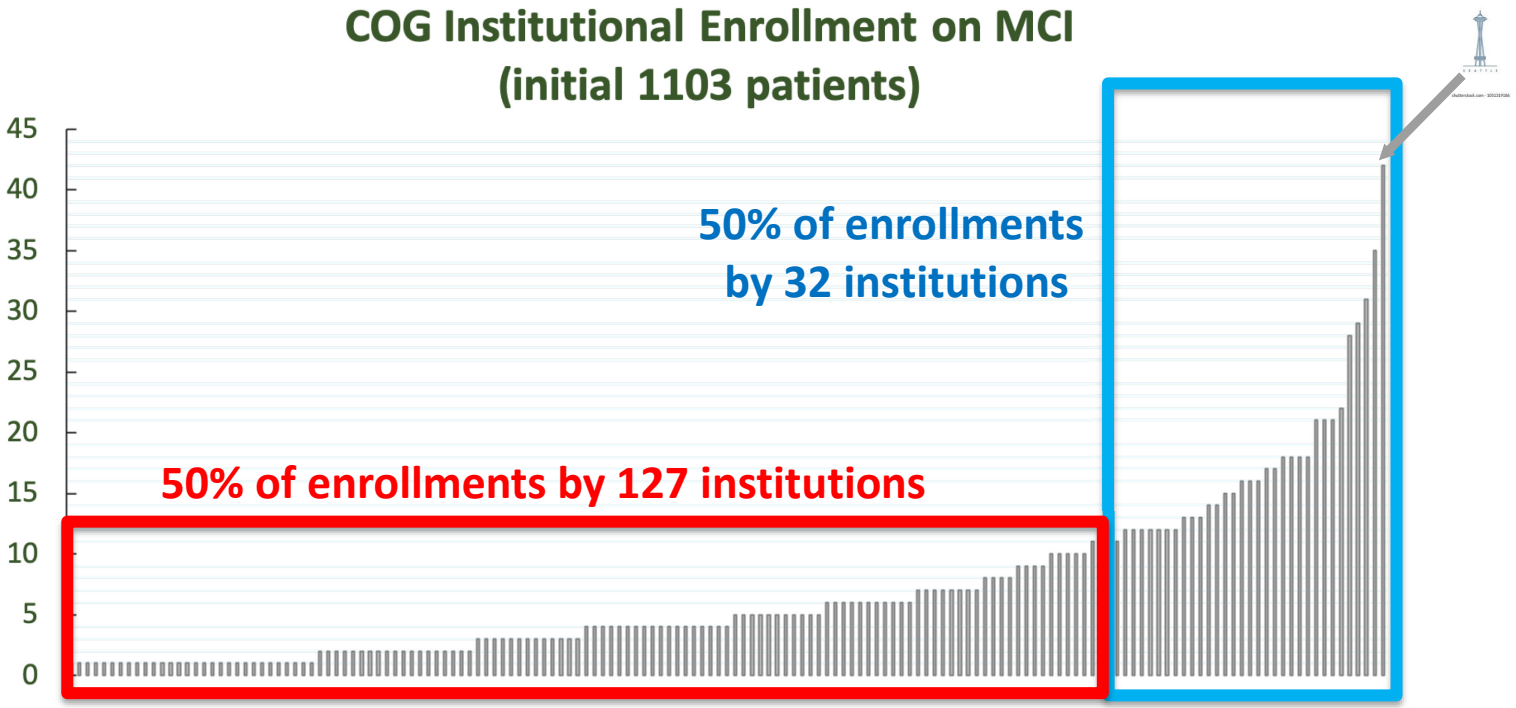
Happy Birthday, MCI!

CCDI Molecular Characterization Initiative?

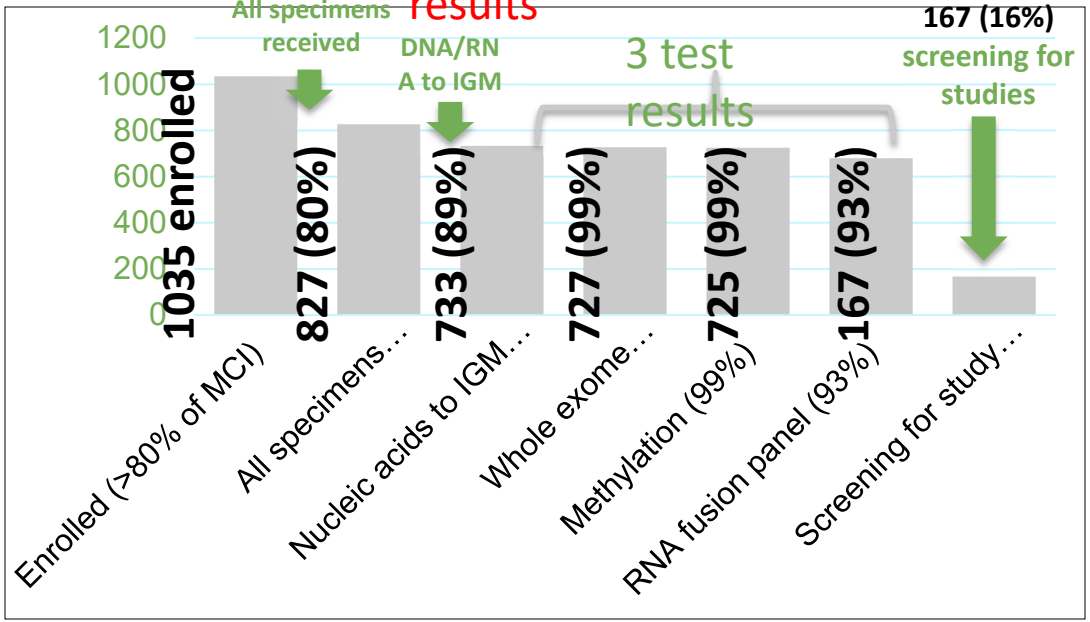


Specimens for Sequencing (monthly)




COG Institutional Enrollment on MCI
(initial 1103 patients)
45
40
35
30
25
20
15
10
5
0
50% of enrollments
by 32 institutions
50% of enrollments by 127 institutions

MCI Progress in CNS Tumors in the first year

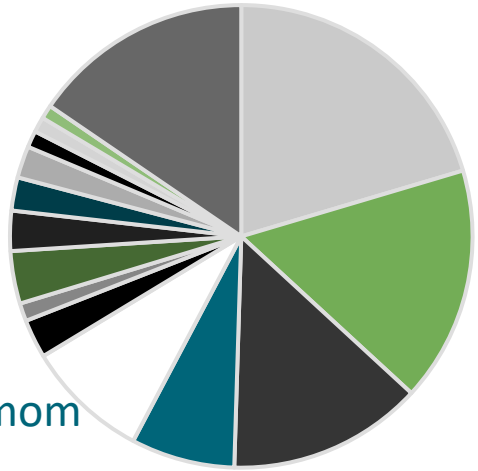


CNS Tumor Diagnoses in the MCI: First 1000 cases

Other < 1%

Medulloblastoma

Rare tumors



Pilocytic astroctyoma

Ependymoma

High grade glioma

- Medulloblastoma
- Pilocytic astrocytoma
- High-grade glioma
- Glioma, unspecified
- Ependymoma
- ATRT
- "PNET"
- Ganglioglioma
- Choroid plexus tumors

Who is not currently included in the MCI

- Children who were diagnosed prior to the launch of the MCI
- Children with tumors at relapse
- Children with subsequent malignancy
- Diseases outside of CNS, STS, RAR

What data is not included in the MCI

- Treatment for children who are not on therapeutic clinical trials
- Functional and Patient-reported outcomes

Children's Brain Tumor Network
Until every child is cured

Accelerating childhood brain tumor research to faster cures

Over 30 types of pediatric brain and spinal cord tumor clinical and molecular data, biospecimens, and cell-lines are available at no cost to academic researchers. Our open science model has shortened research time by up to 20 years.

CBTN

Data Science

CBTN by the Numbers

Brain and CNS tumors are the most common cause of disease related death in children aged 0–19 years in the U.S. and across the globe, with approximately 412,000 children and young adults living with a brain tumor each year.

4842	32	66783	400 Tb	307
Participants	Institutions	Samples	Data Size	Projects

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM Data Resource Center

PedcBioPortal for Integrated Childhood Cancer Genomics

CAVATICA

Kids First Data Resource Portal

The Gabriella Miller Kids First Data Resource Portal provides access to more than 8,000 samples of childhood cancer and structural birth defects genomic data. The Kids First Data Resource Portal s…

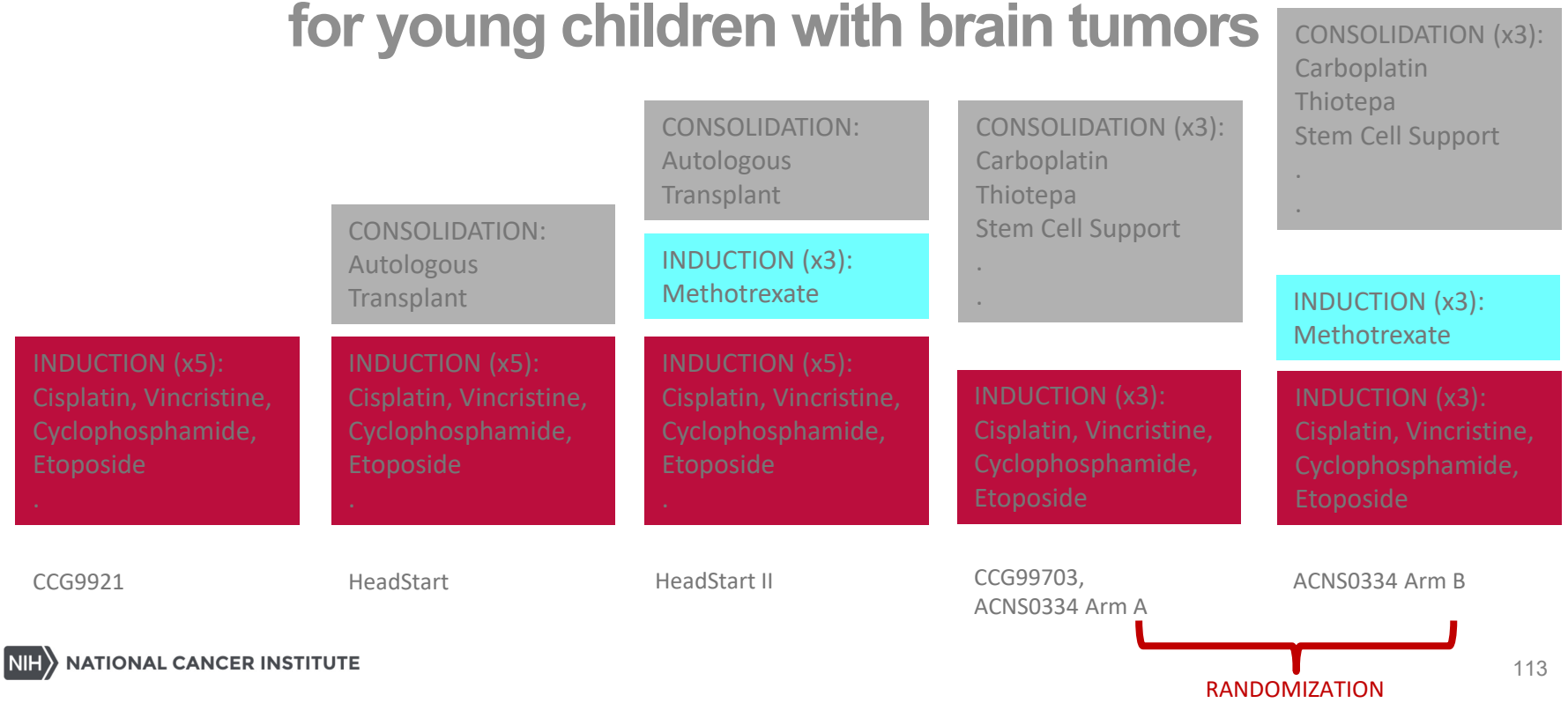
PedcBioPortal

The PedcBioPortal is an open-access resource for childhood cancer genomics which enables users to visualize, analyze and also download large-scale cancer genomics data sets. These data allow resear…

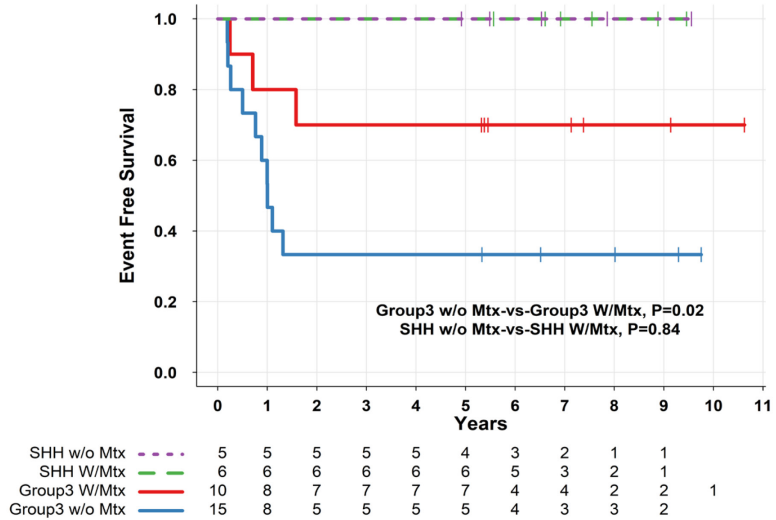
Cavatica

Cavatica is a cloud-based portal environment developed to securely store, share and analyze large volumes of pediatric brain tumor genomic data to accelerate collaboration in research. Named for the …

Twenty years of clinical trials of radiation avoidance for young children with brain tumors



ACNS0334 Trial evaluating efficacy of Methotrexate



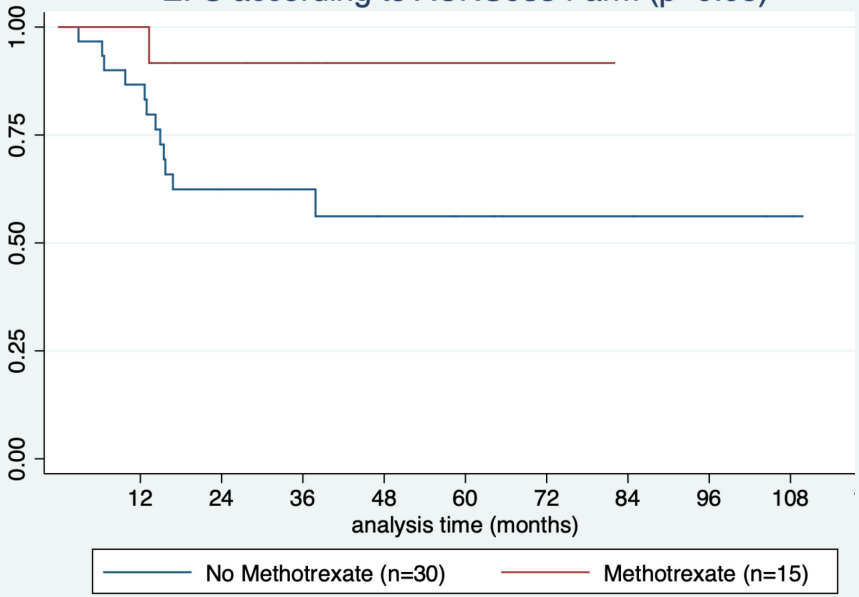
SHH (n=11)

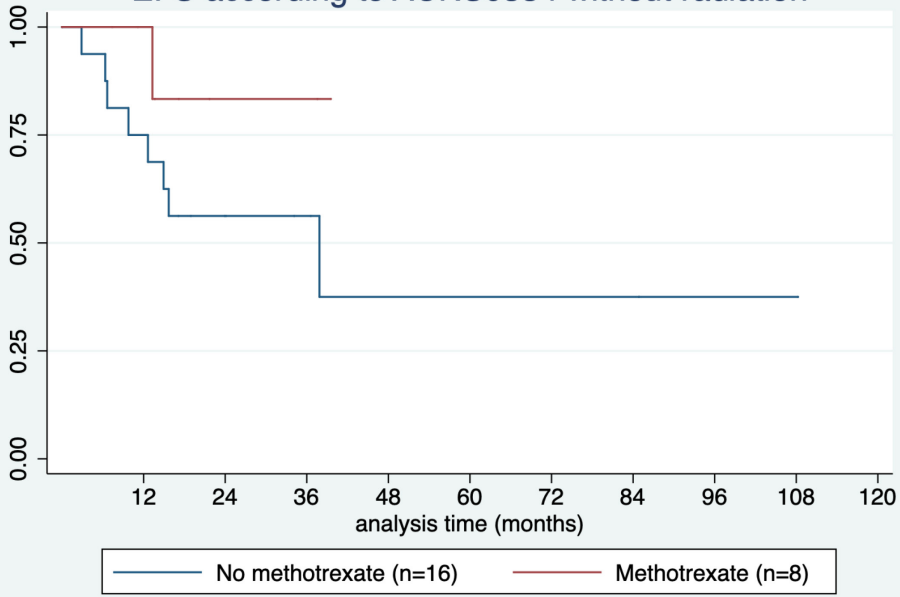
Group 3 Arm B with methotrexate (n=10)

Group 3 Arm A without methotrexate (n=15)

Majewski et al *Presented at ASCO Annual Meeting* 2020

CBTN Young Child Medulloblastoma Cohort
ACNS0334-like analysis



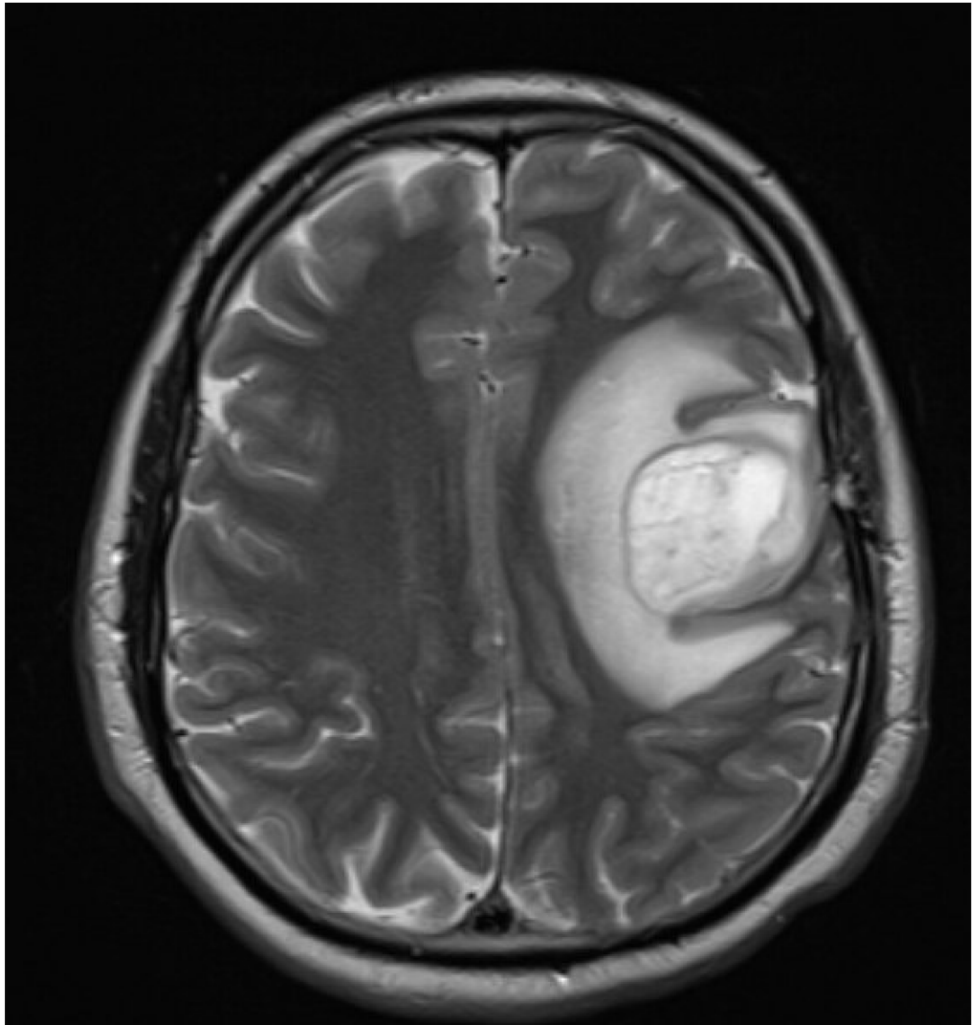


Paradigm shift:
In 2017, the FDA approved a drug (PD-1 inhibitor) for solid tumors with mismatch repair deficiency or microsatellite instability.

Agnostic to histology

Included children

WHO List of Essential Medicines



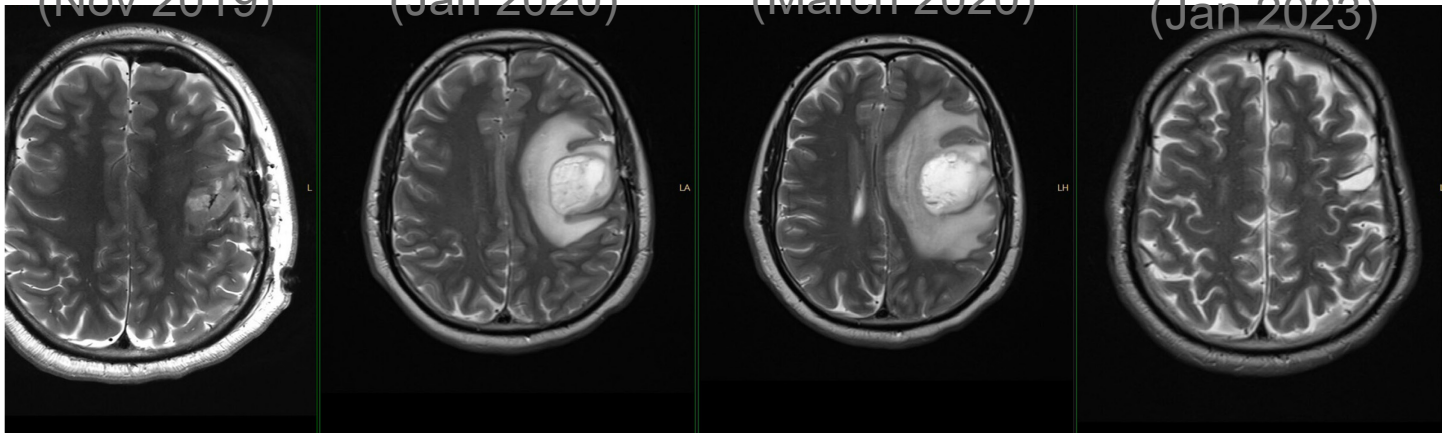
“GBM” with complete response to immune therapy (checkpoint inhibition)

Post op residual (Nov 2019)

During Radiation (Jan 2020)

Start of maintenance (March 2020)

Off therapy maintained CR (Jan 2023)



Reasons this patient's data is not in the CCDI (yet):

- Diagnosis: subsequent malignancy
- Medical History: leukemia and allogeneic transplant
- Medical condition: other chronic health problems
- Language: parents not English speaking
- Age: young adult

Childhood Cancer Data Initiative (CCDI) Participant Index

Cross-referencing Disparate Data

NIH NATIONAL CANCER INSTITUTE

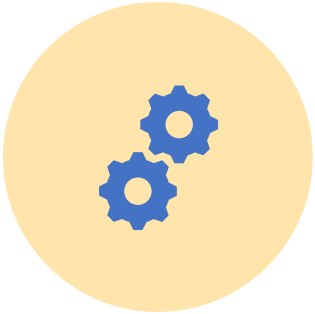
Subhashini Jagu, Ph.D.

CCDI Symposium

3/24/2023

Outline

WHY DO WE NEED A PARTICIPANT INDEX?



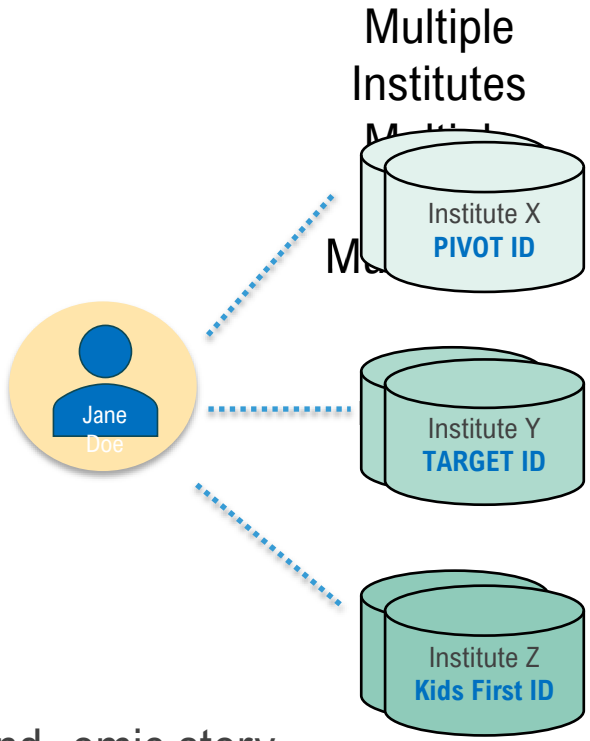
HOW DOES THIS SYSTEM WORK?

WHAT CAN YOU DO FOR THE PARTICIPANT INDEX?

What are the challenges to cross-reference data?

Data cannot be cross-referenced by wider investigator community

- Childhood cancer data generated are often under different:
  - Protocols, studies, data types, repositories, institutions, times
  - Labeled with different research IDs
    - unique to their own entities



Power of the data are limited by fragmented clinical and -omic story

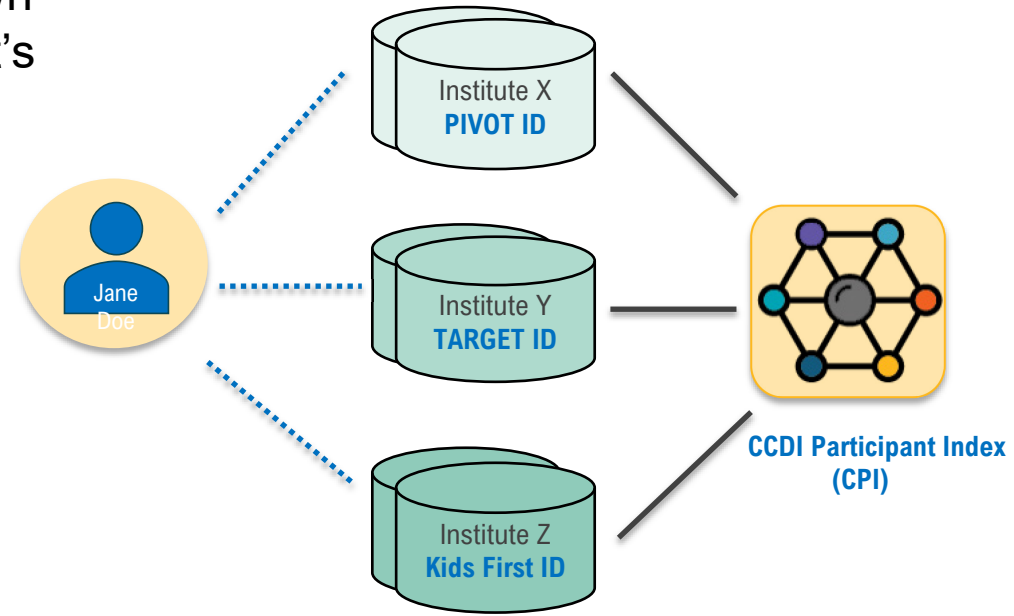
Why do we need a CCDI Participant Index?

Its critical to connect data from multiple sources to:

- Address multifaceted research questions
- Understand the disease
- Develop new therapies
- Advance existing treatments

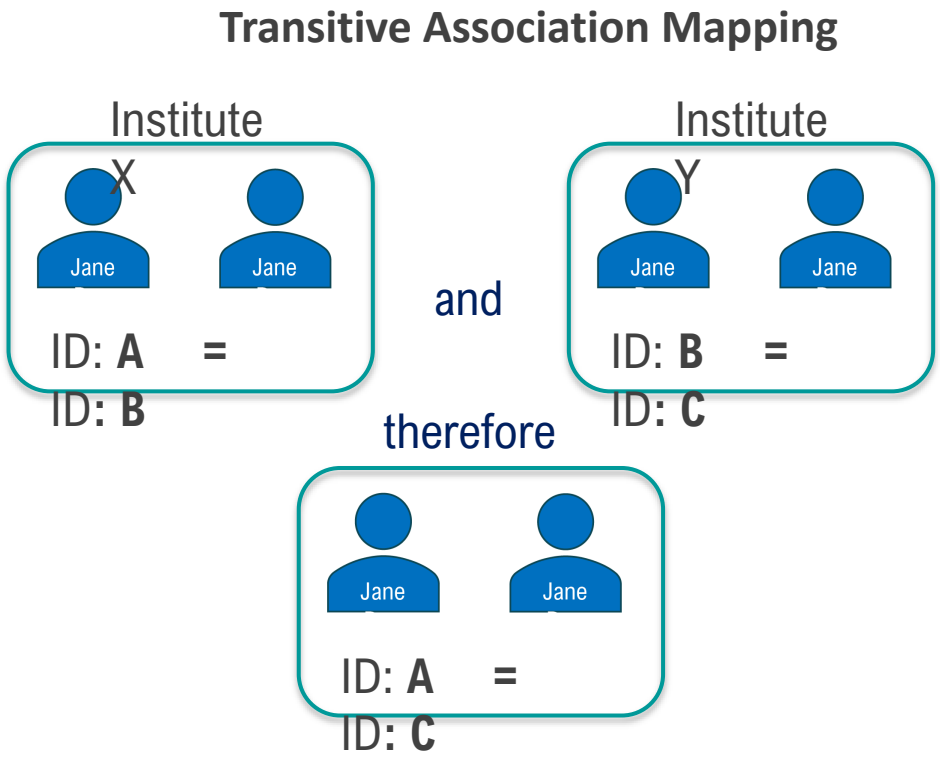
How can we help solve this problem?

- Collect and cross-reference all known IDs attached to the same participant's data in different:
  - Institutes
  - Primary data sources
  - Studies



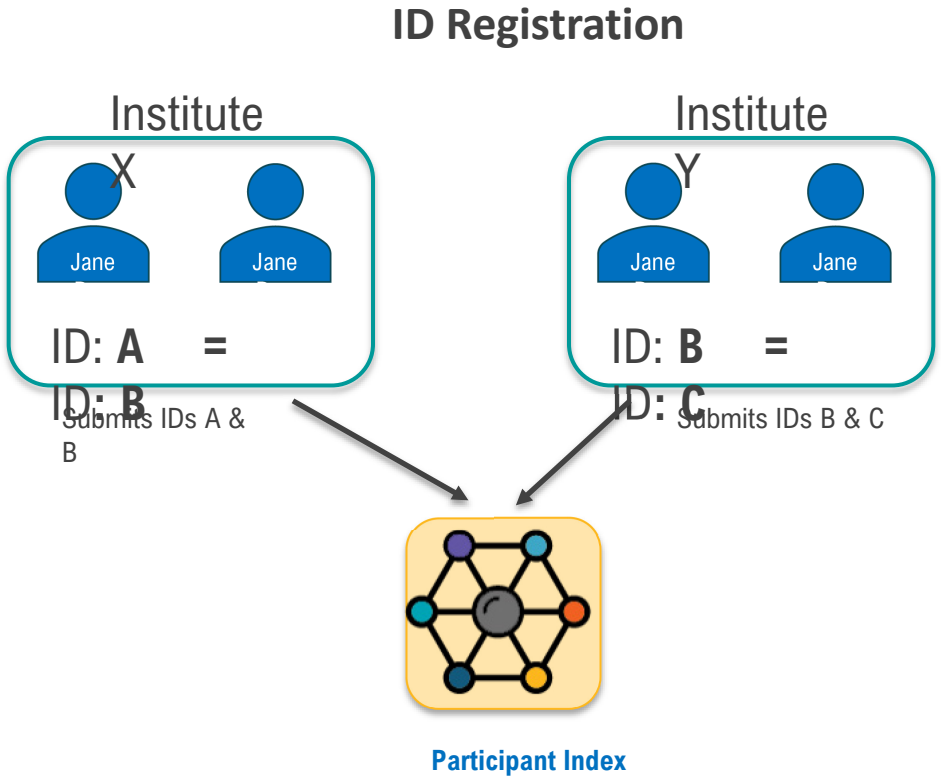
How will Participant Index enable data integration?

- CCDI Participant Index (CPI) will be a digital ID mapping and matching reference service to the CCDI Data Ecosystem
  - Primary resource controls data access
- Leverages direct and transitive associations between known identifiers that represent the same person
- Two broad operationally separate categories:
  - ID registration and management
  - ID query and retrieval



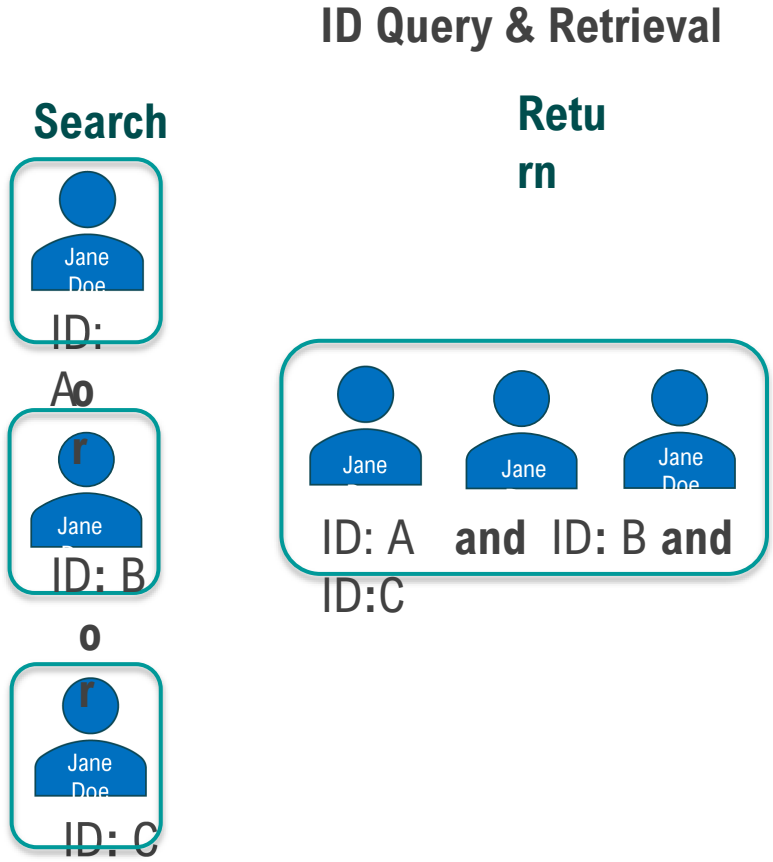
Registration of IDs into the CPI

- Institutions supply pairs of IDs known to represent the same person are authorized as ID registrants
  - Publicly shareable research IDs
  - PII IDs using Privacy-Preserving Record Linkage (PPRL) software
- These ID pairs are loaded into the CPI resulting in directly and transitively mapped IDs

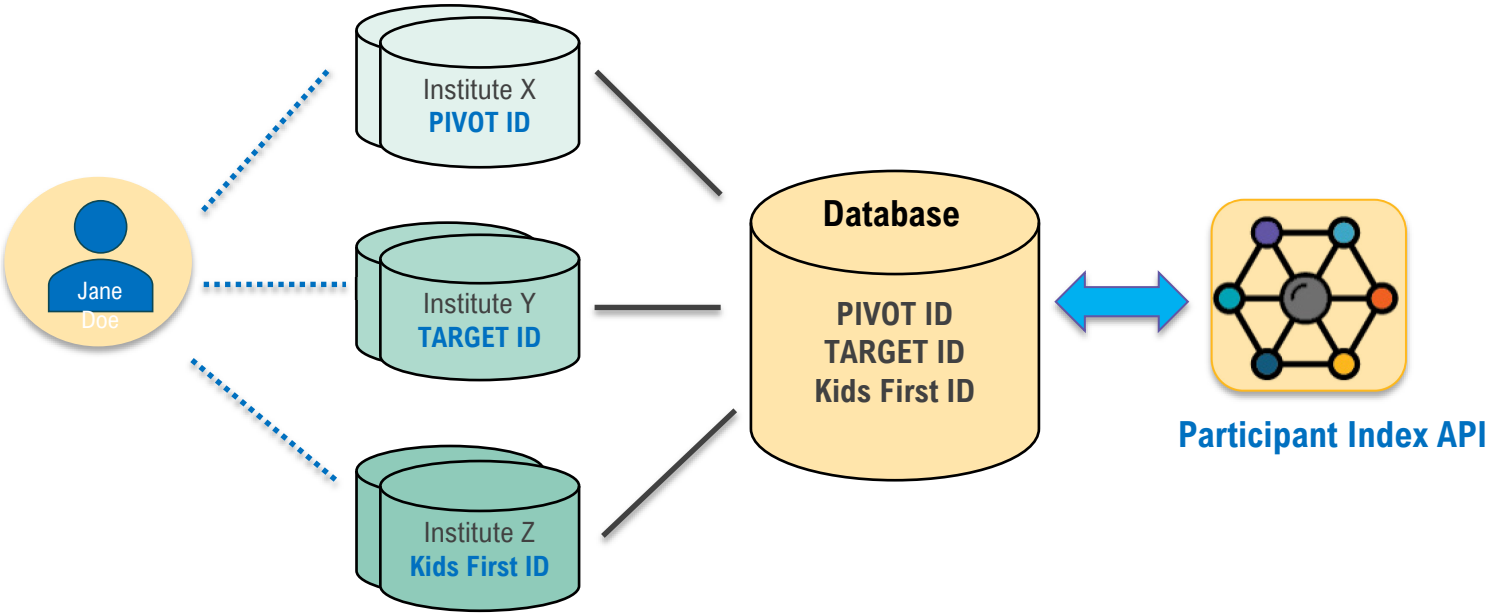


ID Query and Retrieval

- Query the CPI with a known ID
- The CPI returns all deidentified publicly shareable research IDs
  - If the ID is associated directly or transitively with other known IDs



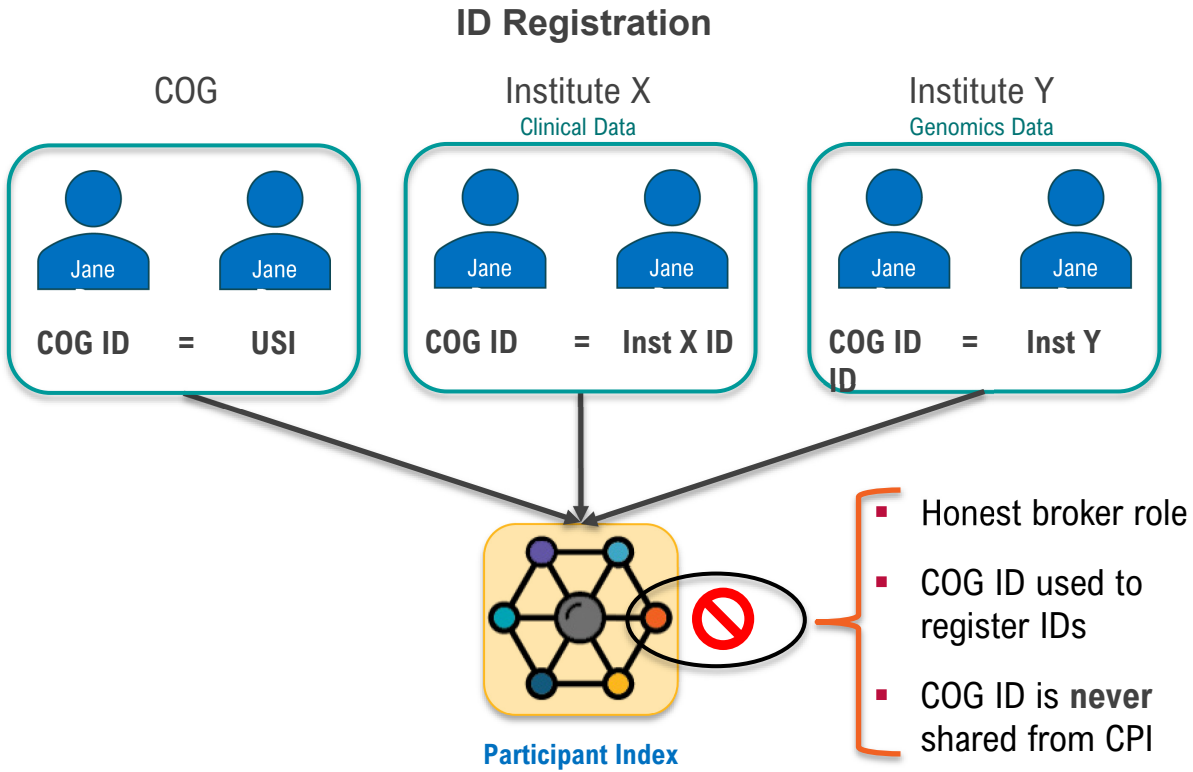
Phase 1: Collect and Cross-reference with Public Shareable Research IDs



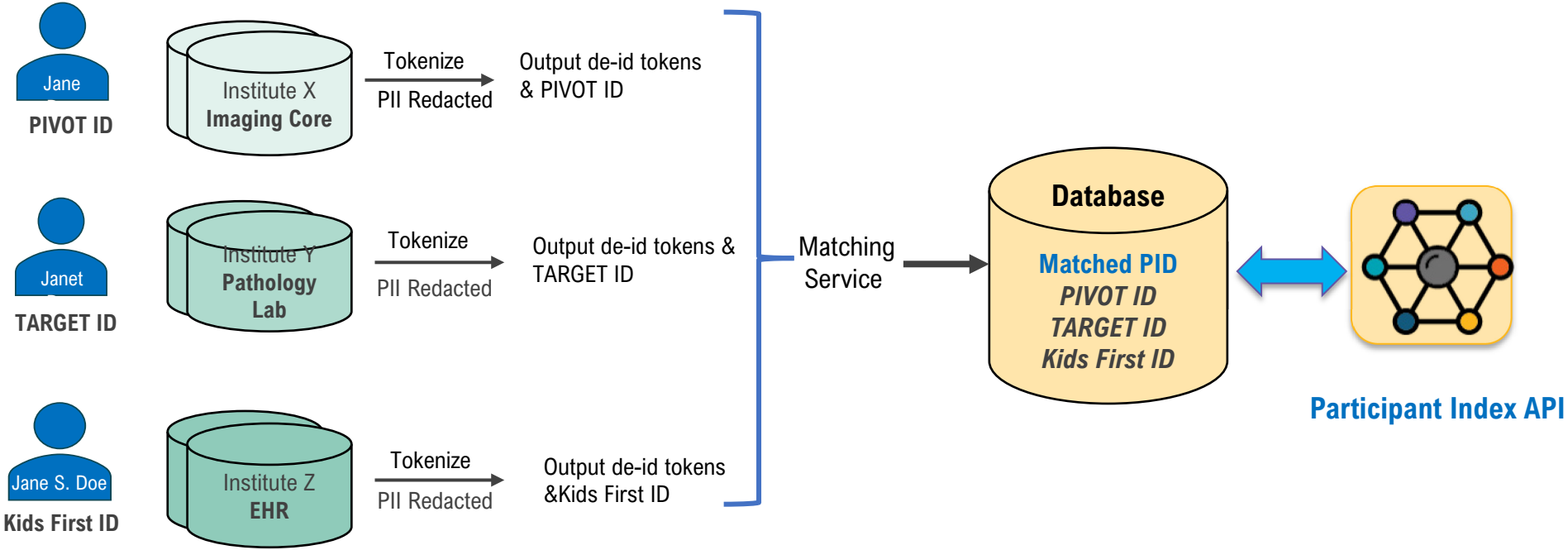
Registration of COG IDs and Research IDs into the CPI

COG ID is the most ubiquitous ID in the pediatric Cancers

- Most institutions have COG IDs along with the local research IDs
- COG ID is only used for mapping and never shared

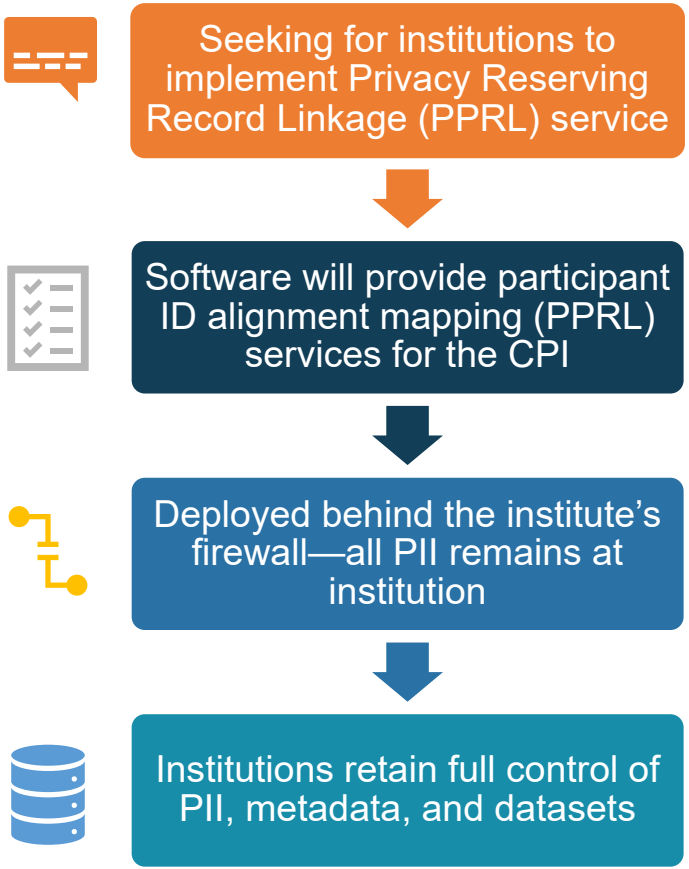


Phase 2: Collect and Cross-reference with Hashed PII IDs



Tokenization is a process of replacing sensitive data with random numbers

Call for Volunteers



Contact Information

- Ask questions through CCDI Mailbox: NCIChildhoodCancerDataInitiative@mail.nih.gov
- Learn more on the CCDI Website: https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative
- Subscribe to CCDI's RSS feed: https://public.govdelivery.com/accounts/USNIHNCI/subscriber/new?topic_id=USNIHNCI_223

Panel Discussion: Cohorts for Clinical and Translational Research

Stephen Chanock, MD

Greg Armstrong, MD, MSCE

Lia Gore, MD

Philip J. Lupo, PhD, MPH

Subhashini Jagu, PhD

Sarah Leary, MD, MS

Ann Ramer, MPH

Childhood Cancer Data Initiative

Suzanne George, MD

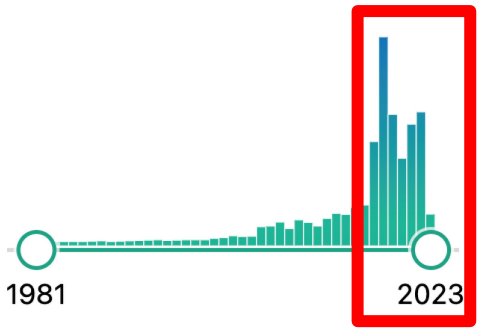
Scott Hammond, MD

March 24, 2023

Most consent platforms are simple consents

- Capture patient preferences in a specific context
- Increasingly, these consents are obtained by digital means

- Clinical trial participation – therapeutic, interventional
- Clinical research consent – database, cohorts
- Data-sharing consents – within/outside an organization for clinical records, specimen sharing, genomic data sharing



Digital consents are ubiquitous throughout many parts of our lives

<u>Intersection between consumer and patient – health data generated all the time</u>

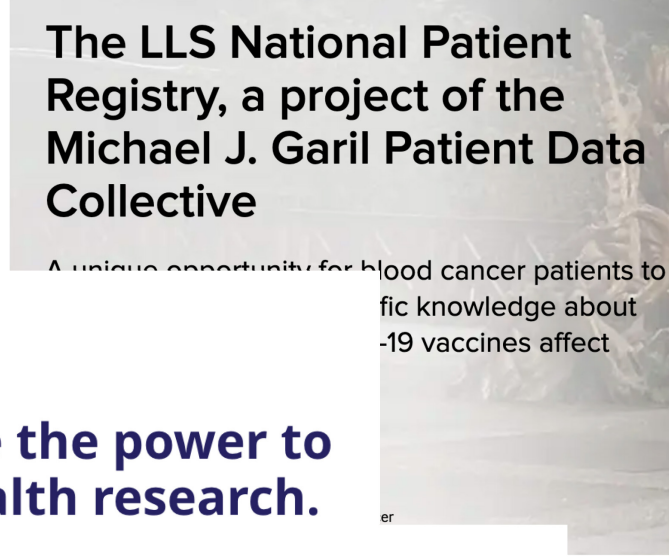
Apple

- Tech services – apps, wearables
- Pharmacy discounts
- Supermarket discounts

WHOLE FOODS MARKET

Digital consent platforms are increasingly part of the traditional medical research experience

- E-consenting for standard of care
- E-consenting for Institution based clinical trials
- Direct to patient online registries



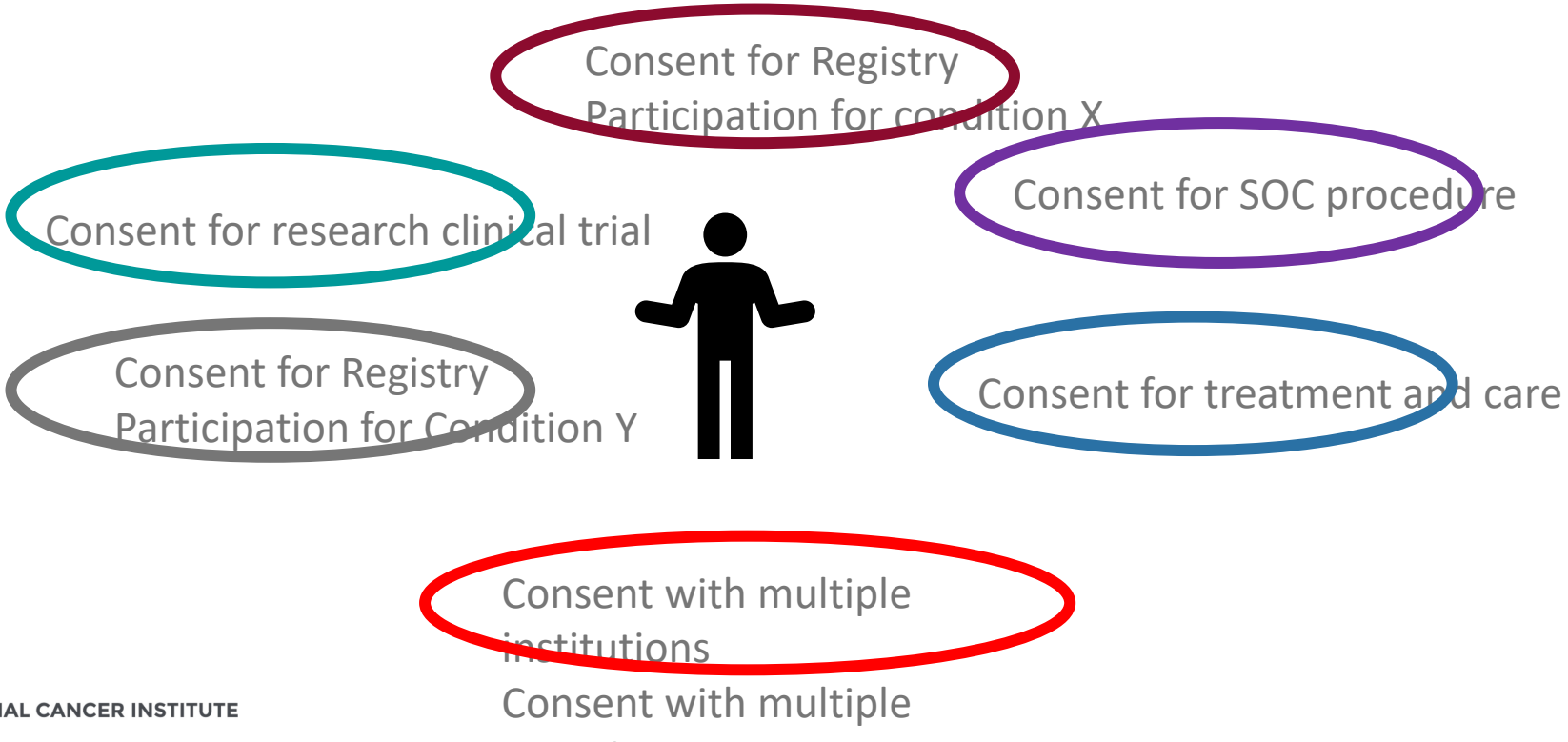
All of Us RESEARCH PROGRAM

You have the power to drive health research.

Without you, it

Count Me In

This approach leads to multiple siloed consents and siloed data – which impacts patients and research



Although a patient consent may be captured digitally...

- *it may not be easily modifiable*
- *it may not readily allow for use of the consented information*
  (ex: broad consent to record release from EHR for research, but how to get those records)

cting patient intent to allow continuous control over data and data usage

This can lead to either over-usage or under-usage depending on the context

pep™
Alliance Participant Engagement Portal

Alliance Participant Engagement Portal

- Aims to embed consent within a consent
- Patients consent to a master clinical trials
- Given an option to engage a secondary platform which allows for future research, serial individualized surveys, queries and **clinical trial updates, followup over time**
- Alliance version - many others are doing similar and have been over time

MITRE

R INSTITUTE

pep™
Alliance Participant Engagement Portal

- Bidirectional communication at key touch points throughout trial
- Unique participant surveys connected to a public facing website
- Future – tool that allows participants to know how their data has been used

Detection (MCED) Biobank Study

You're a hero! You're helping us fight cancer. Thank you for being part of the Alliance MCED Biobank Study.

Click on a topic button to get started:

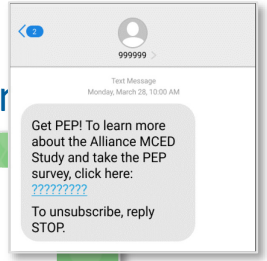
Purpose

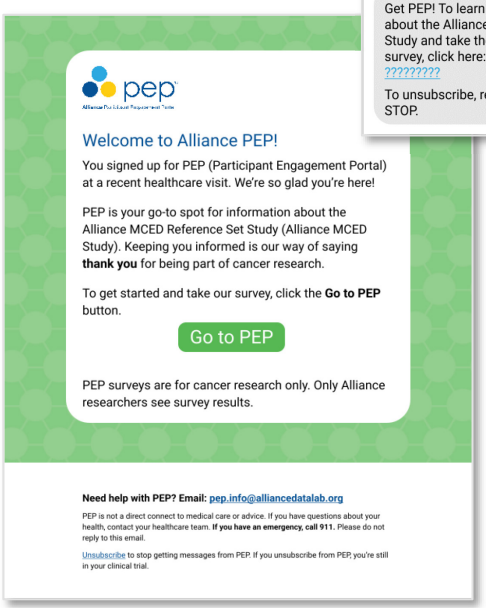
Participants

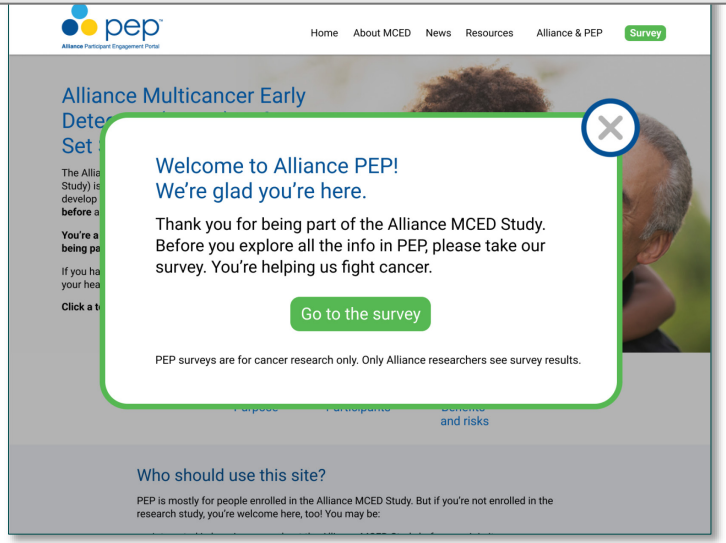
Benefits and

Participant signs IRB approved consent for main trial and then is given the option to provide contact information for PEP enrollment

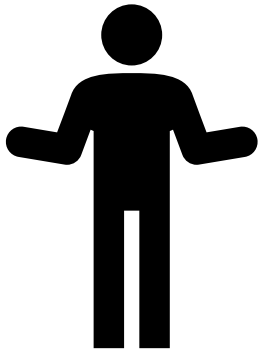
1. Participant gets a **welcome text or email** with a lir







2. Link goes to the **welcome pop-up**. Participant clicks the **go-to button** to link to the **PEP Surveys page**.



What are the opportunities to improve?

- What if someone changes their mind over time?
  - Consent YES/NO –the only option?
  - Consent to subsets –tracking in an accessible environment
- What if someone wants to extend consent to more than one entity but not to others?
- How can this be addressed in a patient centered way?

Ideally, consent utilizes standards for efficiency and multi-operability while achieving a patient centered approach

standards *for the data elements themselves*

standards *for the technical process that handles these standardized elements*

Computable Consent

- Allows for a **decision service** to parse and process patient preferences
- Allows for an **API** to query/response for consent decisions/requests for access
- Allows for **patients** to change preferences over time and provenance is maintained

Source: ONC LEAP Computable Consent Project; San Diego Health Connect, September 2021

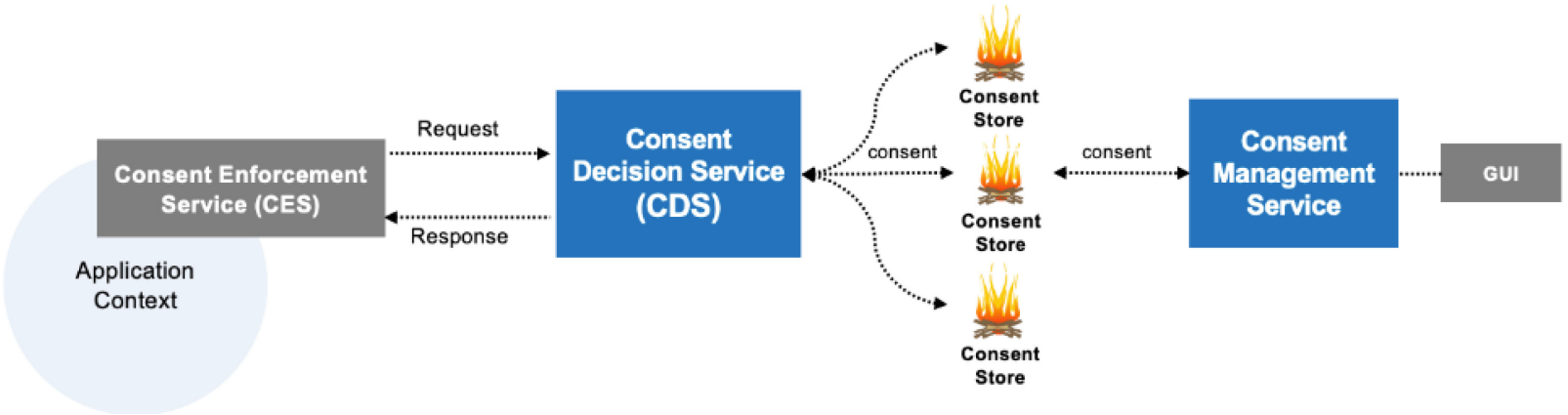
Goals

Patient Consents that are:

- Interoperable
  - FHIR Consent resource and a standard access API
  - An aggregation service to retrieve applicable consent from all sources
- Computable
  - A consent decision service to parse and process patient consents
  - An API for query/response about consent decisions
- Applicable
  - Different Types of Consent
    - Privacy, Research, Treatment, Advanced Health Directive
  - Proof of concept for various use-cases
    - HL7v2 Exchange, eHealth Exchange, Direct Exchange, FHIR (embedded and

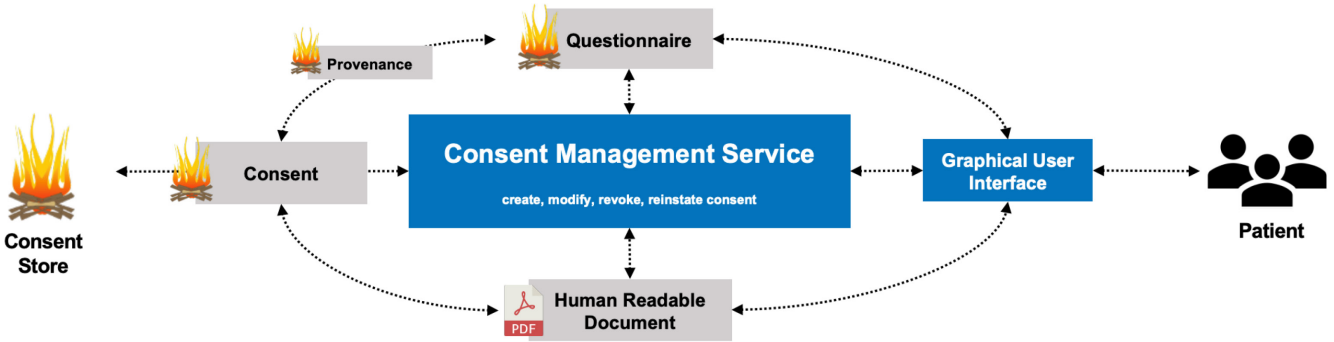
ONC LEAP Consent Project – High Level Architecture

- ONC LEAP Patient Consent Project Mohammad Jafari, Ph.D. ONC LEAP Consent Project Director, San Diego Health Connect (SDHC)



Consent Management Service

A service for patients to create, modify, revoke, and reinstate consents.



ONC LEAP Consent Project

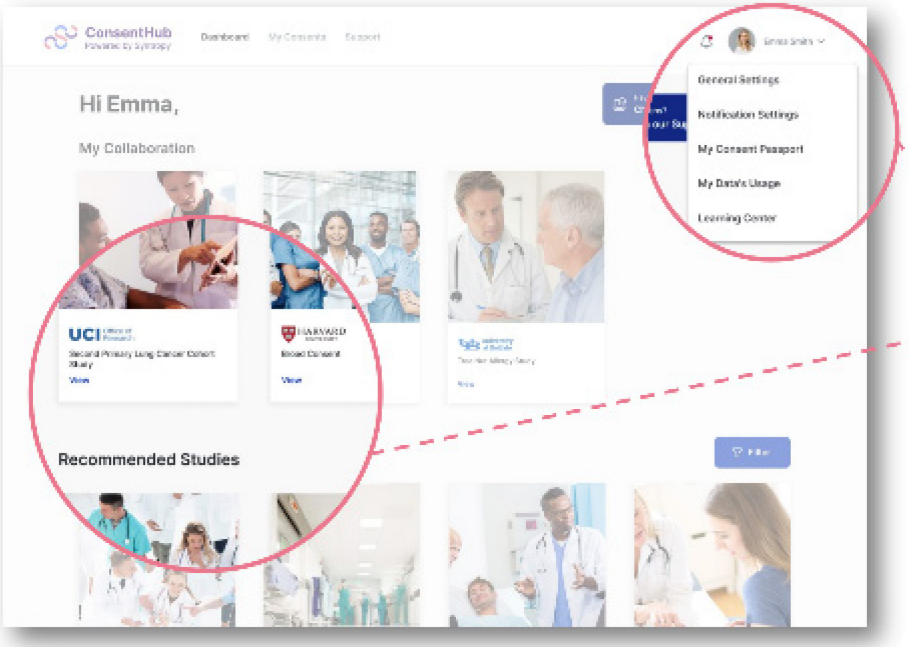
- ONC LEAP Patient Consent Project
Mohammad Jafari, Ph.D. ONC LEAP Consent Project Director, San Diego Health Connect (SDHC)

ConsentHub
Powered by Syntropy

- Centralized patient interface
- Visualizes relationships *across different entities*
- Delivers patient options for research participation based on

HIGHLIGHTED SOLUTION DETAILS

ConsentHub Dashboard



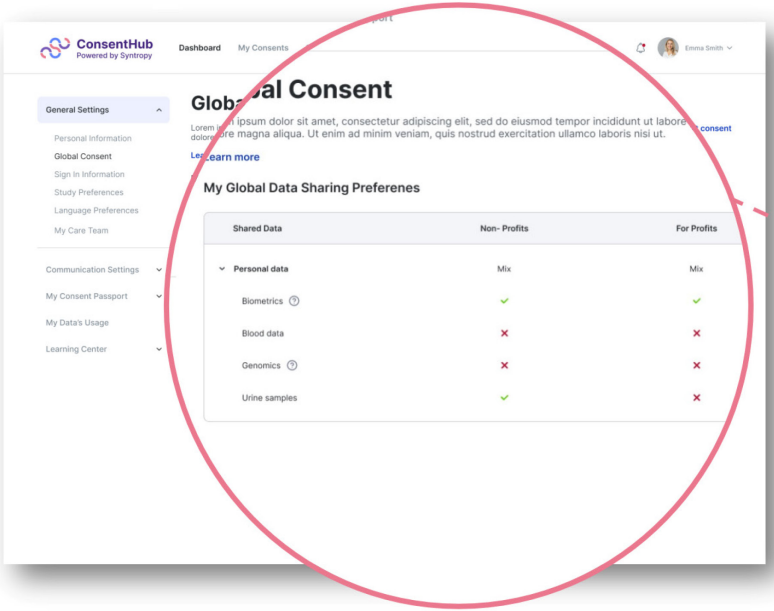
From the ConsentHub dashboard, patients can easily see their active and existing relationships with participating institutions. They manually filter or scroll through system recommended studies (based on their Study Preferences) as well as toggle to their profile settings.

EPAM CONTINUUM

HIGHLIGHTED SOLUTION DETAILS

Updating Global Consent Preferences

- Preferences for what data are used
- Preferences for what entity uses specific dat



Global Consent is the concept of breaking down a single consent record into what we call "consent features" to allow a patient to control their data sharing preferences at a more granular level.

EPAM CONTINUUM

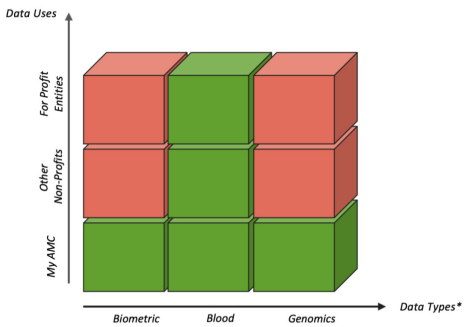
*Data Types are illustrative, demonstrative in nature

ConsentHub
Powered by Syntropy

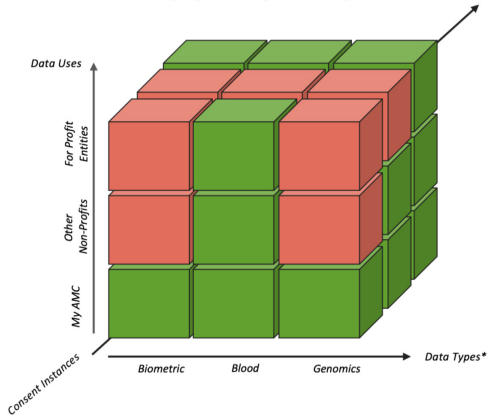
HIGHLIGHTED SOLUTION DETAILS

Computable Consent – Introducing Granularity in Data Sharing Preferences

*Introducing granular, computable consent would allow a patient to not only **understand** but **control the data type and use they are comfortable sharing** with significantly finer detail.*



*Then, with this power to read computable consent, we can provide historical views into their data sharing consent history and **empower the patient to control these preferences from a single location.***



EPAM CONTINUUM

*Data Types are illustrative, demonstrative in nature

A *computable consent* is a representation of patient consent in which privacy preferences are encoded in the form of machine-readable rules.

Such rules can be processed by a decision engine to adjudicate whether the consent permits a specific given activity, such as sharing the patient information with a requester, or enrolling the patient in a research project.

- Consents need to meet people where they are in their own health data journey **and adapt to changes in that journey**

- Allow patients to control data use over time with multiple entities

- Ensuring the patient data is used in a way that is always consistent with patient consent/control

Extracting Clinical/Demographic Data from EHRs: Manual Approaches and Expectations from AI

Tamara P. Miller, MD, MSCE

Emory University/Children's Healthcare of Atlanta

NIH NATIONAL CANCER INSTITUTE

March 24, 2023

Overview

- Challenges with electronic health record (EHR) data
- Landscape of oncology EHR data extraction
  - Single institution efforts
  - Extraction across different installations
  - Post-extraction processing of data
  - FHIR
  - CCDI/EHR pilots
- Lessons learned from EHR data extraction

Challenges with Electronic Health Record (EHR) Data

- EHR data are collected for clinical purposes as part of routine patient care
  - Documentation useful for clinical purposes but perhaps not sufficient/understandable for research
- EHR data input and storage are not standardized
  - Multiple data types: Structured, unstructured, semi-structured
  - Data storage varies by hospital based on EHR system build
- Data standards variably implemented
  - Minimal Common Oncology Data Elements (mCODE) developed in 2018 by American Society of Clinical Oncology to create computable oncology data standards
    - Not all variables needed for research or patient care included (Wang, *JCO CCI,* 2022), especially in pediatrics

Challenges with EHR Data and Potential for Improvement

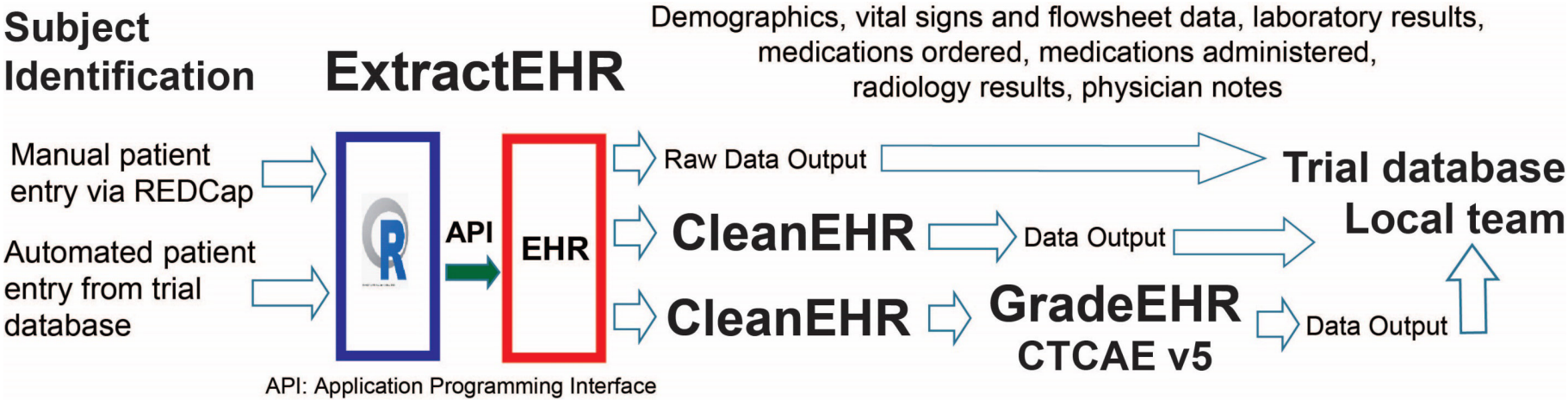
- Creates challenges for manual and automated data collection
  - Vast majority of childhood cancer data collection is performed manually
    - Studies have shown inaccuracy in data manually collected (Miller, *JCO*, 2016)
  - Automated EHR data extraction has potential to improve current methods
    - More efficient
    - Standardizes collection
    - Can overcome some underlying EHR data challenges by coding extraction

Extraction of EHR Data

- Multiple single institution platforms implemented for extraction of specified data elements
  - Clinical Data Collector (CDC) extracted and mined real-world data to identify patients with metastatic renal cell carcinoma and classify outcomes (van Laar*, Clin Pharm Therapy,* 2020)
  - Algorithm to combine structured billing records with processed narrative text to identify colorectal cancer at a single institution had high accuracy (Zu, *AMIA Annual Symposium Proceedings,* 2011)
  - Integration of institutional cancer registry and EHR data to develop a childhood cancer survivorship cohort (Noyd, *PBC*, 2021)
- Multi-institutional extraction platforms crucial for broader improvement of childhood cancer data collection
  - e.g. ExtractEHR

ExtractEHR

- R package that extracts data from EHR data warehouse



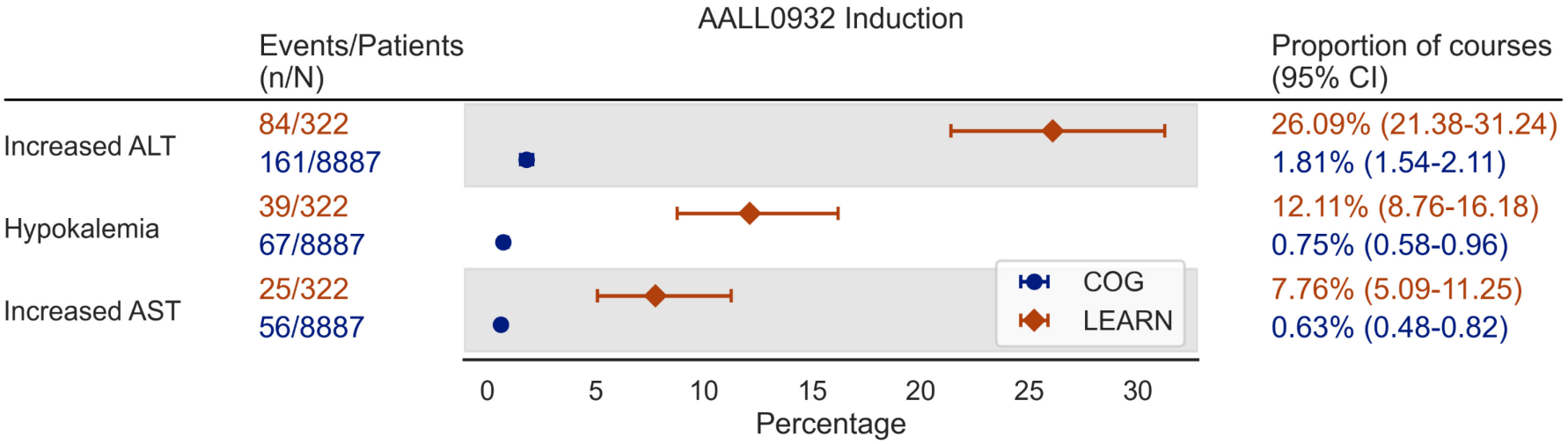
ExtractEHR Implementation

- Implemented at 4 institutions to develop a network for clinical research using real-world data
  - Includes Epic and Cerner sites
  - 3 additional sites in process of implementation ExtractEHR (2 Epic, 1 Cerner)
- Extracted data require processing for use (CleanEHR, GradeEHR)
  - Cleaning, processing and grading performed centrally for consistency
- Extracted, processed data can be used to create analytic grade datasets to answer clinical questions that currently cannot use clinical trial data to answer
  - e.g. Accurate rates of laboratory adverse events (AEs) experienced during treatment

ExtractEHR Use Case: Laboratory Adverse Events

- Data from 3 large pediatric hospitals to identify laboratory AEs
  - Acquired using ExtractEHR
  - Processed and cleaned to remove false positives using CleanEHR
  - Graded using GradeEHR
- Highly accurate compared to gold standard physician chart abstraction
  - 0.2% of lab AEs missed, 0.5% of lab AEs incorrect (Miller, *BJH*, 2017)
- Describe granular rates of laboratory AEs by chemotherapy course
  - Laboratory AEs inaccurately captured in Children's Oncology Group (COG) trial data
  - e.g. Daily neutrophil counts collected describe duration of neutropenia after chemotherapy (Miller, *PBC,* 2020)

Automated Ascertainment is More Comprehensive than Manual Ascertainment



LEARN data ascertained using ExtractEHR

Miller, *BJH*, 2017,
Miller, *Lancet Haematol*, 2022

Extraction of EHR Data: HL7 FHIR

- Fast Healthcare Interoperability Resources (FHIR) can access EHR data across EHR vendors
  - Created by Health Level Seven International (HL7) health care standards organization for exchange of EHR data across platforms
  - EHR vendor must support FHIR
  - Extracted data need processing for use
    - FHIR facilitates data extraction but does not normalize data post-extraction
    - Requires post-extraction data processing for data to be usable
  - Has not been widely tested in pediatric oncology

CCDI ExtractEHR Pilots

- PEPN21EHR/PBTC-N15 (NCT05020951)
  - Open at 7 sites across COG and Pediatric Brain Tumor Consortium (PBTC)
    - Epic and Cerner EHRs included
  - Goal: Automatically extract EHR data and directly import into trial electronic data capture system (Medidata Rave) across institutions
    - Demonstrating feasibility in retrospective patients treated on early phase trials
    - Plans to implement into prospective trials
  - Successful uploads at multiple hospitals for both COG and PBTC
  - Permits comprehensive and accurate data capture to assess tolerability

CCDI ExtractEHR Pilots

- Surveillance, Epidemiology, and End Results (SEER)
  - Extracting raw data for transfer to SEER registry
    - Hospital encounters, laboratory test results, medications, procedures, vital signs, radiology reports, pathology reports, oncology clinical notes
    - Limiting to oncology-related data elements
  - In process to transfer data from Children's Healthcare of Atlanta to Georgia Cancer Registry
  - Plans to extend to other registries

Lessons Learned from EHR Data Extraction: Data Structure

- EHR systems vary by institution
  - Epic and Cerner are most common and cover >60% of large children's hospitals
  - Range of other systems in use, including homegrown systems
- Data storage structure varies by EHR vendor and between individual site implementations
  - Capabilities of technical terms vary
    - Familiarity with underlying data structure and ability to comprehensively identify desired data elements is variable
- Extracted EHR data are not ready for immediate use
  - Collected for clinical use so require careful processing with clinician guidance

Lessons Learned from EHR Data Extraction: Mapping

- Installation requires mapping to identify data elements of interest
  - Requires time and clinician involvement to be comprehensive and specific
  - Same EHR system may have customized components at individual sites
- Once mapped, code can be used repeatedly for different use cases
  - Changes only required when underlying EHR system updates
    - e.g. new laboratory system implemented where test names change
- Extraction of all data elements with planned post-processing to identify desired elements alleviates part of mapping process
  - Cleaning/processing packages such as CleanEHR and GradeEHR can standardize post-extraction cleaning across sites

Lessons Learned from EHR Data Extraction: Unstructured Data

- Unstructured and semi-structured data vary by site (notes, radiology, pathology)
- Natural Language Processing (NLP) can process extracted unstructured data
  - Requires successful identification of negation terms and training of the model
- NLP may not be 100% accurate, but can reduce number of charts requiring manual review to identify an outcome of interest
  - Reduced EHR charts needed to identify breast cancer recurrence by 90% (Carrell, *Am J Epi*, 2014)
  - Reduced chemotherapy courses needing manual review to identify typhlitis by 96% (Miller, *JCO CCI*, 2022)
- Could be improved by improved approaches to standardizing documentation

EHR Data, Informed Consent and Data Sharing

- Informed Consent
  - EHR data typically included in consents for clinical trials
  - Cancer surveillance does not require informed consent
  - EHR data can be included in retrospective IRB-approved research
  - Some institutions may require specific consent for EHR data or specific components
    - e.g. genomic data
- De-identification processes may be required for data sharing
  - More challenging with free text/unstructured data

Conclusions

- EHR data can be leveraged to widely capture demographic and clinical data
  - Multiple single and multi-institution processes implemented to accurately extract EHR data
  - Currently some outcomes can be fully automated, e.g. laboratory AEs
- EHR data extraction has challenges that require trained and/or centralized teams to help manage
  - Guiding data extraction
  - Processing extracted data for use
- Automated EHR data extraction permits development of comprehensive, granular real-world datasets that can improve knowledge in pediatric oncology

Children's Oncology Group Clinical Data Release

Implications For Linkage To Genomic And Other Datasets And Discovery

Douglas S. Hawkins, MD

Group Chair, Children's Oncology Group

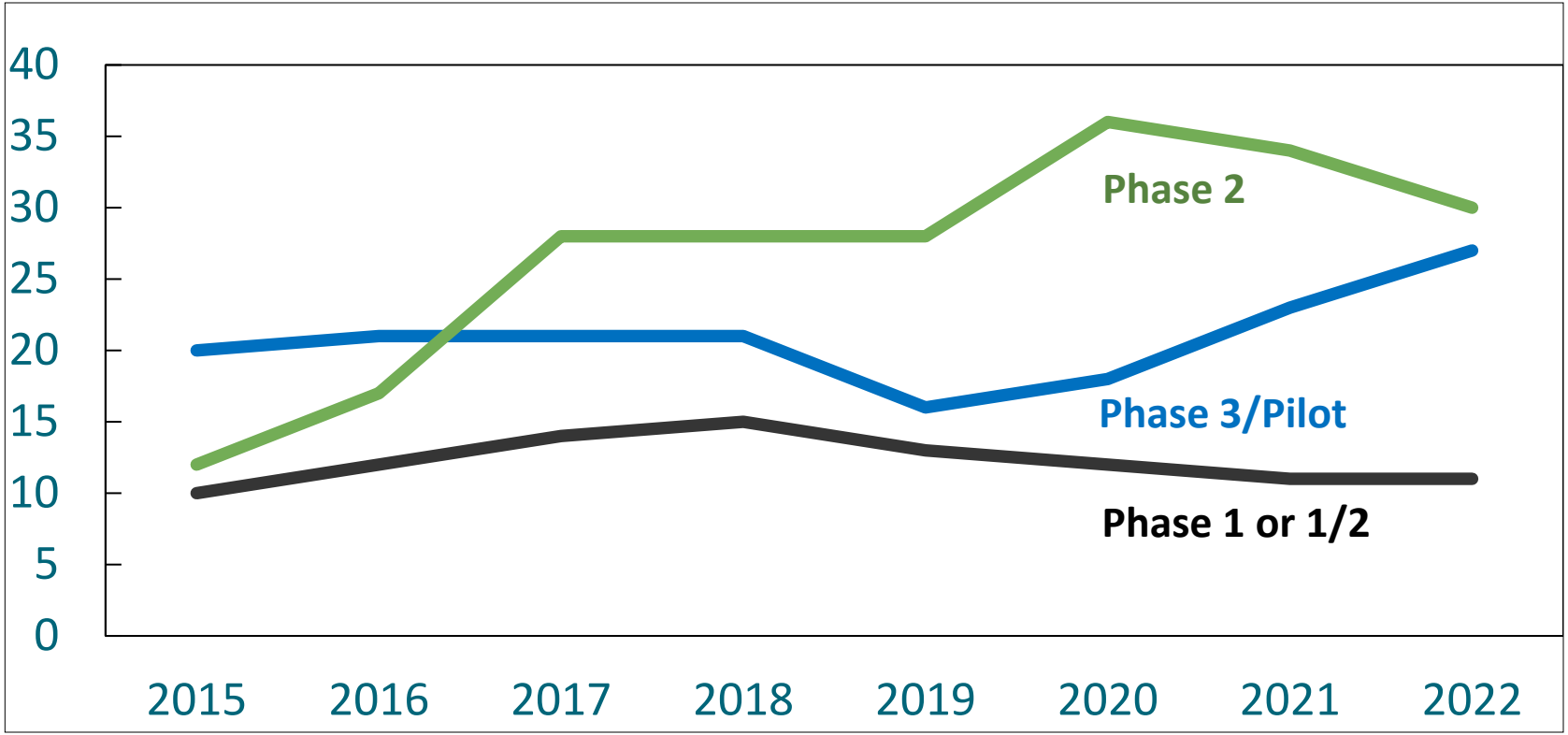
NIH NATIONAL CANCER INSTITUTE

March 24, 2023

Children's Oncology Group (COG)

- Formed in 2000 by merger of four legacy pediatric oncology cooperative groups
- NCI-funded National Clinical Trial Network (NCTN) member; four other US adult cooperative groups
- Fast facts:
  - > 220 institutions in US (~200), Canada, Australia, New Zealand
  - > 8000 members
  - ~3000 therapeutic enrollments/year
  - ~9000 non-therapeutic enrollments/year (70% Project:EveryChild)

Active COG Studies: 2015-2022



Ways to access COG data

- NCI NCTN/NCORP Data Archive
- Database of Genotypes and Phenotypes (dbGaP)
- Pediatric Cancer Data Commons (PCDC)
- Database Requests
- Project:EveryChild (APEC14B1)

NCI Data Archive

NIH NATIONAL CANCER INSTITUTE
NCTN/NCORP Data Archive

- NCI-supported phase 2/3 or 3 studies since January 2015
- 2021: scope narrowed to phase 3 primary publication, secondary publication with updated survival
- Patient-level data used in publications
- As of January 2023:
  - 36 COG studies available in NCI Data Archive
  - 69 COG studies/metadata submitted to NCI Data Archive, upload pending

All data used to generate these publications are publicly available

CHILDREN'S ONCOLOGY GROUP

NCI NCTN/NCORP Data Archive

Features	Bugs
Limited restrictions on access	Backlog in uploading datasets
All data to reproduce manuscript	Frozen datasets
Major clinical trials included	Phase 1 or 2 now excluded
USI available to link to other COG datasets	USI currently cannot be linked to non-COG datasets

Database of Genotypes and Phenotypes (dbGaP)

- Developed to archive and distribute data and results from studies that investigated genotype/phenotype
- As of March 2023:
  - 27 studies with “Children’s Oncology Group” as search term
  - TARGET
  - Gabriella Miller Kids First
  - MP2PRT
  - Molecular Characterization Initiative
  - Rhabdomyosarcoma, germ cell tumors, etc

Database of Genotypes and Phenotypes (dbGaP)

Features	Bugs
Limited restrictions on access	Selected tumors represented
Clinical data included	Frozen datasets
Some datasets derived from clinical trials	Most datasets unrelated to clinical trials
USI available to link to other COG datasets	USI currently cannot be linked to non-COG datasets

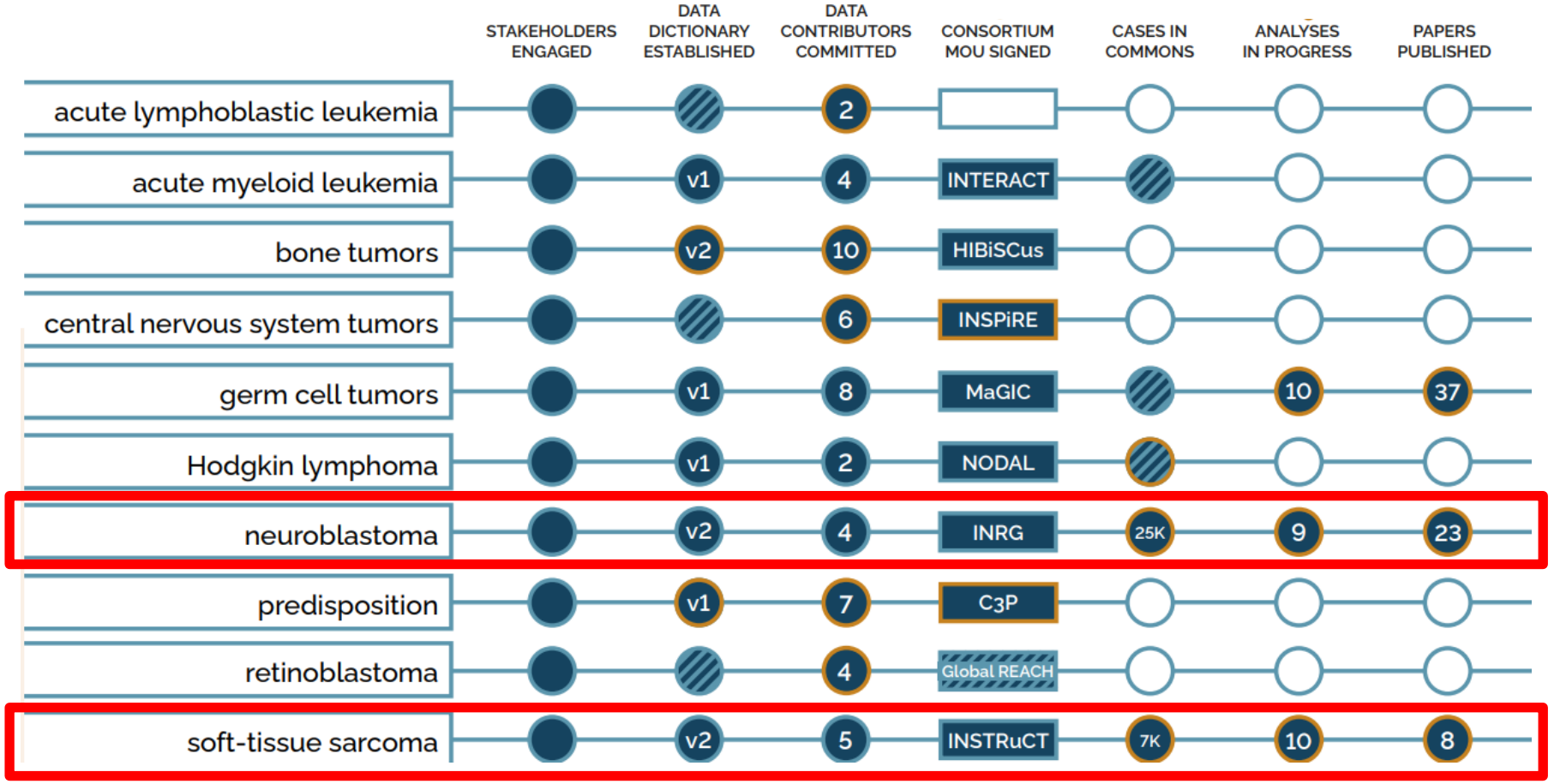
Pediatric Cancer Data Commons (PCDC)

- Formed in 2011 to build upon neuroblastoma data commons (INRG)
- COG has master agreement for data transfers to PCDC
- *International collaboration*
- As of March 2023:
  - COG data from two diseases in PCDC
  - 8+ disease consortium plan to contribute data to PCDC

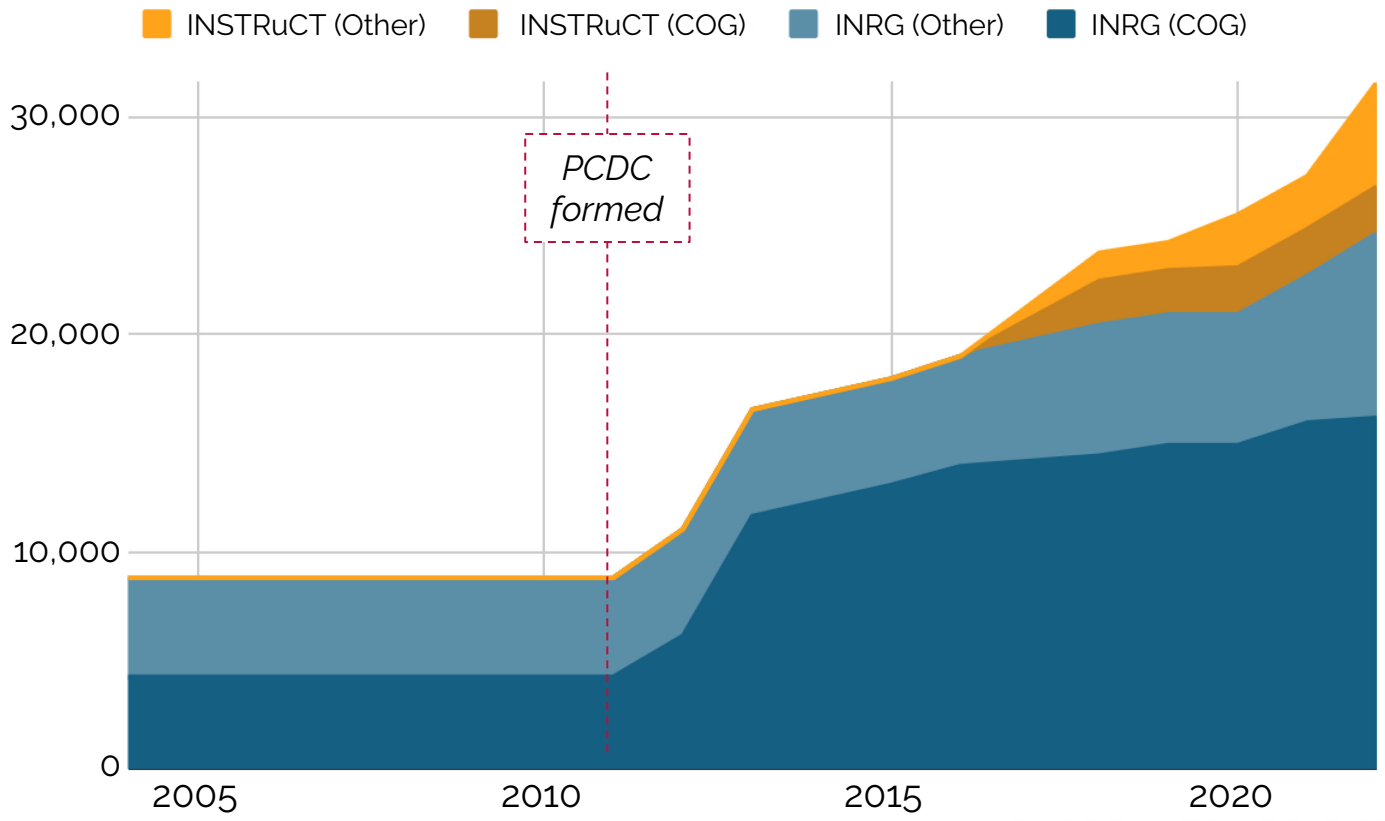
CHILDREN'S ONCOLOGY GROUP

PEDIATRIC CANCER DATA COMMONS

Pediatric Cancer Data Commons (PCDC)



Pediatric Cancer Data Commons (PCDC)



Pediatric Cancer Data Commons

Features	Bugs
Limited restrictions on access	Only two diseases currently
Common data dictionaries used	Predominantly clinical data
International contributions	COG > other groups
USI available to link to other COG datasets	European data do not have USI-equivalent (yet)

COG Database Requests

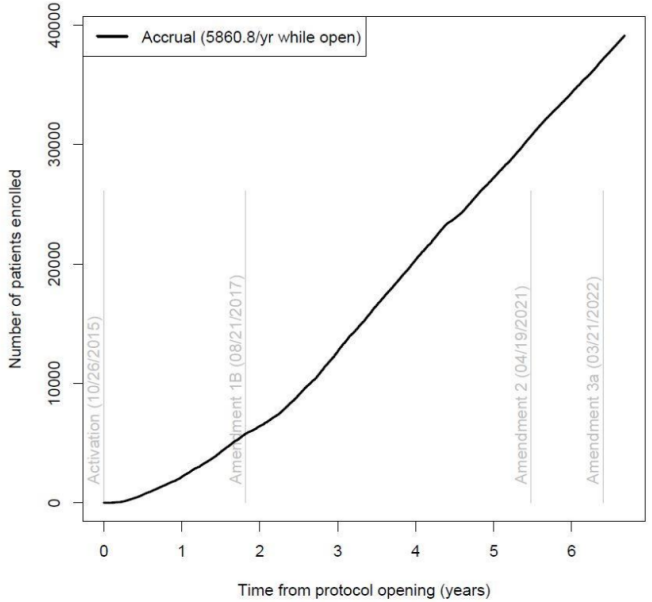
- COG has data sharing policy: https://childrensoncologygroup.org/data-sharing
- Data from completed studies
- Request from both COG and non-COG investigators
- In 2022, there were 35 requests

COG Database Request

Features	Bugs
Clinical trial data are rich	If not collected, it is not available
Data request process open to all	Timelines may be long due to COG statistical bandwidth
Updated data possible	Data may not match publications
USI provided to link to other COG datasets	USI currently cannot be linked to non-COG datasets

Project:EveryChild (APEC14B1)

- COG Biospecimen Bank at BPC (Columbus, OH)
- Launched in 2015
  - > 38,000 children enrolled
  - 5500-6000 enrollments/year
  - >200,000 biospecimens collected
  - Mechanism to enroll on MCI
  - Clinical annotation with outcome
  - Permission for future contact



CHILDREN'S ONCOLOGY GROUP

PROJECT:EVERYCHILD

Project:EveryChild (APEC14B1)

Features	Bugs
Very large dataset	“Everychild” is still aspirational
Most diseases included	Not neuroblastoma, renal tumors
Clinical features and outcome included	Annotation not as rich or complete as clinical trial
Biobanking included	Not 100% collection, mostly diagnosis
Consent for future contact to support epidemiology	Contact requires approved and funded project

Panel Discussion: Clinical Data and Annotation

Allison Heath

Wendy Gilmore Baskins

Kristine R. Broglio, MS

Suzanne George, MD

Doug Hawkins, MD

Tamara Miller, MD

Externally Controlled Trials in Pediatric Oncology: An FDA Oncology Perspective

Donna R. Rivera, PharmD., MSc.
Associate Director for Pharmacoepidemiology
Oncology Center of Excellence, US FDA

Recently Released FDA RWE Guidances

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
Draft Guidance for Industry, September 2021

Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Draft Guidance for Industry, October 2021

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry
Draft Guidance for Industry, November 2021

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
Draft Guidance for Industry, December 2021

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products
Guidance for Industry, September 2022

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
Draft Guidance for Industry February 2023

RWD Source
Submissions
Design

Considerations for the Design and Conduct of **Externally Controlled Trials** for Drug and Biological Products Guidance for Industry

Overview

Definition: An externally controlled trial (ECT) measures outcomes in participants receiving the investigational treatment according to a protocol compared to outcomes in a group of people external to the trial who did not receive the same treatment.

Appropriateness: The suitability of an externally controlled trial design depends on the clinical setting. Consult the relevant FDA review division early in drug development to determine if an externally controlled trial is reasonable.

Rationale for ECT

Context for use

- Feasibility Challenges
- Ethical Concerns
- Questionable Equipoise

Rationale for ECT

Context for use

- Feasibility Challenges
- Ethical Concerns
- Questionable Equipoise

Potential Applications

- Pediatrics
- Rare Diseases
- Significant unmet medical need
- Molecular subgroups
- Under-represented populations

Rationale for ECT

- Primary Concern: Lack of randomization

- Before an ECT →consider the likelihood that such a trial design would be able to distinguish the effect of a drug
  - ECTs are more likely to provide convincing results when the effect size on a well-characterized outcome of interest is anticipated to be large
  - Well-defined natural history of the disease and understanding of relevant prognostic factors

- In many situations, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low

External Control Arm Designs

Sources

- Real World Data
- Clinical Trial Data
- Literature Based

Temporality

Concurrent Control

- Patient population treated during the same or similar time period, reflecting a similar standard of care

Historical Control

- Non contemporaneous patient population where retrospective or retrospectively analyzed data is used as comparator

Purpose

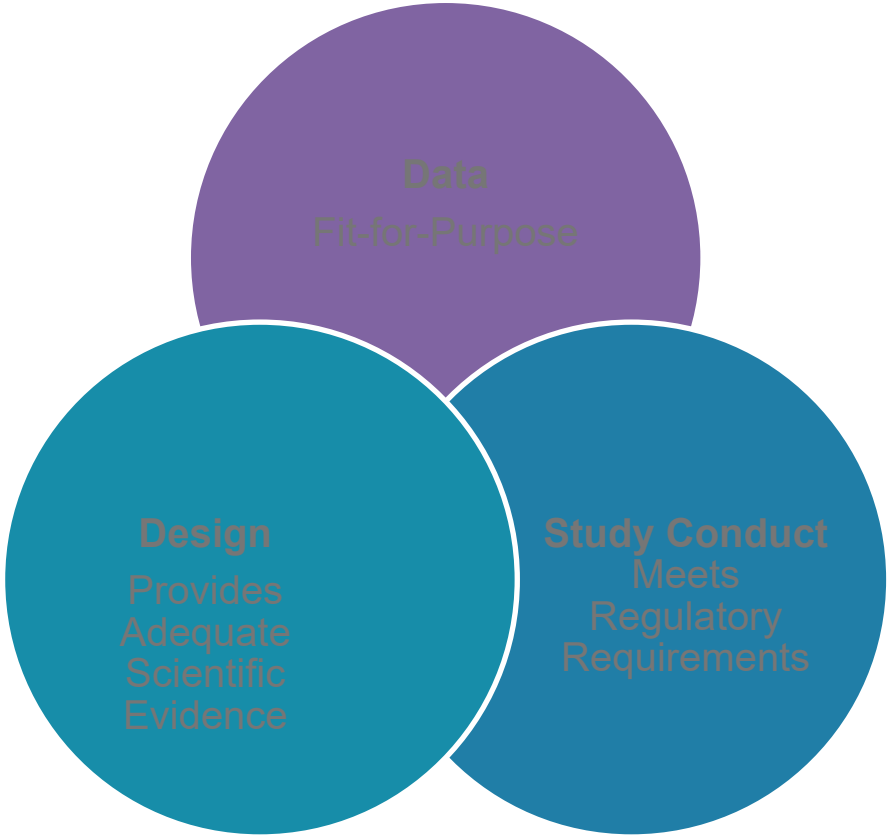
Benchmark

- As benchmark, baseline, or natural history study [epidemiology]

Comparator

- As individual patient level matched data for formal comparative study [effectiveness]

Overall Considerations



Data must be Fit-for-Purpose

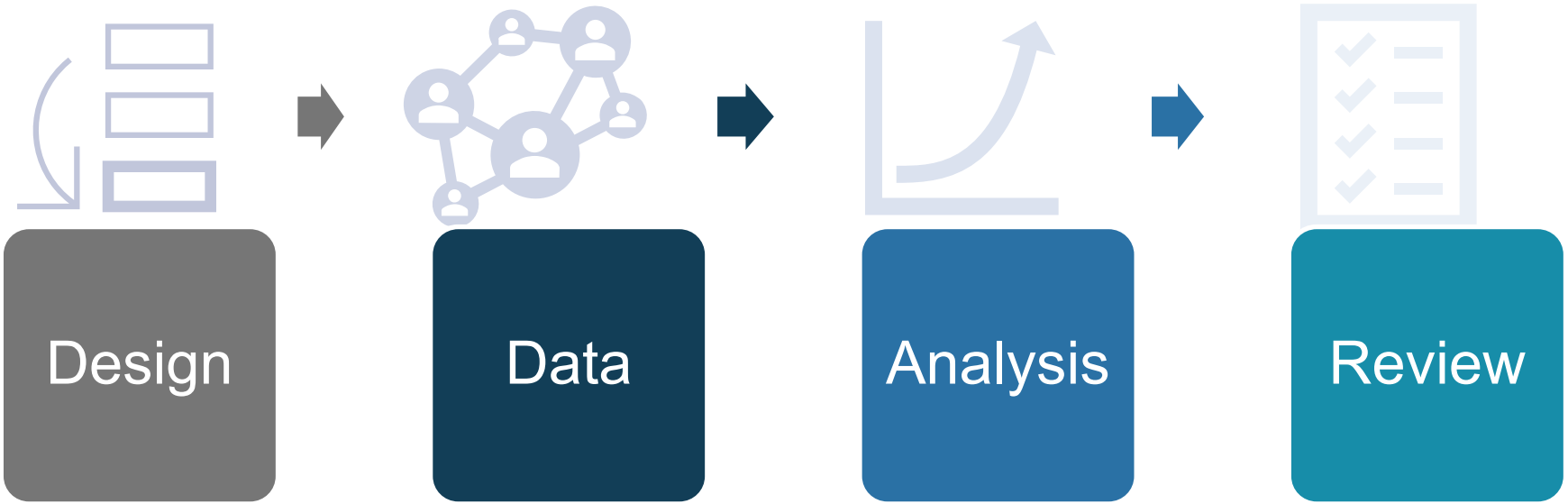
Relevance

includes the availability of key ***data elements*** (exposure, outcomes, covariates) and sufficient numbers of representative patients

Reliability

includes data ***accuracy***, **completeness. provenance,** and ***traceability***

ECT Considerations



Considerations

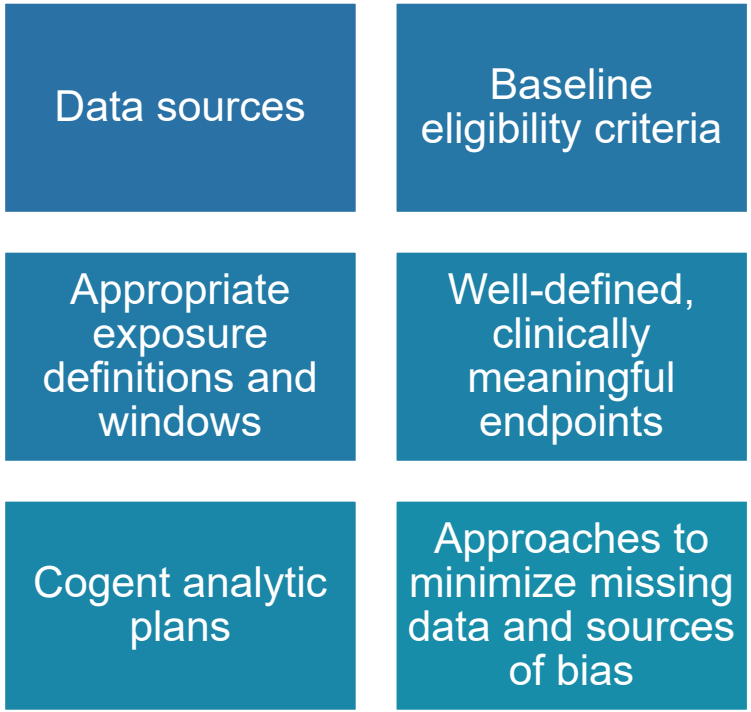
ECT Design

- **Prespecified Protocol→**

  Careful planning in the design phase with respect to reducing the potential for bias prior to study initiation

- Sponsors should finalize study protocol and SAP before initiating the ECT

- The estimand framework can be used to help design an EC trial



Considerations

Selection Bias

A systematic error in a study that occurs due to factors that influence study participation or eligibility.

Factors May Include

Geography

Treatment era

Eligibility Criteria

Healthy User Effect

Confounding

Distortion of the measure of the effect of a medical product on an outcome due to another factor

- Associated with the exposure
- Causal risk factor for the outcome (disease)
- Not on the causal pathway (not an intermediate cause)

To establish effectiveness, it is essential to distinguish the effect of the drug "from influences, such as spontaneous change in the course of the disease, placebo effect, *or biased observation"*

Sec. 314.126

Adequate and well-controlled studies

Index Date Selection

A specific and difficult challenge is specifying the index date

Determination of the index date in the treatment arm and the EC arm should avoid analyses that include a period of time (immortal time) during which the outcome of interest could not have occurred in one of the two arms

Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 2007 Mar;16(3):241-9. doi: 10.1002/pds.1357.

Lavesque L E, Hanley J A, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes BMJ 2010; 340 :b5087

Data Considerations

Summary of Considerations for Assessing Comparability of Data

Time Periods
- Standard of Care

Geographic Region
- Access to Care

Diagnosis
- Expected variation

Prognostic Factors
- available and similar

Treatments
- Factors such as dose and duration

Other Treatment-Related Factors
- LOT, Concurrent Treatment Regimen

Follow-up periods
- Index date

Intercurrent events

Outcome
- Measurement

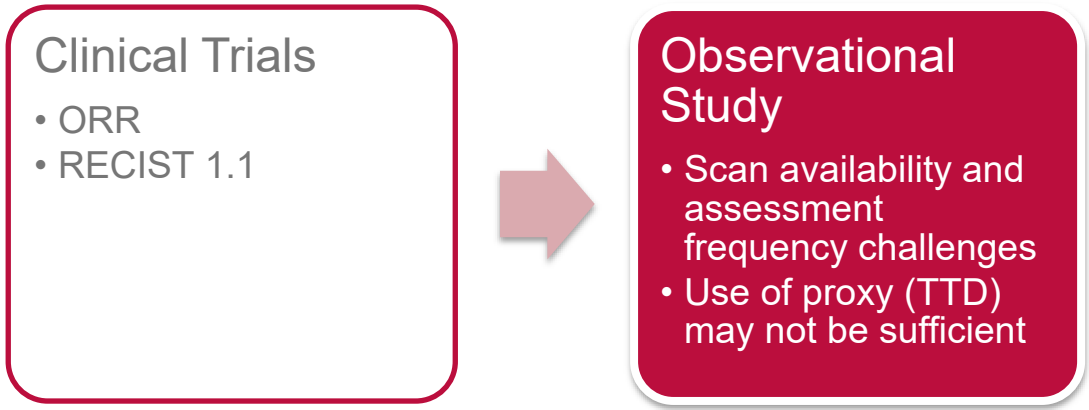
Missing Data

Summary of Considerations for Assessing Comparability of Data

Example: Outcome Ascertainment

- **Well defined outcome**: Availability, accuracy, and completeness

- FDA recommends defining an outcome of interest based on the clinical, biological, psychological, and functional concepts of the condition



Analysis Considerations

Analysis Considerations

Missing Data

- The proposed analytical methods should include a strategy for missing data
  - ✓ data that may not be available (e.g. type and frequency of assessments)
  - ✓ patient follow-up data

Misclassification

- Misclassification can occur when the value of a measurement is assigned to an incorrect category for subsequent analysis, potentially affecting estimates of the observed drug-outcome association

Review Considerations

Considerations for Review

Communication

Communicate early and often

(Include justification for ECT design, fit-for-purpose data proposal, planned analyses, data submission)

Document Access

Marketing applications require relevant patient-level data

If sponsors do not own the data, they must have agreements for FDA to access sources documents and data for auditing

Review: ECT Study Conceptualization

Define Study Objective and Key Design Elements

Determine if EC data is Fit for Purpose

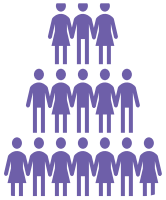
Detailed Study Protocol

Robust Statistical Analysis Plan *a priori*

Completeness of Capture

Comparability of Populations

Data Source



Patient Population

Appropriate Comparator

Available Data

Measurement

Endpoints

Possibility

Challenge

Project Pragmatica

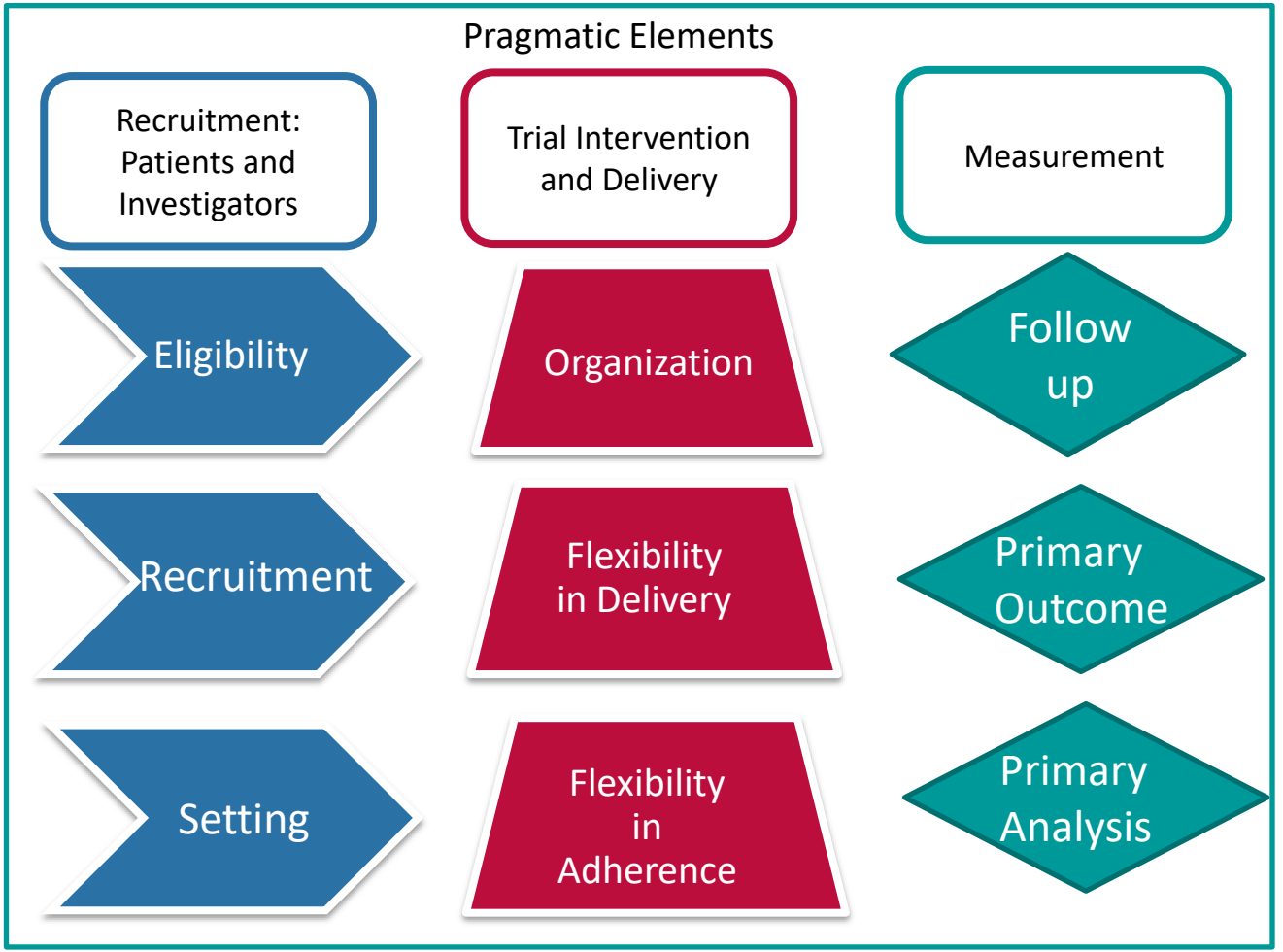
Advancing evidence generation for approved oncology medical products by exploring innovative trial design approaches that introduce functional efficiencies and patient centricity through integration with real-world routine clinical practice.

Trials need to be designed to address relevant questions,. “We’ve made these trials way too complicated, just mind-bogglingly complicated .

-Richard Pazdur, OCE Director

Pragmatic Clinical Trials

1) Intent to inform decision-makers
2) Intent to enroll a population relevant to the decision in practice and representative of the relevant patients/populations
3) Intent to
   (a) streamline procedures and data collection or
   (b) measure a broad range of outcomes



Adapted from Ford I, Norrie J. Pragmatic Trials. N Engl J Med 2016; 375:454-463. Aug 4, 2016.

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Oncology RWE Program

Paul Kluetz

Donna Rivera

Jennifer Lee

Fatima Rizvi

Catherine Lerro

TEAM FoRWD comprises FDA scientists with expertise in pharmacoepidemiology, hematology and oncology, epidemiology, biostatistics, and regulatory science to evaluate opportunities for RWD in regulatory contexts that can complement our understanding of medication risks and benefits for patients.

OCE Leadership
- Richard Pazdur
- Paul Kluetz
- Marc Theoret
- Tamy Kim

OOD and OB
- Harpreet Singh
- Martha Donoghue
- Pallavi Mishra-Kalyani
- Amy Barone
- Diana Bradford
- Sonia Singh
- Elizabeth Duke

- CDER
- OMP
- CBER
- CDRH

Thank you!

Additional Questions?

Please email OCERWE@fda.hhs.gov

BACK UP

Population Comparability

Examples

Baseline attributes

- Age
- Sex
- Race
- Socioeconomic

Disease characteristics

- Severity
- Duration
- Signs and symptoms
- Performance status
- Prognostic or predictive biomarkers
- Comorbidities
- Prior and current treatments

Potential challenges

- Availability of relevant confounding factors are known and well-characterized
- Confounding factors are captured
- Factors assessed with appropriate methods and measured similarly across compared groups
- Analytic methods sufficiently address the differences
- Eligibility Criteria can be applied to the ECA

Example Data elements

Unique patient identifier

Consent date for registry participation

Demographic characteristics

- Birthdate
- Sex
- Race
- BMI, lifestyle
- SDOH*

Clinical characteristics

- Diagnosis
- Comorbidities
- Biomarkers*
- Cytogenetics*

Treatment information

- Chemical name
- Drug product name
- Formulation and dosage
- Initiation and completion dates
- Procedures
- ADEs

Outcome information

- Clinical events
- Date of occurrence

Covariate Ascertainment and Validation

- **Confounding**
  - Associated with the exposure
  - Causal risk factor for the outcome (disease)
  - Not on the causal pathway (not an intermediate cause)

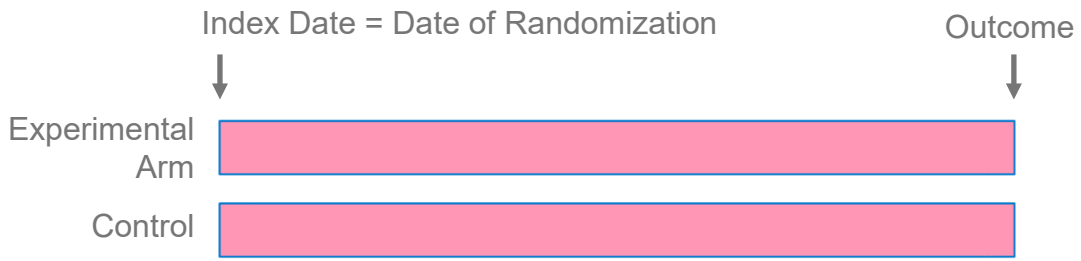
- **Effect Modifier**
  - A factor that biologically, clinically, socially, or otherwise alters the effects of another factor (Porta 2014)

Type of confounders	Examples	Strategy
Measured	Age and sex	Restriction
		Matching
		Stratification
		Standardization
		Regression analysis
		Propensity scores
Unmeasured but measurable	Smoking	External adjustment
	Body mass index	Proxy measures
	Disease severity	Imputation
Unmeasurable	Frailty	Self-controlled design
		Instrumental variable
		Mendelian randomization
		Active comparator
		Regression discontinuity design
		Sensitivity analyses

Norgarrd M. et al. Confounding in observational studies based on large health care databases: Problems and potential solutions – a primer for the clinician. Clinical Epidemiology. 2017

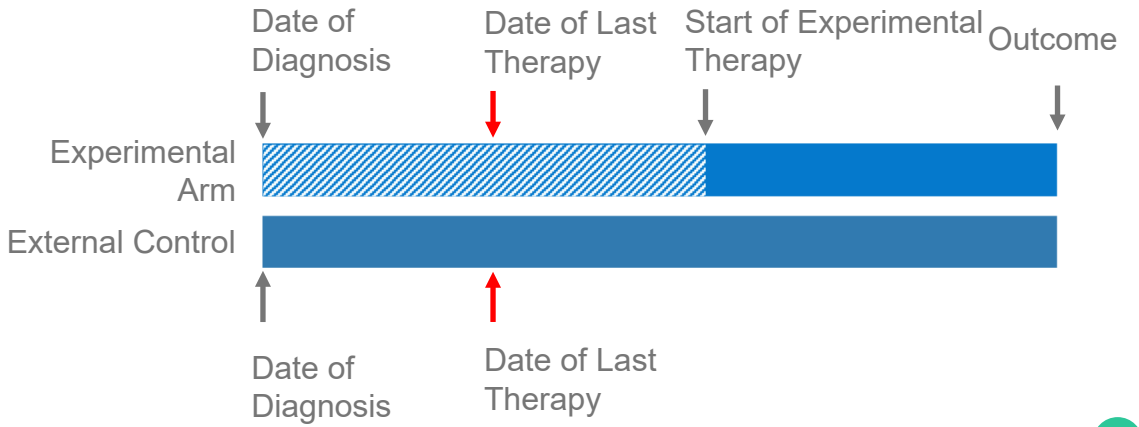
Index Date Selection

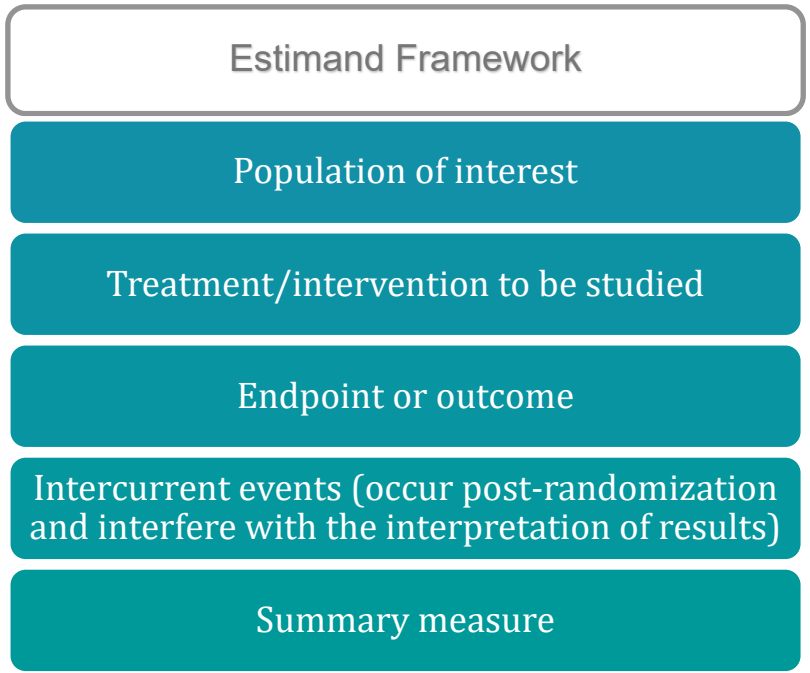
Randomized Controlled Trial



Externally Controlled Trial

A specific and difficult challenge is specifying the index date (start of the observation period for assessing endpoints)





Design is a pivotal step!

Careful planning in the design phase prior to study initiation can reduce issues in the analysis phase.

Rationale

The suitability of an externally controlled trial

- heterogeneity of the disease
- preliminary evidence regarding the drug product under investigation
- approach to ascertaining the outcome of interest
- the goal of the trial (superiority or non-inferiority)

Design

- Design considerations should be prespecified in a protocol and SAP, including:
  - selection of a suitable data source
  - availability of baseline characteristics and eligibility criteria
  - exposure definition
  - well-defined, clinically meaningful endpoints
  - key baseline clinical covariates
  - concomitant therapies
  - index date designation*
  - consistency of outcome assessments
  - analysis plan

*Given the lack of randomization in externally controlled trials, differences in the way the index date is determined across trial arms may lead to biased effect estimates.

Data

- External control data from another trial may offer advantages. Regardless of data source, it is important to establish the comparability of participant characteristics for trial and external control data :
  - Time periods
  - Geographic regions
  - Diagnosis
  - Prognostic factors
  - Treatment related factors
  - Follow-up periods
  - Intercurrent events
  - Outcome ascertainment, and
  - Missing data

Analytic

- Various statistical methodologies may be appropriate, and FDA does not recommend a specific approach.
- Sponsors should develop a prespecified statistical analysis plan that includes:
  - Analysis of all primary, secondary, and exploratory endpoints
  - Statistical power and sample size calculations
  - Approaches to control the chance of erroneous conclusions, specifically with strategies to deal with →
    missing data, description of sources of misclassification that may result in bias, and a robust sensitivity and subgroup analysis plan.

Improving clinical trials with the use of tumor genomic classification

Elly Barry, MD, MMSc

SVP, Head of Clinical Development

Day One Biopharmaceuticals

NIH NATIONAL CANCER INSTITUTE

24 March 2023

Disclosures

- I am an employee and stockholder of Day One Biopharmaceuticals, Inc.
- Tovorafenib is is an investigational product. Safety and effectiveness have not been established by any health authority.
- The views and opinions expressed in this presentation are solely my own and do not reflect the views or positions of Day One Biopharmaceuticals, Inc.

Precision Medicine: Finding the right drug for the right patients

the promise…

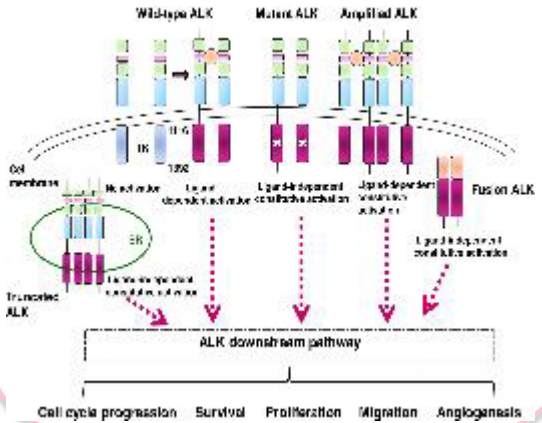
vs. the reality

Case study 1
ALK as a tumor target

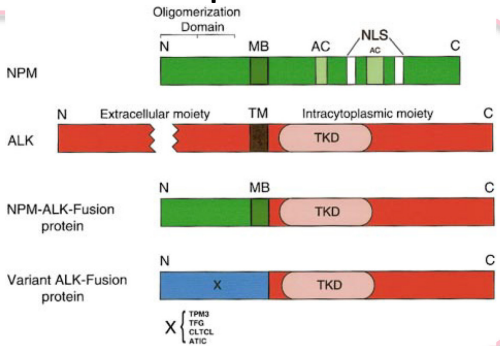
ALK: Anaplastic Lymphoma Kinase

- ALK is a receptor tyrosine kinase, that activates multiple downstream signal transduction pathways (e.g., MAPK-ERK, PI3K-AKT, and JAK-STAT)[1]
- Normal ALK plays a pivotal role in cellular communication and in the development and function of the nervous system[1, 2]
- ALK aberrations →constitutive activation of ALK→ → cancer development and progression[2]
- **ALK Alterations in Cancer**
  - NSCLC: ALK fusions 3-7%[3-5]
  - ALCL: ALK fusions 90+%[6]
  - IMT: ALK fusions 50%[7]
  - Other tumors: NB, HGG

ALK signaling in normal and cancer cells[2]



ALK fusion protein domains[8]



1. Webb et al., Expert Rev Anticancer Thera, 2009.Mar;9(3):331-56. 2. Takita, Cancer Sci 108 (2017) 1913–1920. 3. Chia et al., Clinical Epidemiology 2014:6 423–432. 4. Poon et al., 2016.Int. J. Cancer: 140, 1945–1954. 5. Halberg and Palmer., Annals of Oncology 27 (Supplement 3): iii4–iii15, 2016. 6. Turner SD, et al. *Br J Haematol*. 2016;173(4):560-72. 7. Lovly CM, et al. *Cancer Discov*. 2014;4(8):889-95. 8. Stein H, et al. *Blood*. 2000;96(12):3681-95.

Study ADVL0912: Phase 1/2 Study of Crizotinib in Pediatric Patients with Relapsed and Refractory Solid Tumors

VOLUME 35 · NUMBER 28 · OCTOBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study

Yael P. Mossé, Stephan D. Voss, Megan S. Lim, Delphine Rolland, Charles G. Minard, Elizabeth Fox, Peter Adamson, Keith Wilner, Susan M. Blaney, and Brenda J. Weigel

Table 2. Clinical Activity in Patients Treated With Crizotinib

Outcome	ALCL165 (n = 6)	ALCL280 (n = 20)	IMT (n = 14)
Best overall response			
Complete response	5 (83)	16 (80)	5 (36)
Partial response	0	2 (10)	7 (50)
Stable disease	1 (17)	2 (10)	2 (14)
Progressive disease	0	0	0
Therapy duration, years, median (95% CI)	2.79 (0.31 to n/a)	0.4 (0.18 to 1.0)	1.63 (0.55 to 2.30)
Time to first PR/CR, days, median (95% CI)	26.5 (24 to n/a)	27 (25 to 29)	28.5 (27 to 134)

ALCL: 26 patients

- ORR for patients treated at doses of 165 (ALCL165) and 280 (ALCL280) mg/m^2 were 83% and 90%, respectively
- CRs observed in 83% (five of six) of ALCL165, 80% (16 of 20) of ALCL280
- 12 ALCL patients proceeding to transplantation

IMT: 14 patients

- ORR 86%
- CRs in 36% (5 of 14)

Mosse YP, et al. *J Clin Oncol*. 2017;35(28):3215-3221.

ADVL0912 Operational logistics

- **6 years to enroll 40 patients[1]**
- Investigator Sponsored trial (IST)
- COG Phase 1 network
- 28 US sites
- ALK testing:
  - Local labs using CLIA certified assays
    - Immunohistochemistry (IHC)
    - Fluorescence in situ hybridization (FISH)
  - No central confirmation

1. Mosse YP, et al. *J Clin Oncol*. 2017;35(28):3215-21. 2. ClinicalTrials.gov identifier: NCT00939770. Accessed March 16, 2023. https://clinicaltrials.gov/ct2/show/NCT00939770

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FDA approves crizotinib for children and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma

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Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Drug Information Summaries in Clinical Oncology [PDQ®]

On January 14, 2021, the Food and Drug Administration approved crizotinib (Xalkori, Pfizer Inc.) for pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive. The safety and efficacy of crizotinib have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

Efficacy was evaluated in Study ADVL0912 (NCT00939770), an open-label trial in patients 1 to <21 years of age that includes

Content current as of:
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January 2021

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FDA approves crizotinib for ALK-positive inflammatory myofibroblastic tumor

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Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

On July 14, 2022, the Food and Drug Administration approved crizotinib (Xalkori, Pfizer Inc.) for adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory anaplastic lymphoma kinase (ALK)-positive myofibroblastic tumors (IMT).

The safety and efficacy of crizotinib were evaluated in two multicenter, single-arm, open-label trials that included 14 pediatric patients from trial ADVL0912 (NCT00939770) and 7

Content current as of:
07/14/2022

July 2022

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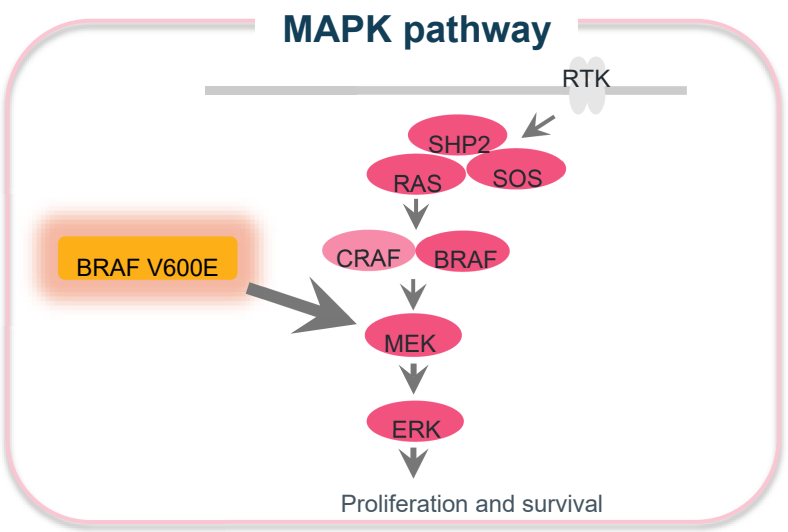
Case Study 2: BRAF as a tumor target

Can we go faster?

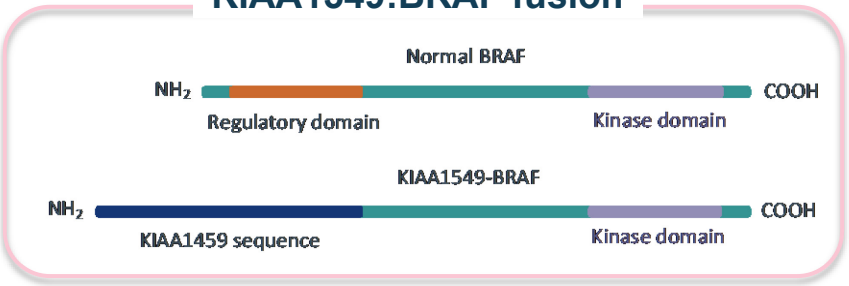
The RAS-RAF-MEK-ERK (MAPK) pathway is frequently dysregulated in human cancer[1-4]



- RAS and BRAF are the most frequently mutated genes in this pathway[1]
- ~90% of all BRAF mutations encoding constitutively active BRAF V600E[1]
- Tumors expressing BRAF V600E mutations are highly sensitive to RAF and MEK inhibitors[1]

BRAF alterations in pediatric low-grade glioma (pLGG)

- pLGG is the most frequent brain tumor diagnosed in children[5]
  - ~ 1000 patients diagnosed/year in US
- Genomic alterations in BRAF occur in up to 75% of pLGG[6,7]
  - *KIAA1549-BRAF* fusion are drivers in ~ 80% of all pilocytic astrocytomas[6,8,9]
  - BRAF V600E in 17% of pLGGs[9]



1. Yaeger R and Corcoran R. Cancer Discov. 2019;9:329–341. 2. Prior I, et al. Cancer Res. 2020;80:2969–2974. 3. Ross J, et al. Int. J. Cancer. 2016;138:881–890. 4. Rankin A, et al. *Oncologist*. 2021;26:e153–e163. 5. Ostrom et al., Neuro Oncology. 2022; 24(S3), iii1–iii38 6.Ryall S, et al. *Acta Neuropathol Commun*. 2020;8(1):30. 7. Faulkner C, et al. *J Neuropathol Exp Neurol*. 2015;74(9):867-72. 8. Sholl LM. *Precis Cancer Med*. 2020;3:26. 9. Ryall S, et al. *Cancer Cell*. 2020;37(4):569-583.e5. .

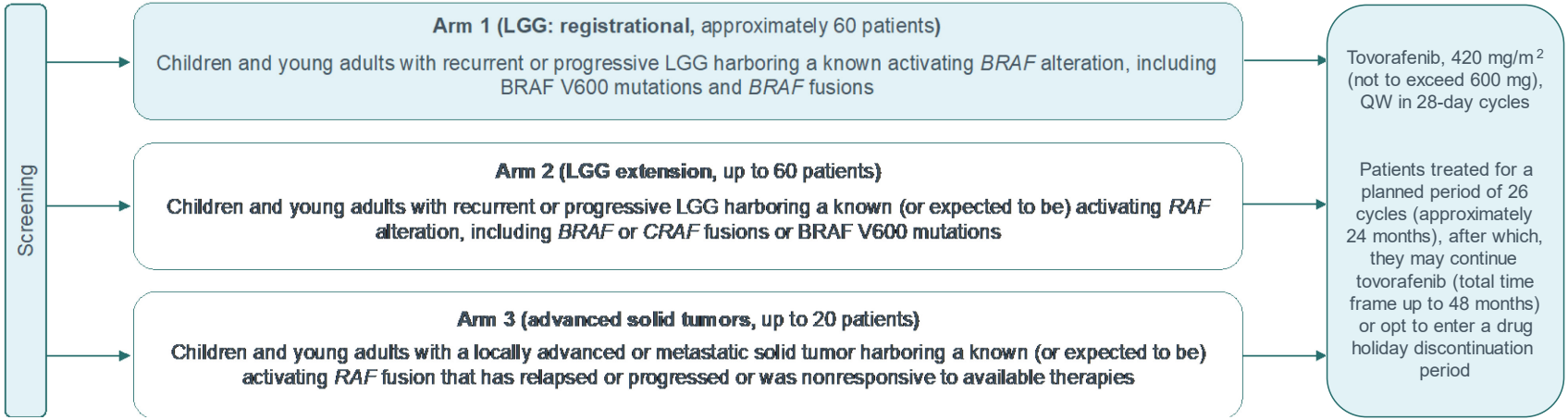
FIREFLY-1: Phase 2 study of tovorafenib monotherapy

14.3.1 Study design[1]

- **Multicenter, open-label phase 2 study evaluating tovorafenib in pediatric or young adult patients with LGG or an advanced solid tumor**
- **Eligibility: patients aged 6 months–25 years, with a *RAF*-altered tumor, and ≥1 prior line of systemic therapy with radiographic progression**
- **3 treatment arms***

14.3.2 Endpoints

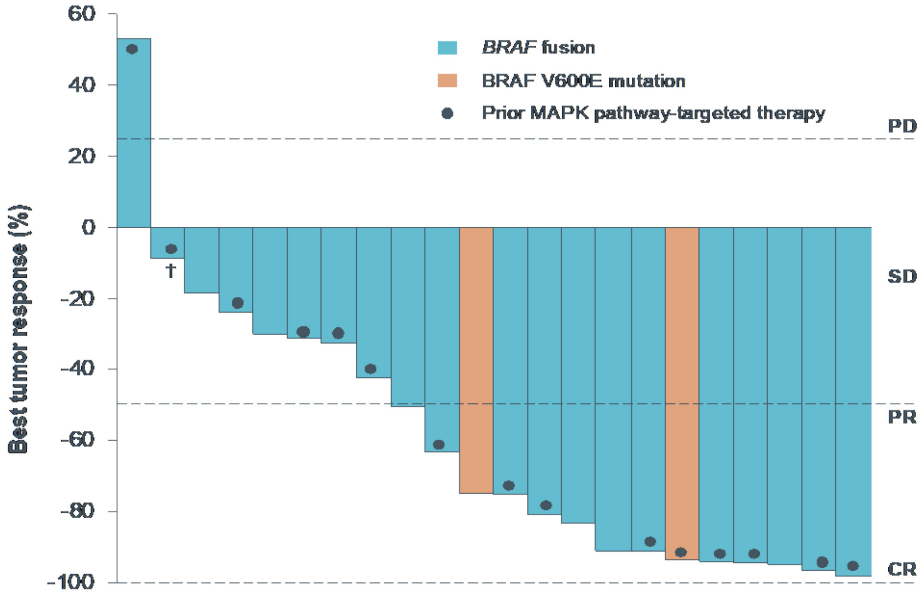
- Primary endpoints are tumor response per independent review (arm 1 by RANO criteria, arm 3 by RECIST v1.1 and safety (arm 2)
- Secondary endpoints (arms 1 and 3) include safety, PK, DoR, PFS, TTR, CBR



Enrollment to arm 1 and arm 2 has now been completed; arm 3 is actively enrolling patients.
ClinicalTrials.gov identifier: NCT04775485. Accessed March 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04775485

FIREFLY-1 interim analysis

Clinical activity of tovorafenib in patients with RANO-evaluable pLGG lesions (n=22)[1]



Response (IRC)	RANO evaluable n=22*
Overall response rate (95% CI)	64% (41–83)
BRAF fusion (n=20)	60%
BRAF V600E (n=2)	100%
Clinical benefit rate#	91%
Best overall response	
Partial response (13/22)	59%
Unconfirmed partial response (1/22)	5%
Stable disease (6/22)	27%

April 14, 2022 data cutoff. *3/25 patients lacked evaluable lesions per RANO criteria based on independent review committee evaluation. †Progressive disease due to presence of new lesions. #Patients with best overall response of complete response, partial response/unconfirmed partial response, stable disease.

Kilburn L, et al. 2022 SNO Annual Meeting: Abstract CTNI-68 and presented poster.

FIREFLY-1 Operational Logistics

- **14 months accrual (Arm 1, N=77)**
- Industry-sponsored, leveraging PNOC network
- 36 global study sites
  - US, Canada, Australia, Denmark, Germany, Israel, S. Korea, Singapore, Switzerland, United Kingdom
- Molecular testing:
  - Local labs using CLIA certified assays
    - FISH, RT-PCR, NGS, Immunohistochemistry
  - Retrospective central confirmation→Development of CDx

Enrollment to arm 1 and arm 2 has now been completed; arm 3 is actively enrolling patients.
ClinicalTrials.gov identifier: NCT04775485. Accessed March 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04775485

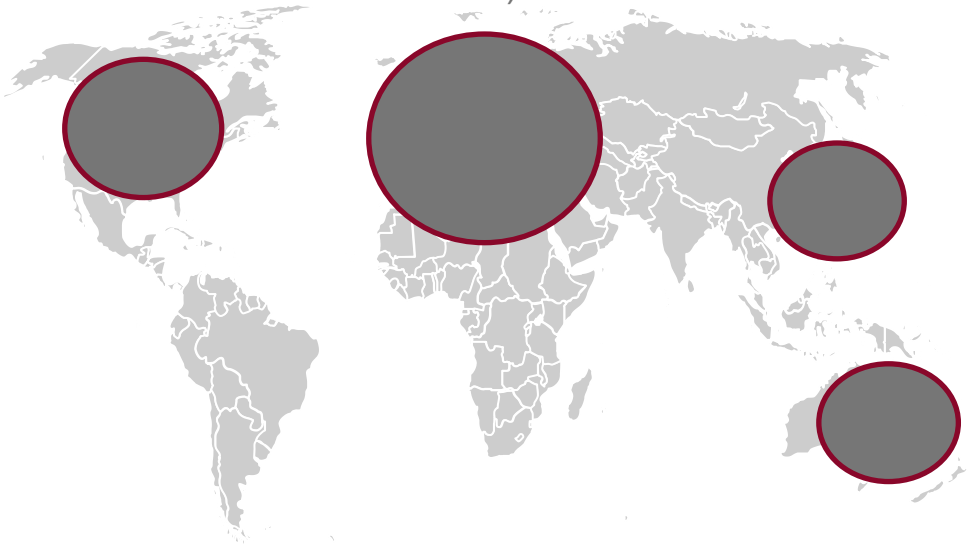
FIREFLY-2/LOGGIC: Pivotal Phase 3 Study Of Tovorafenib (DAY101) In Newly Diagnosed pLGG

- **Randomized trial of 400 patients**
- Collaboration between Day One and the LOGGIC consortium, internationally recognized experts in pLGG research
- Approximately **100 potential sites** (~65 from the LOGGIC consortium)

LOGGIC EUROPE

LOGGIC: LOw Grade Glioma In Children

KiTZ Hopp Children's Cancer Center Heidelberg | German Cancer Research Center (DKFZ) Heidelberg University Hospital Heidelberg University



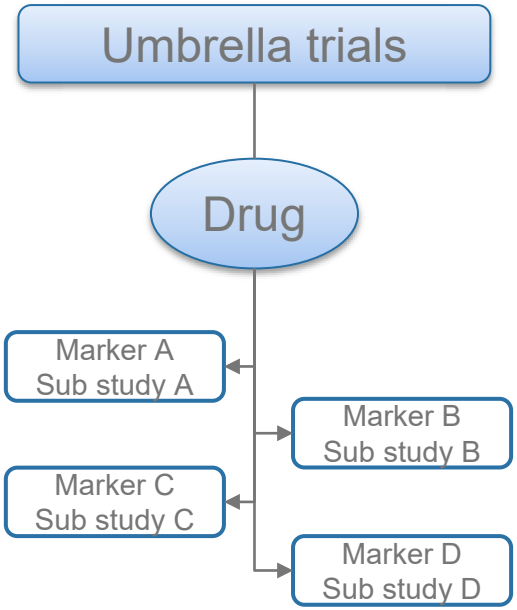
How can we make these types of trials more efficient?

1. These are rare tumors

- Typical approach: Focus on high-volume clinical trial sites/hospitals where genomic testing is routine practice
- Challenges:
  - Access: Molecular testing may not be routine; who pays?
  - Routine testing may not detect rare variants
  - Miss patients outside of high-volume centers
- Potential solutions:
  1. Widespread implementation of molecular testing
  2. Broader patient reach: Global studies; Just-in-time site activation; decentralized clinical trials

2. Data: How do we do more with less?

- Contextualization of outcomes data in rare tumor types
  - Robust historical data on outcomes often not available
  - Randomized trials not feasible or require substantial time to conduct, global collaboration required
- Potential Solutions:
  1. Regulatory flexibility for rare/orphan diseases
  2. Novel trial designs (e.g., platform studies)
  3. Leverage **all** available data (RWE, Registries, Compassionate use, ISTs)



3. The Wild West of diagnostics: Lack of uniformity

- Large variety of testing modalities and methods; requires central confirmation of genomic alteration
  - Retrospective vs. real-time; Discordant results?
- Development of Companion Diagnostic (Commercial test)
  - Requires clinical and analytical validation of assay
  - Availability of tumor tissue; age and quality of sample
  - Ultimate question: will test be used?
- Potential solution:
  1. FDA's pilot program: define minimal performance criteria to allow use of any test meeting those standards

4. Unanswered questions

- Approach to patients with more complex molecular alterations?
- Understanding mechanisms of resistance that may develop in response to targeted therapy → implications for treatment
- Use of combinations
  - Novel-novel
  - Novel + standard of care
  - Can we initiate combinations earlier?

Thank you!

The Potential for Archived Pediatric Cancer Clinical Trial Data to Contribute to RWD and RWE

Bruce Carleton, PharmD, FCP, FISPE

University of British Columbia, Faculty of Medicine, Department of Pediatrics, Division of Translational Therapeutics

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Data Resources

For RWD and RWE

RWData Resources

- Clinical and Translational Data Sources
  - Some existing sources: COG, St Jude LIFE, PanCareLIFE, CPNDS
  - What might be developed

- **Objective:** Make trial data (RWD) as RWE useful in designing and accelerating pediatric cancer clinical trials

Children's Oncology Group (COG)

- 200 centres across North America, Australia, New Zealand, Europe
- 90% of 14,000 children with cancer annually in the US are cared for at COG member institutions
- Demonstrated success in outcomes
- 100 active clinical trials ongoing at any one time
  - Underlying biology, front-line treatment, new/emerging treatments, supportive care, survivorship

PanCare Life - Europe

- Funded by an EU FP7 grant
- 14,000 ”well characterized” childhood cancer survivors
- 17 institutions from 8 European countries
- 11 data providers from 5 other countries
- Specific outcomes of interest for the initial grant (2013-18) include fertility, hearing loss, health-related QoL

St Jude Life

- Activated in 2007; St. Jude and other funders
- Lifetime cohort of childhood cancer survivors (n=4,382)
- Core battery assessment
- Includes annual clinical assessments and questionnaires
- SNP, whole genome, epigenetic and exome sequencing for some patients

Global Databank of the Canadian Pharmacogenomic Network for Drug Safety (CPNDS)

- Funded by Federal and Provincial Grants to the University of BC (2004 to present)
- Globally-accessible databank of pediatric ADR clinical and genomic data
- More than 11,257 patients (still growing); drug-exposed cases (n=11,343) and controls (n=106,408)
- ~ 70% children with cancer
- Longitudinal – up to 40 years of follow up data
- Genomic data increasingly important for proper drug response evaluation

Validation of SLC28A3 in a patient-derived iPSC cardiomyoctes

- ***SLC28A3* variant exhibits increased cell viability when exposed to doxorubicin**

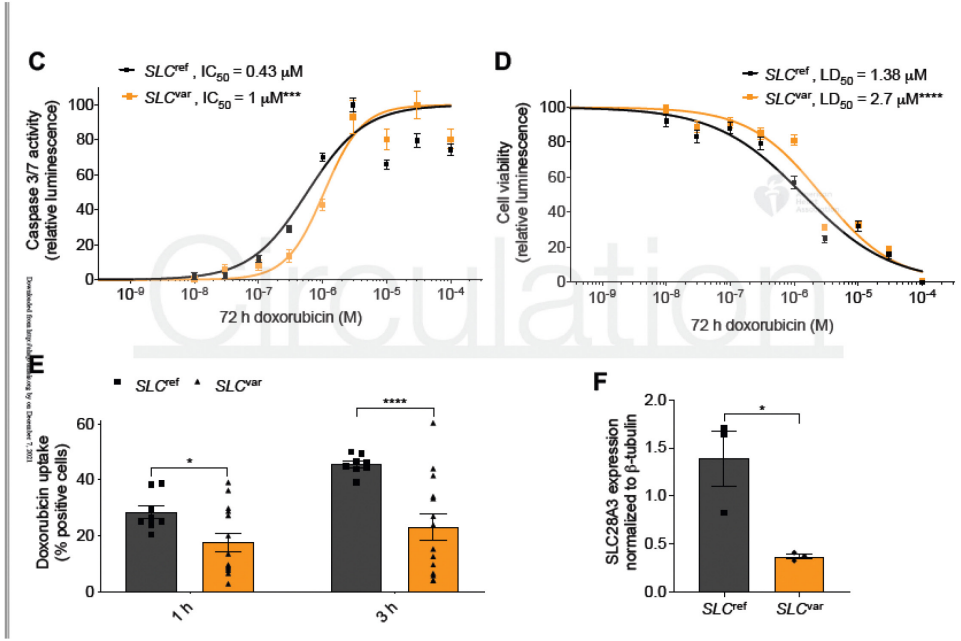
Identification of Drug Transporter Genomic Variants and Inhibitors That Protect Against Doxorubicin-Induced Cardiotoxicity

Tarek Magdy , Mariam Jouni , Hui-Hsuan Kuo , Carly J. Weddle , Davi Lyra-Leite , Hananeh Fonoudi , Marisol Romero-Tejeda , Mennat Gharib , Hoor Javed , Giovanni Fajardo , Colin J.D. Ross , Bruce C. Carleton , Daniel Bernstein and Paul W. Burridge

https://doi.org/10.1161/CIRCULATIONAHA.121.055801

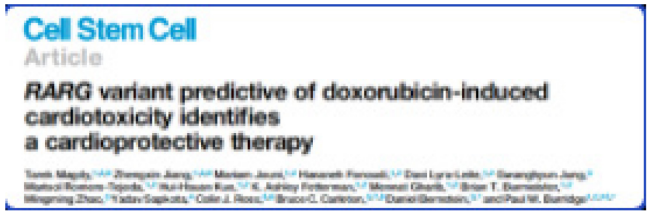
Circulation. 2022;145:279–294

- 2.0-2.3-fold higher LD_{50} (P<0.0001) when exposed to doxorubicin
- 2-fold reduced doxorubicin uptake into cells
- 3-fold reduced expression

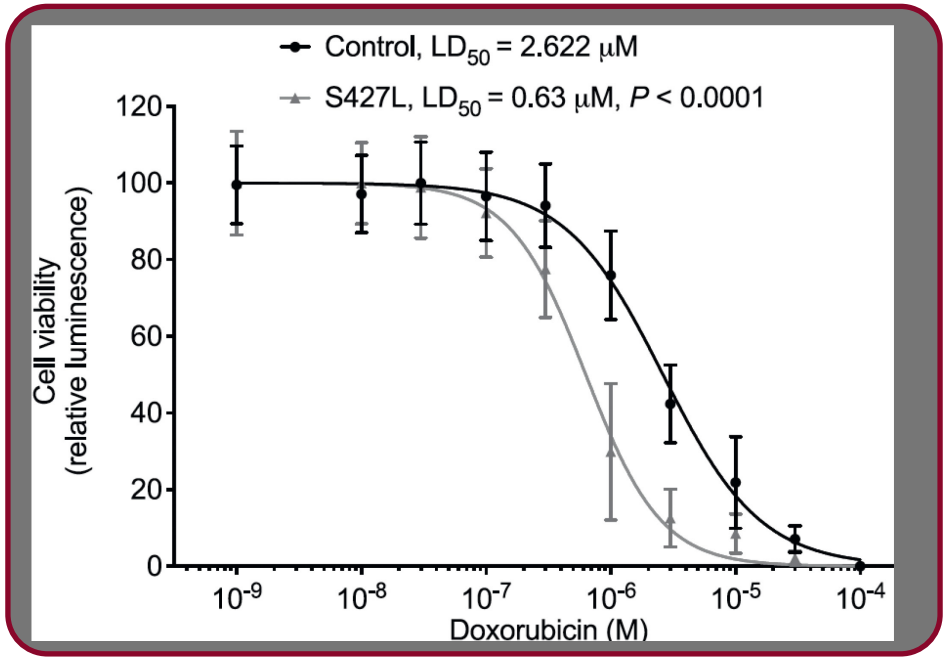


Validation of RARG in patient iPSC-derived cardiomyocytes

- ***RARG*^{S427L} exhibits reduced cell viability when exposed to doxorubicin**



- Patient-derived iPSC cardiomyocytes
- *RARG*^{S427L} carriers exhibit:
  - 4.2-fold lower LD_{50} (P<0.0001) when exposed to doxorubicin



RWD and RWE in Pediatric Oncology

Some History

Some History of what has been done with RWD/RWE

- Improving successive studies
- Defining risk stratification

- RCTs in pediatric cancer are becoming increasingly impossible
  - How might data inform pragmatic trials?
  - How might data be used to construct external controls?
    - *FDA Guidance*

RWD and RWE have improved survival outcomes in adults and in children

- Multidisciplinary molecular tumour board comprehensively reviewed patient clinical and genomic characteristics to develop N-of-one treatment regimens.
- Most patients were adults but some children. Overall, 265/429 therapy-evaluable patients (62%) were matched to ≥1 recommended drug.
- Eighty-six patients (20%) matched to all drugs recommended by the board.
- 38% received physician's choice regimen, generally with unmatched approach/low degree of matching.
- Patients who receive board-recommended regimens have significantly longer progression-free and overall survival, and are better matched to therapy.
- RWD have been also used to demonstrate the beneficial effects of pediatric oncology drugs in combination on overall survival.

Non-clinical trial data using PRO to validate benefit of reduced toxicity of reduced up front treatment

- A recent study from CCSS demonstrated a reduced incidence of severe late effects in the most recent cohort of childhood Hodgkin lymphoma survivors.
- N~ 3,000: females twice as likely as males to experience a CTCAE grade 3-5 event. From the 1970s to the 1990s, there was a 20% reduction in decade-specific risk of CTCAE grade 3-5 events.
- Conclusion: a contemporary regimen for low-to-intermediate risk Hodgkin lymphoma reduces the risk of a grade 3-5 adverse event by 40% v. survivors who received ≥ 35 Gy of chest radiotherapy along with an anthracycline or alkylator (HR 0.6, 95% CI 0.4 - 0.8).

Challenges

In the Use of RWD and RWE

A few challenges

- It still takes up to three years just to get a clinical trial underway and additional years to build the required steps from the RWD that emerged and climb them.
- Despite presumed data quality, there are missing data.
- A system to ensure that appropriate patient-level data are captured, managed and validated is needed.
- Getting the use of RWD and RWE right in pediatric oncology, with its well-developed infrastructure and central governance means similar models can be tried for other conditions and for other drugs.
- A new focus should include health equity, assessing interventions for patients treated off study, assessing implementation for evidence-based cancer control and supportive care interventions.

Are we working with the correct data?

- Previous studies of AVN have investigated protocol-based cumulative doses of corticosteroids rather than actual cumulative dose the patient received
  - **St. Jude TVX** GWAS: Age and **treatment arms** *Blood,* 117(8), 2340–2556. (2011)
  - **AALL0232** GWAS: Age, sex, ancestry and **treatment arms** *Blood,* 126(15), 1770–1776. (2015)

- **CPNDS databank – example patients**

					Dose expected per protocol (mg/m2)		Actual doses received (mg/m2)		
Patient ID	Sex	Chemo Protocol	Arm and/or regimen	Status	Dexamethasone	Prednisone	Dexamethasone	Prednisone	Comments
TOR150463	Female	AALL0232	SER, Arm PH	Alive, completed treatment	280	5,280	260	2,520	Corticoids discontinued due to the development of osteonecrosis.
CAL600057	Male	CCG 1961	Regimen C	Alive; completed treatment	210	8,815	210	8,615	Missed some doses of prednisone due to neuropathy and steroid induced muscle weakness at end of maintenance.
TOR151353	Female	AALL 0331	SER, S/H Risk	Alive; completed treatment	988	0	628	0	Missed dexamethasone doses due to suspicion of osteonecrosis.

Previously reported **Not analyzed in previous studies**

Capturing dose intensity is important

Patient 1 – just under age 24 months

- Treated for Germ Cell tumour on protocol CCG 8882
  - Cumulative dose 400mg/m^2
- Tolerated full-course of cisplatin therapy without hearing loss
  - Normal bilateral hearing 3-years following cisplatin treatment (tested in high frequencies up to 12kHz).
- Cisplatin given as 20mg/m^2 per day x 5 days x 4 cycles

Patient 2 – just over age 12 months of age

- Treated for Hepatoblastoma on protocol POG 9645
  - Cumulative dose 400mg/m^2
- After 3 cycles of cisplatin, developed grade 3 ototoxicity
  - Audiogram results: 250/35, 500/20, 1000/30, 2000/70, 3000/80. No response beyond. Impression: Normal to borderline normal hearing to 1000 Hz sloping to severe loss in the high frequencies for at least the better ear (as no ear specific responses obtained).
- Cisplatin given as 100mg/m^2 per day x 1 day x 4 cycles

Comparing cumulative dose vs dose to the time ototoxicity is first noted

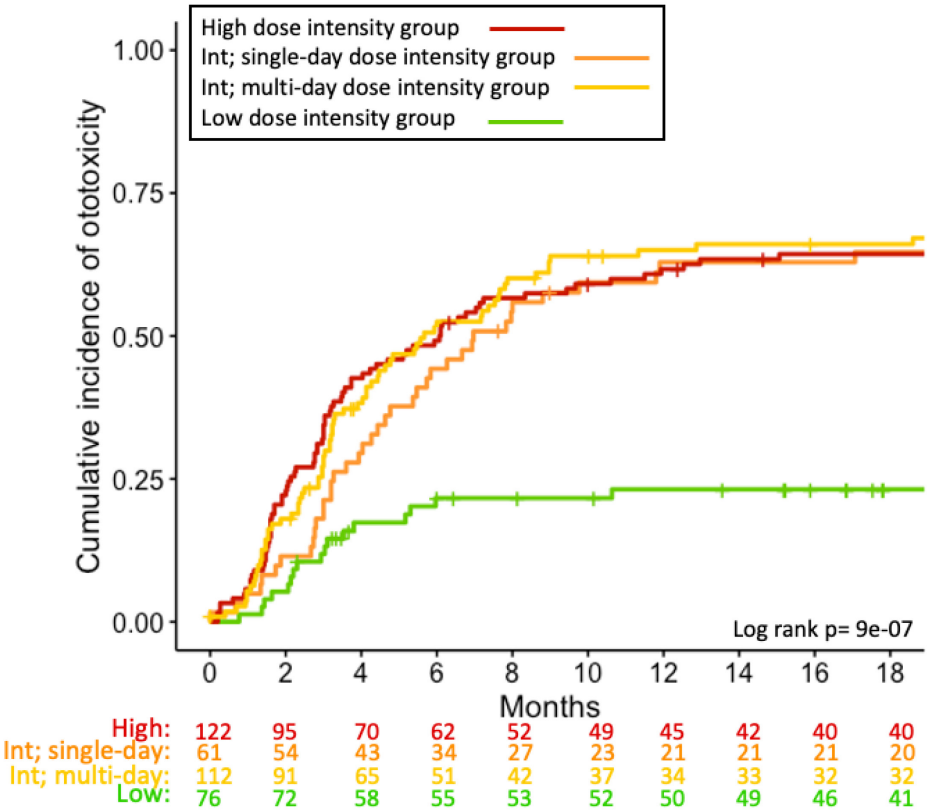
N = 371	Case n = 237	Control n = 134	P-value
Cumulative Dose (mg/m^2)			
Median (range)	400 (120, 800)	400 (55.0, 760)	0.6809
Dose to Toxicity (mg/m^2)			
Median (range)	300 (67.4, 800)	400 (55.0, 768)	**6.309e-06**

Protocols grouped to similar cisplatin dose intensities

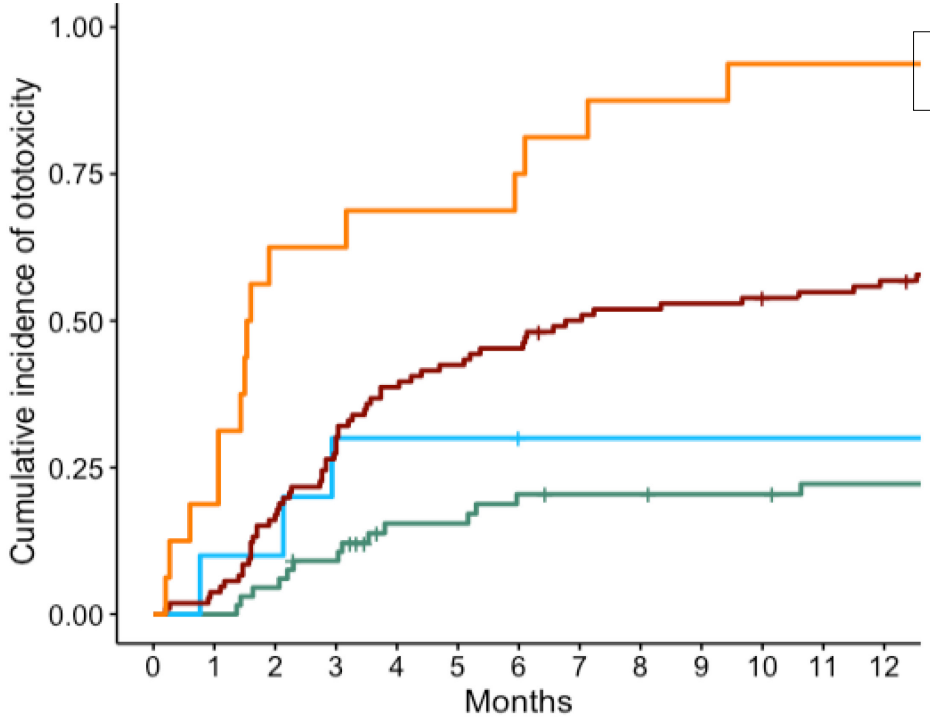
Group (intensity)	Characteristics
1. High	90-100mg/m^2 x 1 day. 21-28 days apart. 4-6 cycles. Cumulative dose 360-600mg/m^2
1. High (longer rest/blocked)	90-120mg/m^2 x 1 day. 35-90 days apart (blocks) 4-6 cycles. Cumulative dose 480-540mg/^{2}
1. High (fewer cycles)	90-100mg/m^2 x 1 day. 21-28 days apart. 2-3 cycles. Cumulative dose 180-300mg/m^2
1. Medium	75mg/m^2 x 1 day. 21-28 days apart. 6 cycles. Cumulative dose 450mg/m^2
1. Medium (longer rest/blocked)	70-75mg/m^2 x 1 day. 34-70 days apart (blocks). 6-8 cycles. Cumulative dose 420-600mg/m^2
1. Medium	60mg/m^2 x 1 day. 21 days apart. 5 cycles. Cumulative dose 300mg/m^2

Group (intensity)	Characteristics
1. Medium 2-day/cycle	50-60mg/m^2 x 2 days. 4-8 weeks apart (blocks) 4-8 cycles. Cumulative dose 450-800mg/m^2
1. Medium 4+ days/cycle	40-50mg/m^2 x 4-5 days. 28-90 days apart (blocks) 2-4 cycles. Cumulative dose 200-800mg/m^2
1. Low	20-33.3mg/m^2 over 3-5 days. 21 days apart. 4-6 cycles. Cumulative dose 400-600mg/m^2

Cumulative incidence of ototoxicity stratified by cisplatin dose intensity



Cumulative incidence of cisplatin-induced ototoxicity by dose intensity and *TPMT* carrier status



High-intensity cisplatin, ≥ 1 *TPMT* risk allele

High-intensity cisplatin, *TPMT* wild-type

Low-intensity cisplatin, ≥1 *TPMT* risk allele

Low-intensity cisplatin, *TPMT* wild-type

Red; wildtype *TPMT*:	106	89	65	58	50	48	44
Red; ≥ 1 *TPMT* variant :	16	6	5	4	2	1	1
Blue; ≥ 1 *TPMT* variant:	10	9	7	7	6	6	6
Green; wildtype *TPMT*:	66	63	51	48	47	46	44

Panel Discussion: Accelerating clinical trials in childhood cancer

Brigitte Widemann, MD

Srivandana Akshintala, MBBS, MPH

David Arons, JD

Elly Barry, MD, MSSc

Julia Glade Bender, MD

Kristine R. Broglio, MS

Bruce Carleton, PharmD, FCP, FISPE

Donna Rivera, PharmD, MSc

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