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

Childhood Cancer Data Initiative (CCDI)

NIH NATIONAL CANCER INSTITUTE

November 18, 2022

Agenda

1. ***Need for a National Initiative***
2. ***Requirements for a National Initiative***

Gregory Reaman, MD, FASCO

Scientific Director, Childhood Cancer Data Initiative

National Cancer Institute

Brigette Wideman, MD

Special Advisor to the NCI Director for Childhood Cancer

National Cancer Institute

Monica Bertagnolli, MD

Director of the National Cancer Institute

Morning Session

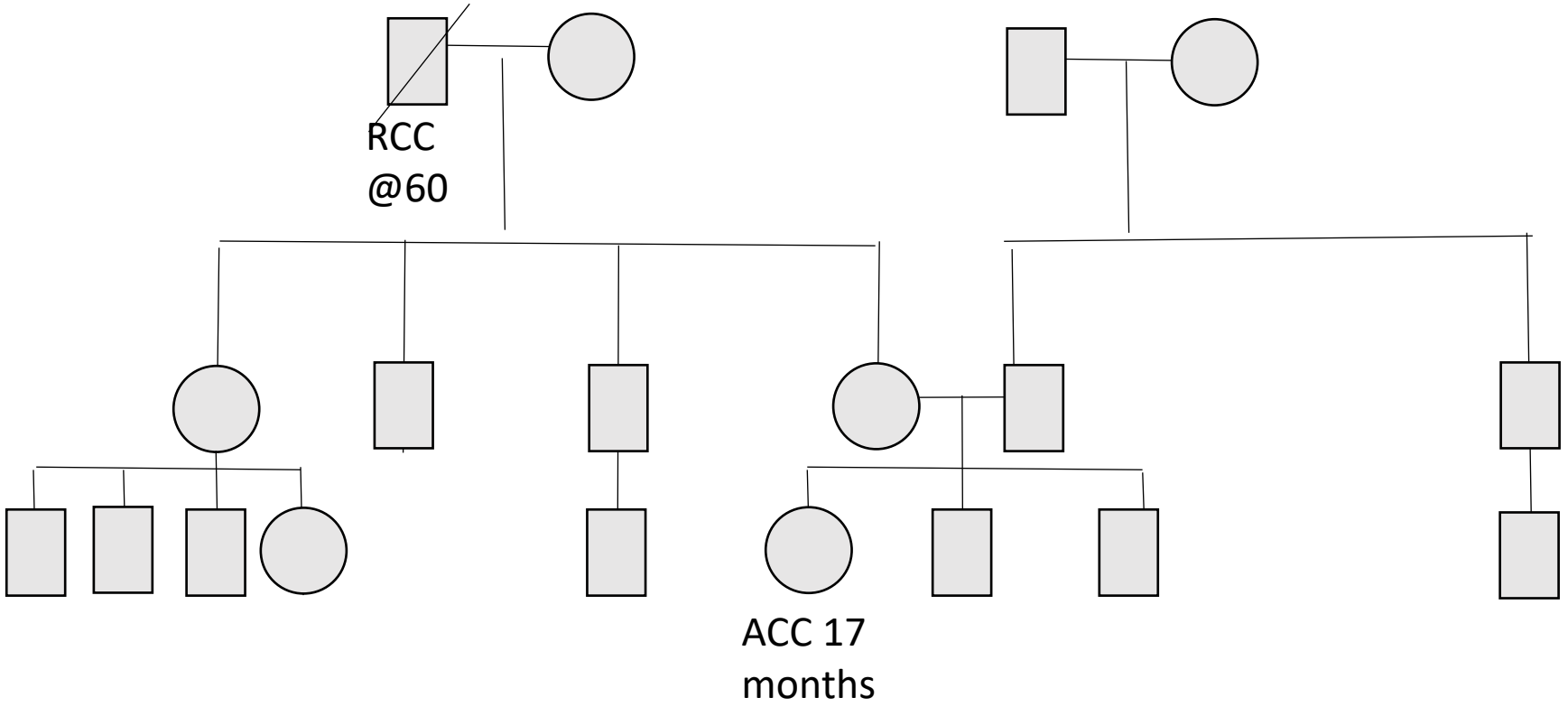
Ann Ramer, MPH

Patient Advocate

Rare Disease: A Case Study

Ann Ramer

November 18, 2022



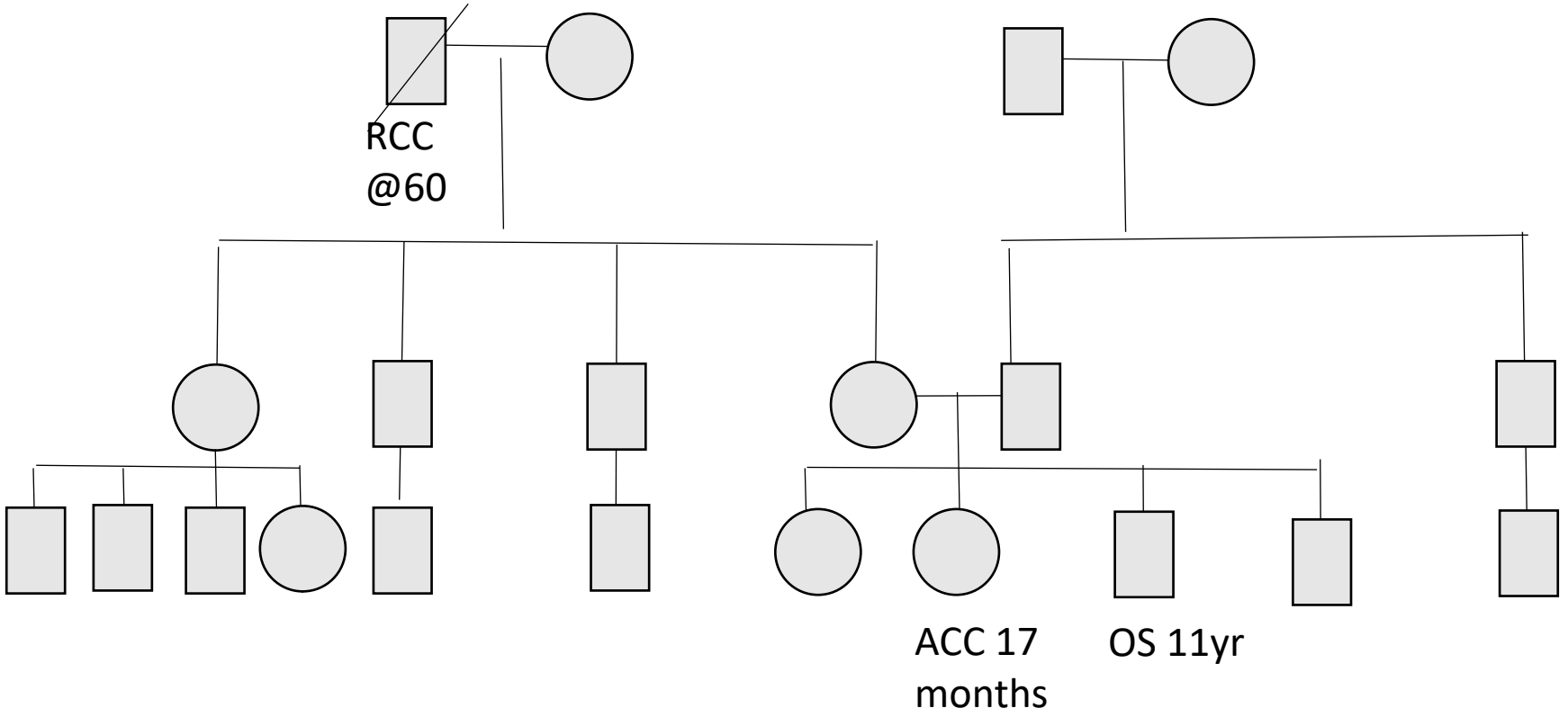
March 2004

Clinical decisions in 2004

- Surgical resection (negative margins)
- No chemotherapy approved for this 4 cm tumor
- Adrenal Cancer is highly suspicious for Li-Fraumeni Syndrome, which has implications for the two brothers.
- Tumor sample was sent out to test for excess TP53 protein
- One month later, results showed no excess p53 protein in the tumor.
- Regular CT imaging and bloodwork was conducted looking for elevated testosterone
- Ended follow-up in late 2005, NED

"Pretend this never happened."

Seven years later.....



Aug 2011

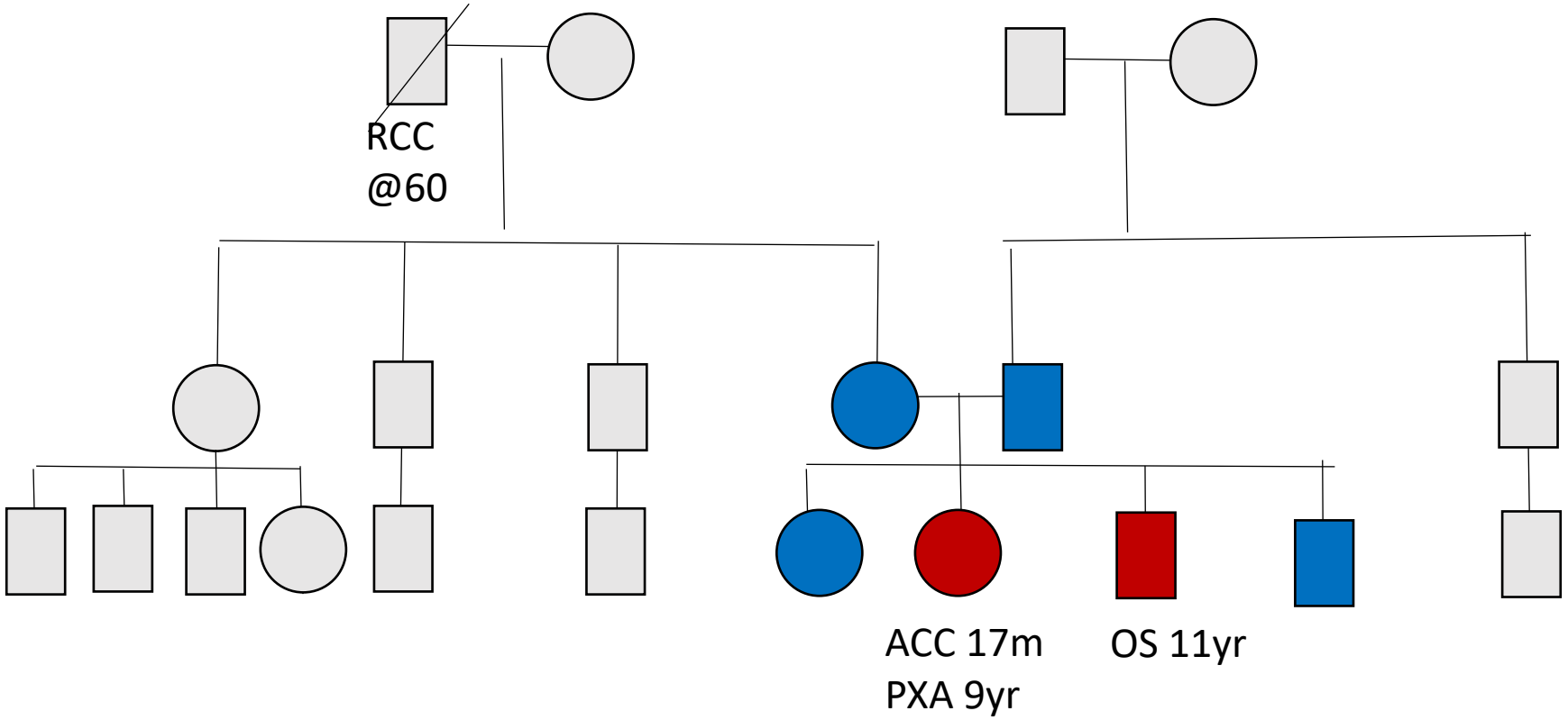
Armed with information

Test: **p53 gene, full gene sequencing**

Result and Interpretation: **Positive, predicted to be deleterious: a heterozygous deletion of TTTCC and insertion of AAAA at nucleotides 12248 to 12252 resulting in a frameshift mutation at codon 108 in the p53 gene (g.12248_12252delTTTCCinsAAAA; p.Gly108GlyfsX15).**

A change from the "normal" or wild type sequence of the p53 gene was detected in this sample.

This genetic alteration creates a frameshift mutation at codon 108, resulting in premature truncation of the p53 protein. To our knowledge, this alteration has not been previously reported in the literature, nor has it been previously detected in our laboratory. This alteration results in major disruption in the structure of the p53 protein and is predicted to be deleterious to the normal function of the protein. This sample is heterozygous for this alteration, having an apparently "normal" or wild type copy of the p53 gene along with the altered copy. This result does not rule out the possibility of a sequence alteration in one or more regions of the gene that have not been analyzed. Furthermore, DNA sequence analysis will not detect certain large genetic alterations, such as duplications, deletions or inversions. Although DNA sequence analysis is very sensitive, there remains some possibility that a sequence alteration in the regions analyzed will not be detected due to technical or systematic error. The results of testing should always be interpreted in the context of clinical and familial data.



December 2011

Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: a prospective observational study

Anita Villani, Uri Tabori, Joshua Schiffman, Adam Shlien, Joseph Beyene, Harriet Druker, Ana Novokmet, Jonathan Finlay, David Malkin

Summary

Background Individuals with Li-Fraumeni syndrome have a high lifetime risk of developing cancer. We assessed the feasibility and potential clinical effect of a comprehensive surveillance protocol in asymptomatic *TP53* mutation carriers in families with this syndrome.

Methods We implemented a clinical surveillance protocol, using frequent biochemical and imaging studies, for asymptomatic *TP53* mutation carriers on Jan 1, 2004, and did a prospective observational study of members of eight families with Li-Fraumeni syndrome who either chose to undergo surveillance or chose not to undergo surveillance. The primary outcome measure was detection of new cancers. The secondary outcome measure was overall survival.

Findings As of Nov 1, 2010, 33 *TP53* mutation carriers were identified, 18 of whom underwent surveillance. The surveillance protocol detected ten asymptomatic tumours in seven patients, including small, high-grade tumours and low-grade or premalignant tumours. All seven mutation carriers were alive after a median follow-up of 24 months (IQR 22–65 months). 12 high-grade, high-stage tumours developed in 10 individuals in the non-surveillance group, two of whom (20%) were alive at the end of follow-up (p=0·0417 for comparison with survival in the surveillance group). 3-year overall survival was 100% in the surveillance group and 21% (95% CI 4–48%) in the non-surveillance group (p=0·0155).

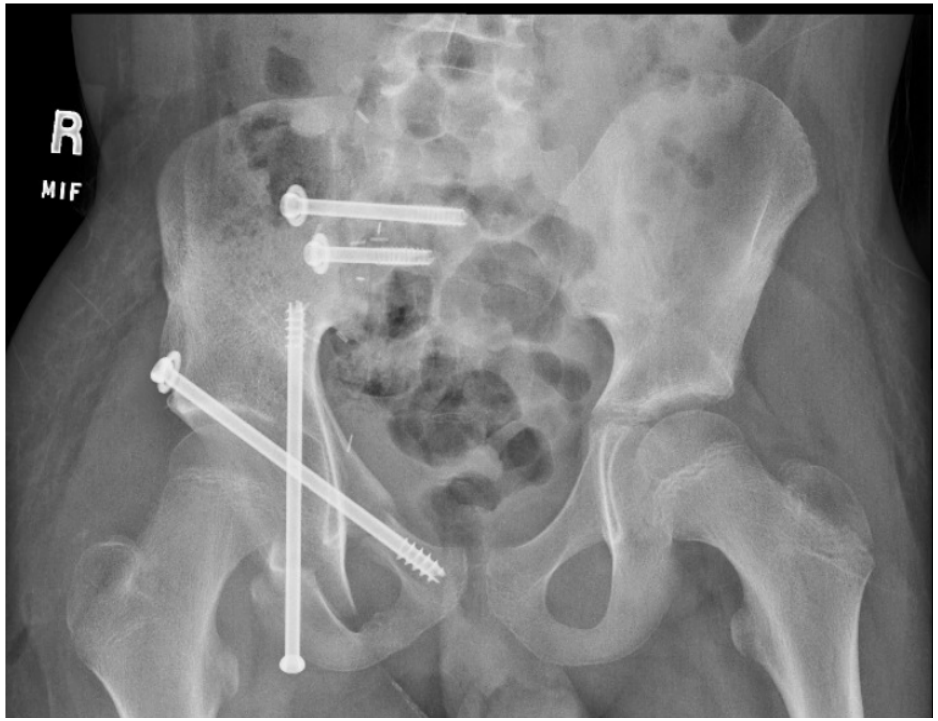
Interpretation Our findings show the feasibility of a clinical surveillance protocol for the detection of asymptomatic neoplasms in individuals with germline *TP53* mutations. This strategy offers a management option for affected individuals, and its benefits lend support to the use of early genetic testing of at-risk individuals and families.

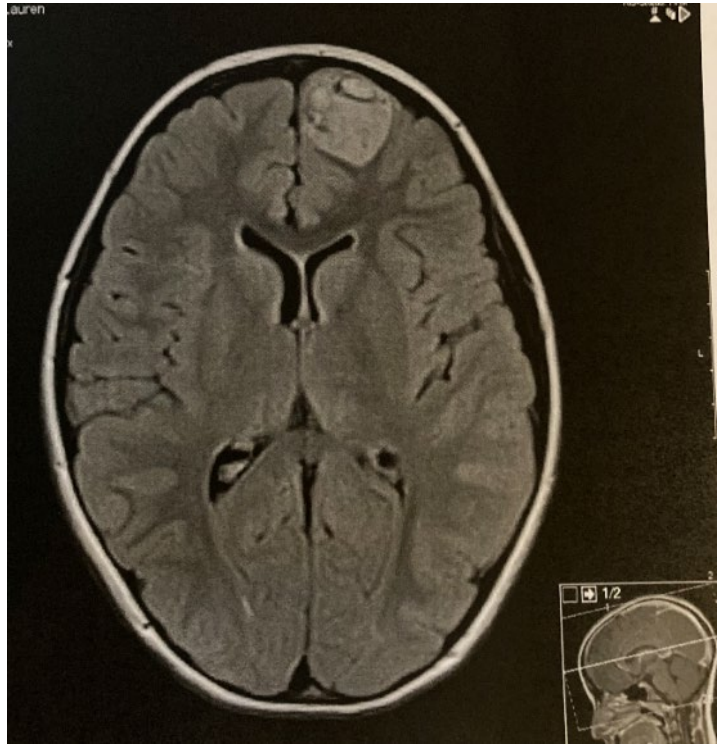
Lancet Oncol 2011; 12: 559–67

Published Online
May 20, 2011
DOI:10.1016/S1470-2045(11)70119-X

Department of Pediatrics (A Villani MD, U Tabori MD, Prof D Malkin MD), **Division of Hematology/Oncology** (A Villani, U Tabori, H Druker MSc, Prof D Malkin), **Genetics and Genomic Biology Program** (U Tabori, A Shlien PhD, A Novokmet BA, Prof D Malkin), **The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; Division of Pediatric Hematology/Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA** (J Schiffman MD); **Program in Population Genomics, Department of Clinical Epidemiology and Biostatistics, Faculty of Health**

Radiological Snapshot





Family Snapshot

Research efforts supported

Dr. Raul Ribero St. Jude ACC study

Dr. Anna Mitchell- Germ cell mosaicism

NCI Metformin Study

IMPACT study

EDI-SYN study

PROMPT Study

Tumor wrangling for over a year

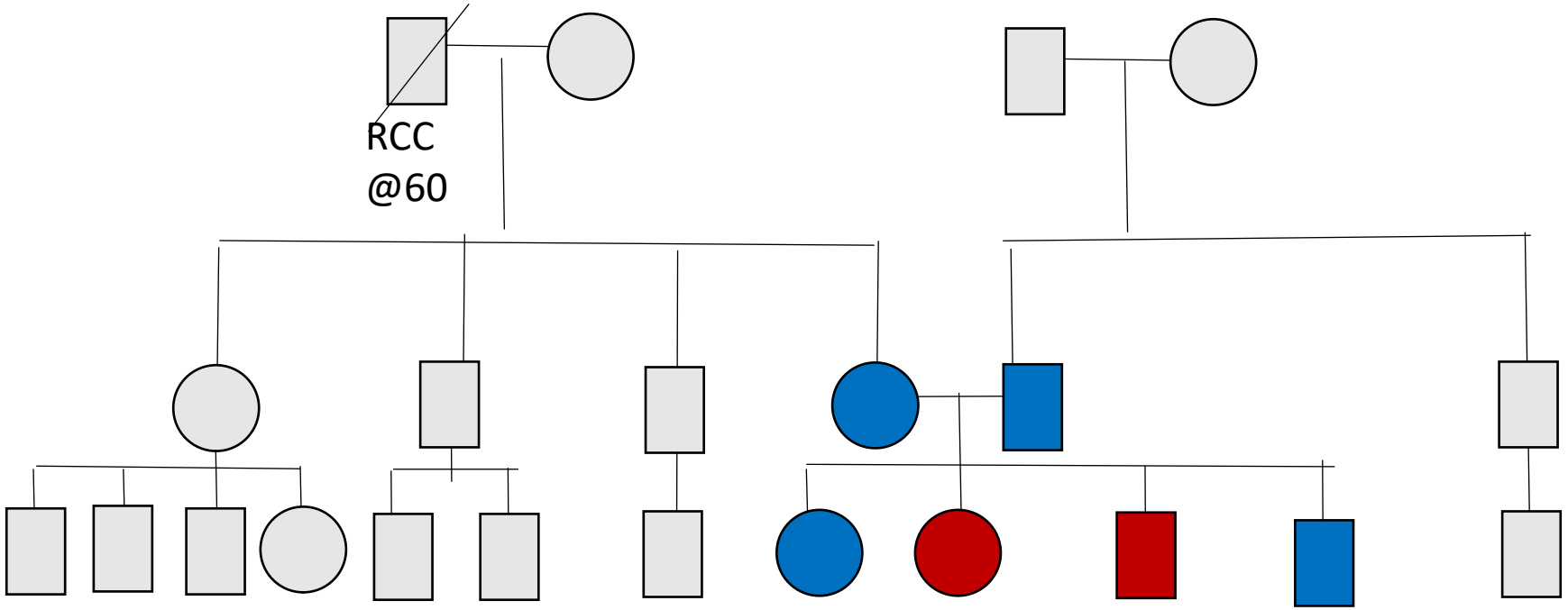
Clinical implications for family

Excluded for age, mosaicism

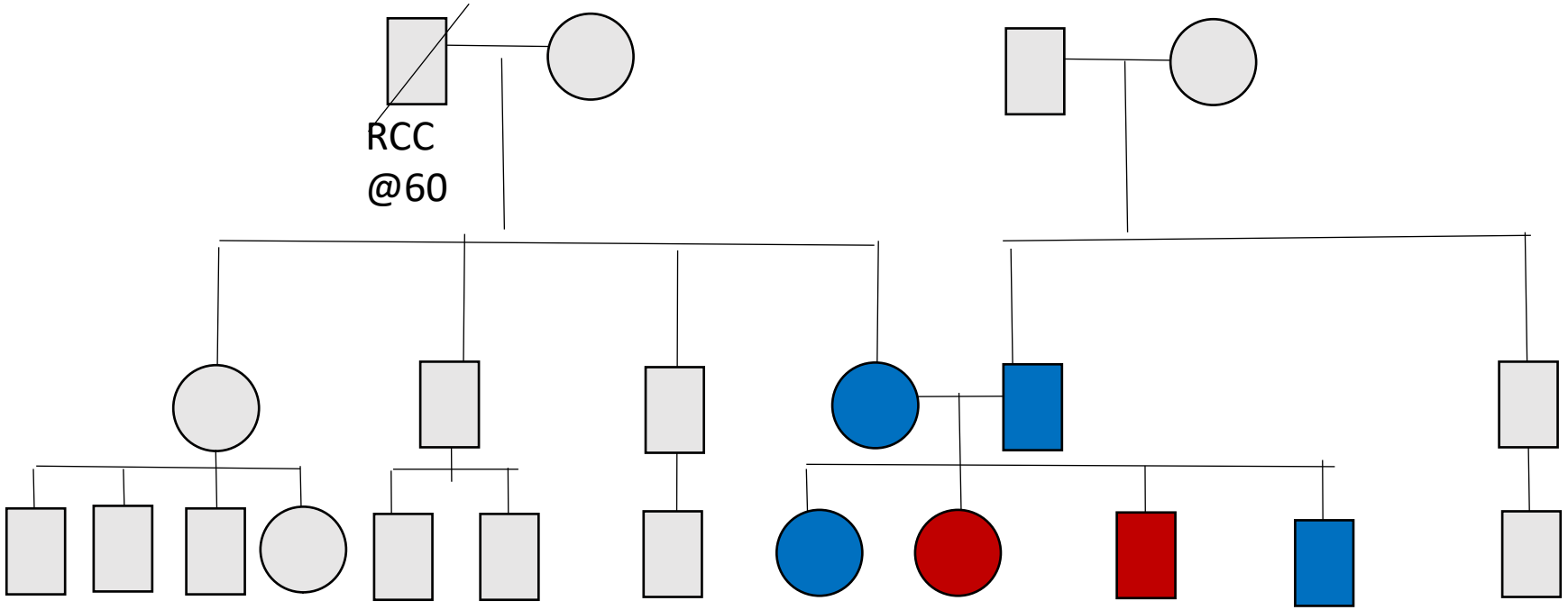
MSK-IMPACT basket trials

Liquid biopsy in LFS

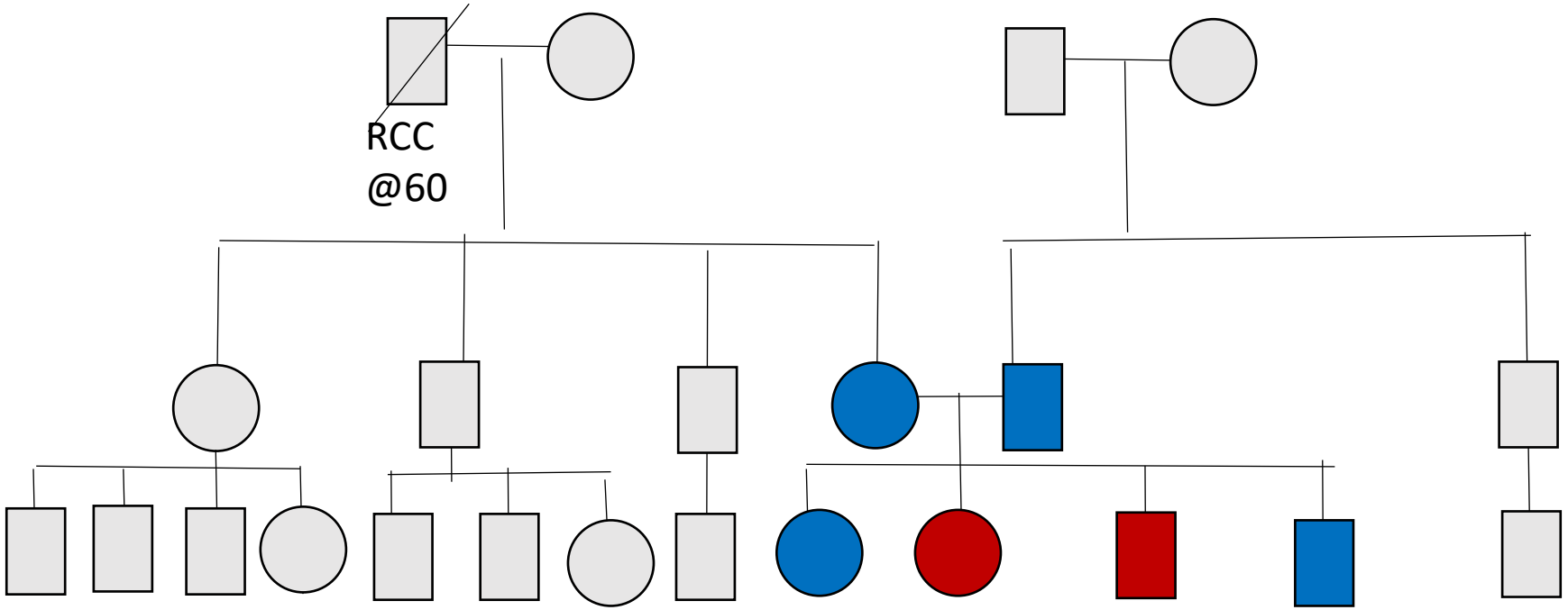
Enrolled
and encouraged participation in online support groups


RCC
@60
ACC 17m
PXA G2 9yr
PXA Gr3 12
OS 11yr
Melanoma
3a 14yr
MDS
T-AML 15yr
BMT

August 2015



January 2016

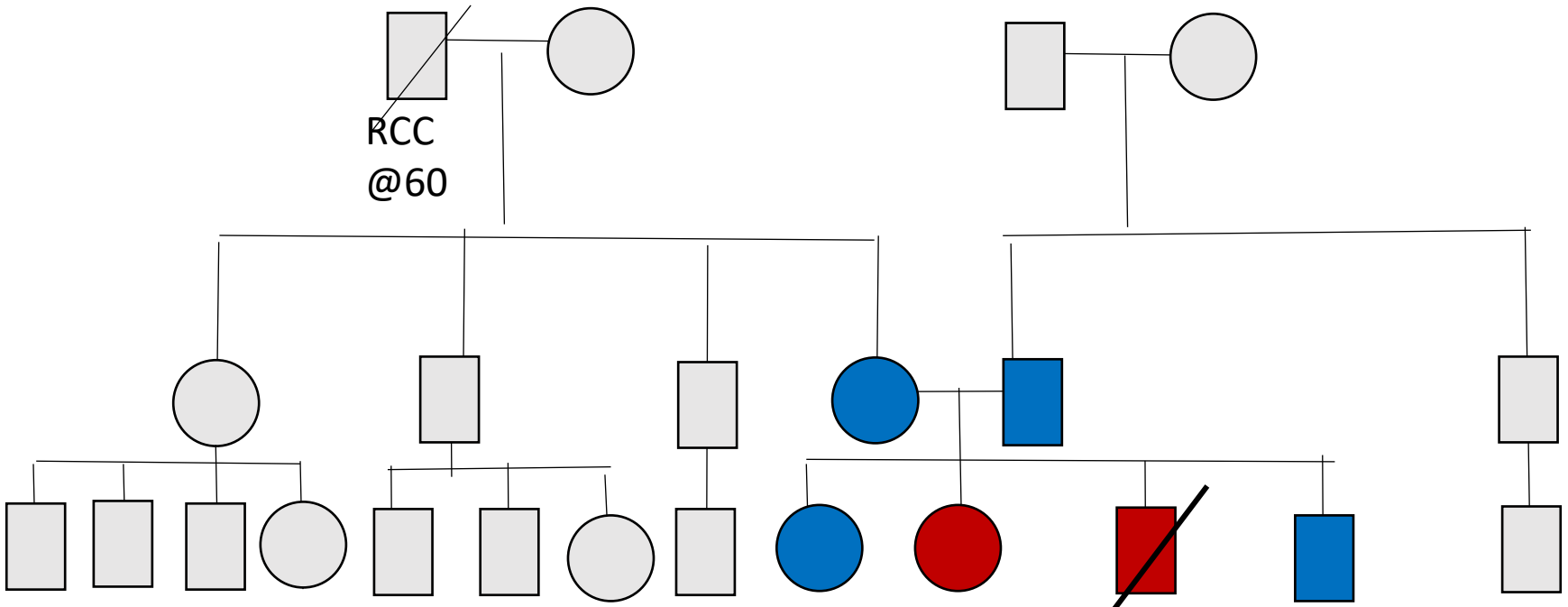

RCC
@60
ACC 17m
PXA-2 9yr
PXA-3 12yr
Suspected
relapse
OS 14yr
OS 11yr
Melanoma
3a 14yr
T-AML 15yr
BMT
Relapse
Second relapse

July 2017

Christmas 2017

MAP Chemotherapy

Waiting for CD-33 CAR-T clinical trial



ACC 17m
PXA-2 9yr
PXA-3 12yr
Suspected relapse
OS 14yr
Metastatic OS
15yr

OS 11yr
Melanoma
3a 14yr
T-AML 15yr
BMT
Relapse
Second relapse
Died 18yr 2mos

March 2018

Looking forward with optimism, rather than looking back with regret

- Tumor and germ line testing
- Clinical data is paired with genomic data
- Analysis across tumor types
- Fewer barriers between research and clinical care
- Engagement with advocacy groups
- Centralized data and biorepository
- Data can be queried to answer multiple questions
- Larger more robust data sets


Thank
YOU!

Morning Session

Ted Laetsch, MD

Pediatric Oncologist

Cancer Center at Children's Hospital of Philadelphia

NEED FOR COORDINATED EFFORT IN PEDIATRIC RARE CANCERS

Theodore W. Laetsch, MD
Associate Professor of Pediatrics
Children's Hospital of Philadelphia/University of Pennsylvania

November 18, 2022

Children's Hospital of Philadelphia®
Cancer Center

PEDIATRIC RARE TUMORS

- NCI defines rare cancer as occurring in <40,000 people/year in US
  - All pediatric cancers are rare by this definition
- EXPeRT (European) consortium proposes definition of <2 cases/million/year and/or not considered in clinical trials
- COG generally uses the definition of extra-cranial solid tumors not included in other disease groups' clinical trials
- Definitions become more challenging in molecular era:
  - ALK-mutated neuroblastoma – incidence ~1 case/million/year
  - NTRK fusion cancers – pediatric incidence 1-3 cases/million/year
- Comprise ~10% of pediatric cancers
  - Improvement in outcomes substantially less than common pediatric cancers

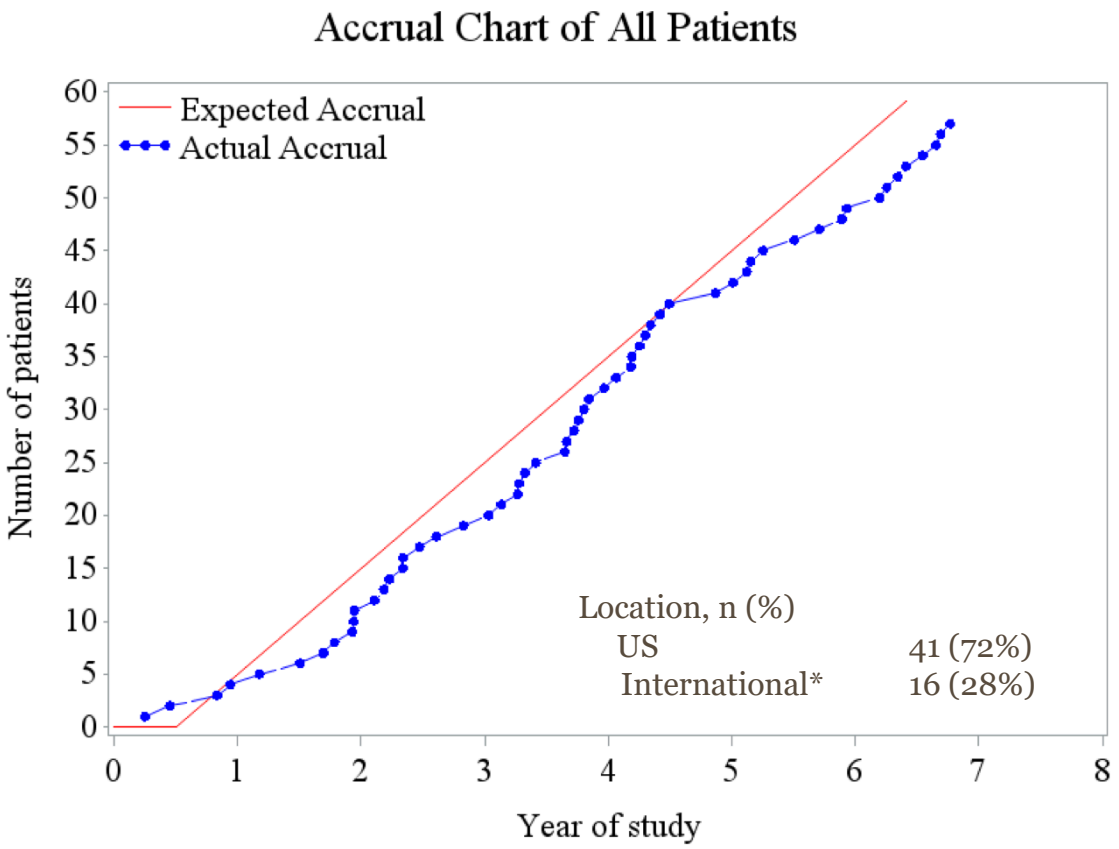
Pappo. JCO. 2015. Trigg. Cancers. 2018. Zhao. JCO PO. 2021.

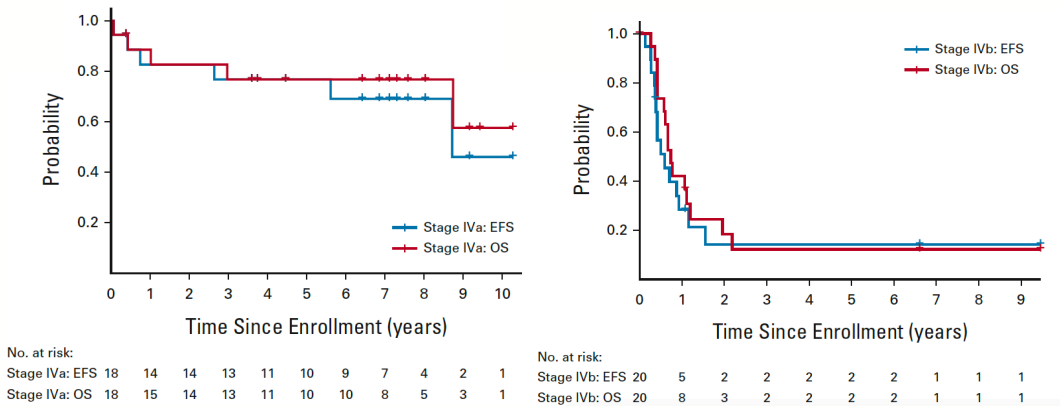
SUCCESSFUL RARE TUMOR INITIATIVES

Children's Hospital of Philadelphia®
Cancer Center

ARET0321 – METASTATIC RETINOBLASTOMA

- Very rare in US





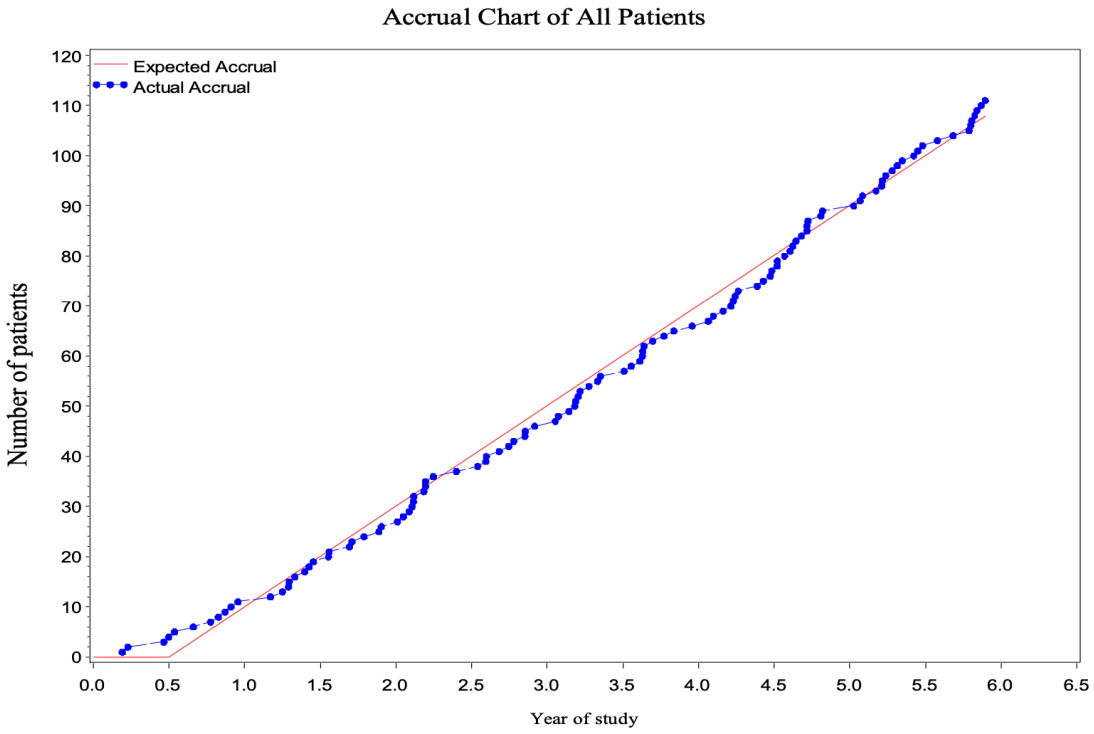
- Defined SOC in patients with extra-cranial metastases
- Spurred ongoing international discussion of trial for patients with CNS metastases
- GlobalREACH – International Rb data commons

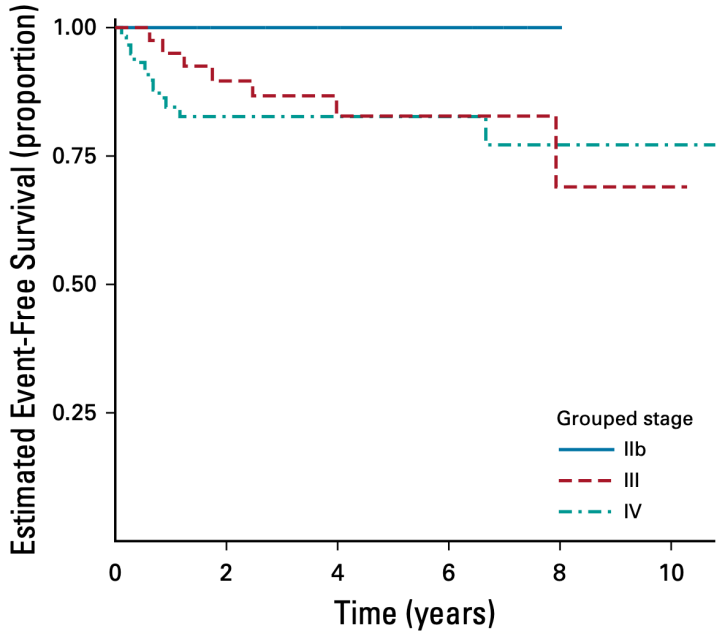
Children's Hospital of Philadelphia® Cancer Center

Rodriguez-Galindo. JCO. 2019

ARAR0331 – NASOPHARYNGEAL CARCINOMA

- ~50 cases per year in US





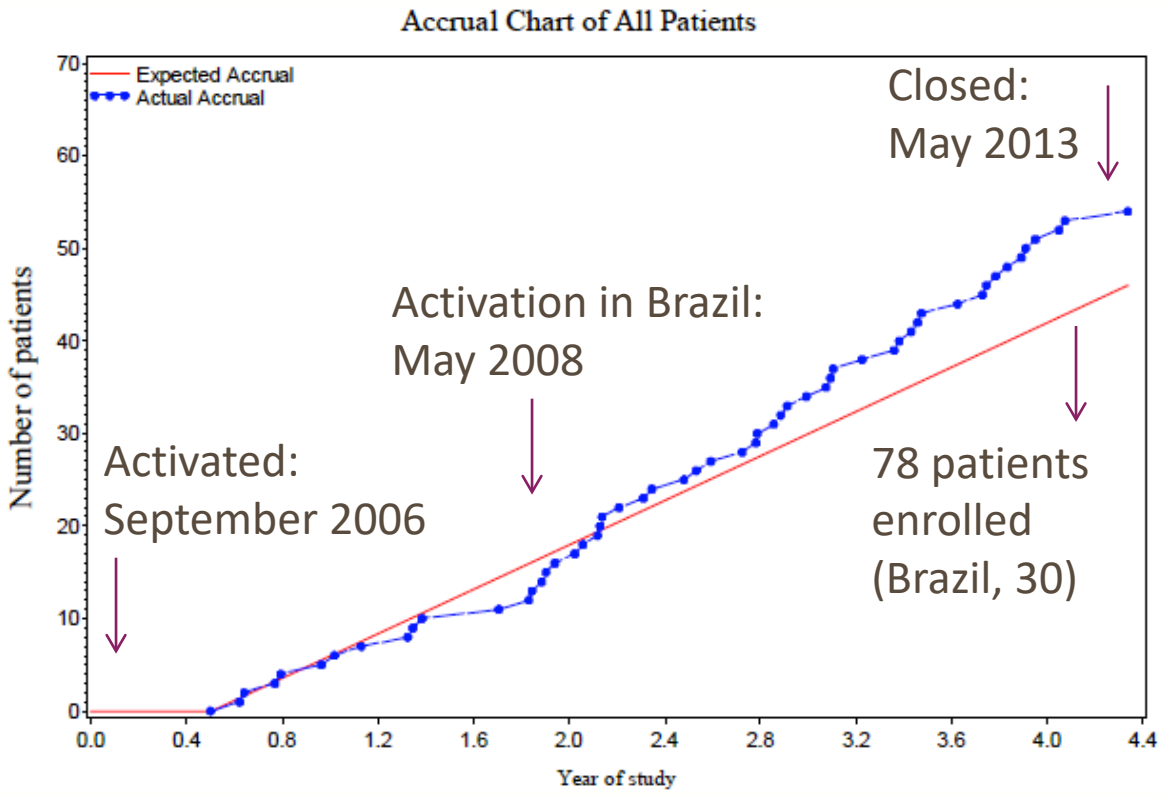
- Identified African American predominance in this disease
- Defined SOC in children
- International NPC data commons in development

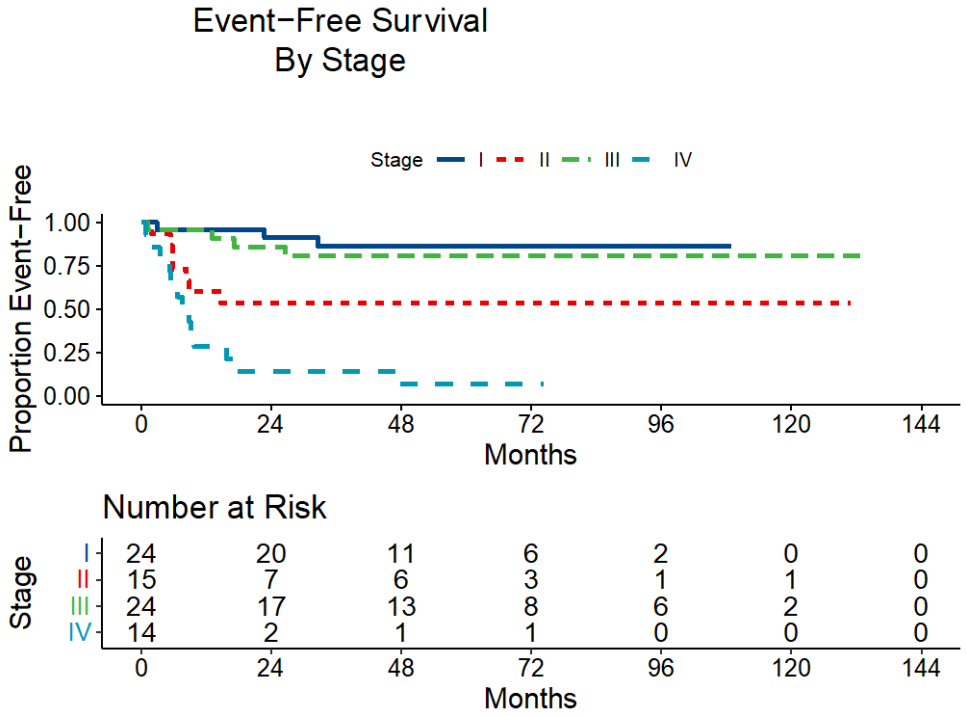
Children's Hospital of Philadelphia®
Cancer Center

Rodriguez-Galindo. JCO. 2019

ARAR0332 – ADRENOCORTICAL CARCINOMA

- ~25 cases per year in US





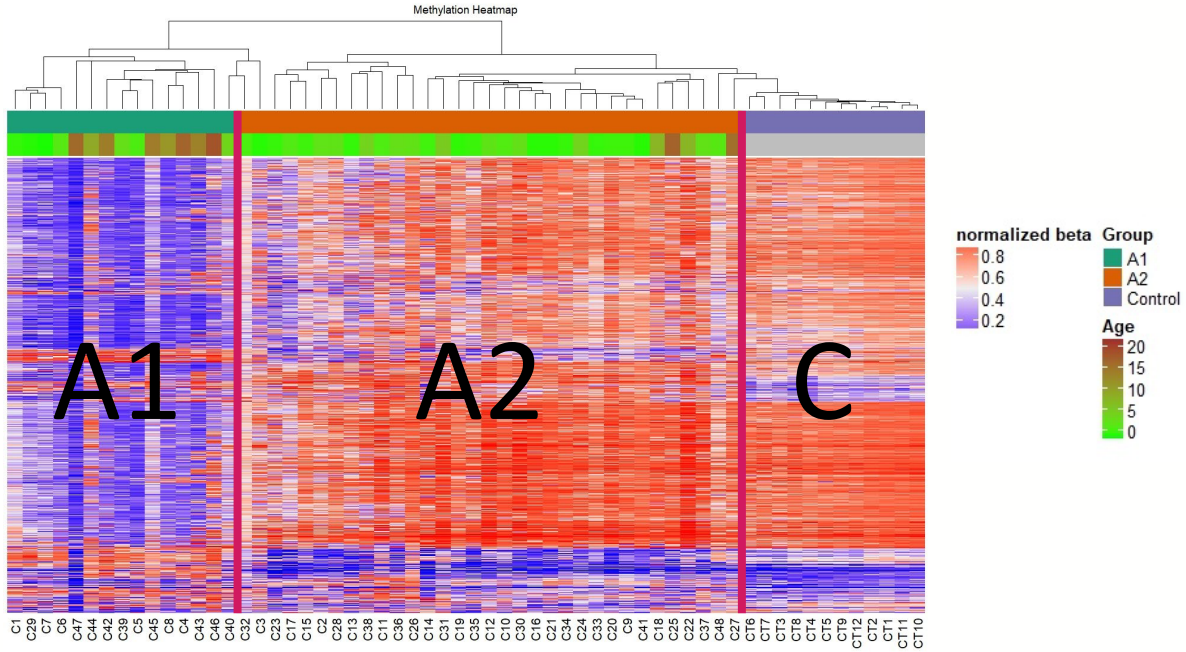
- Defined SOC for patients with stage I and III disease
- Demonstrated therapy inadequate for patients with stage II and IV disease

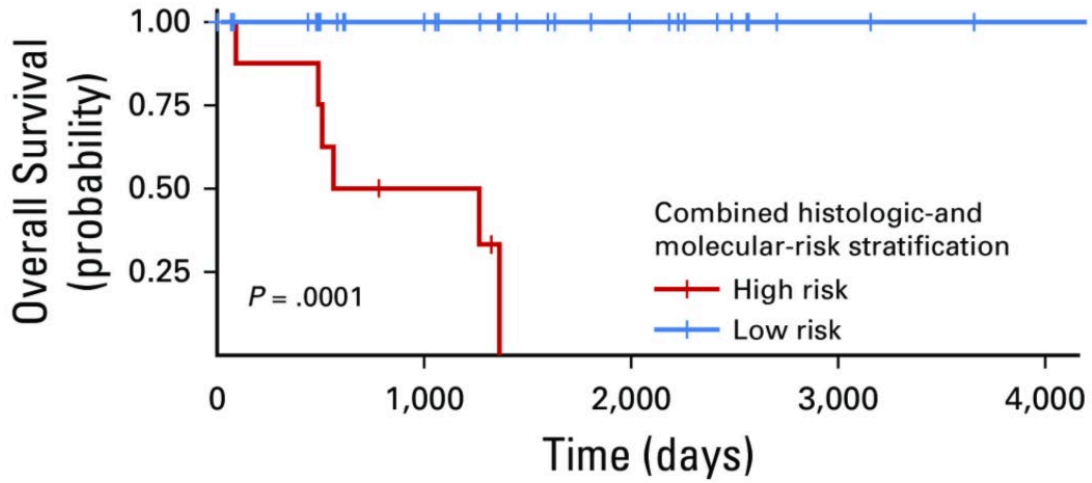
Children's Hospital of Philadelphia® Cancer Center

Rodriguez-Galindo. JCO. 2021

INTERNATIONAL PEDIATRIC ADRENOCORTICAL TUMOR REGISTRY

- Detailed histology and clinical outcomes
- Methylation profiling, WGS/WES





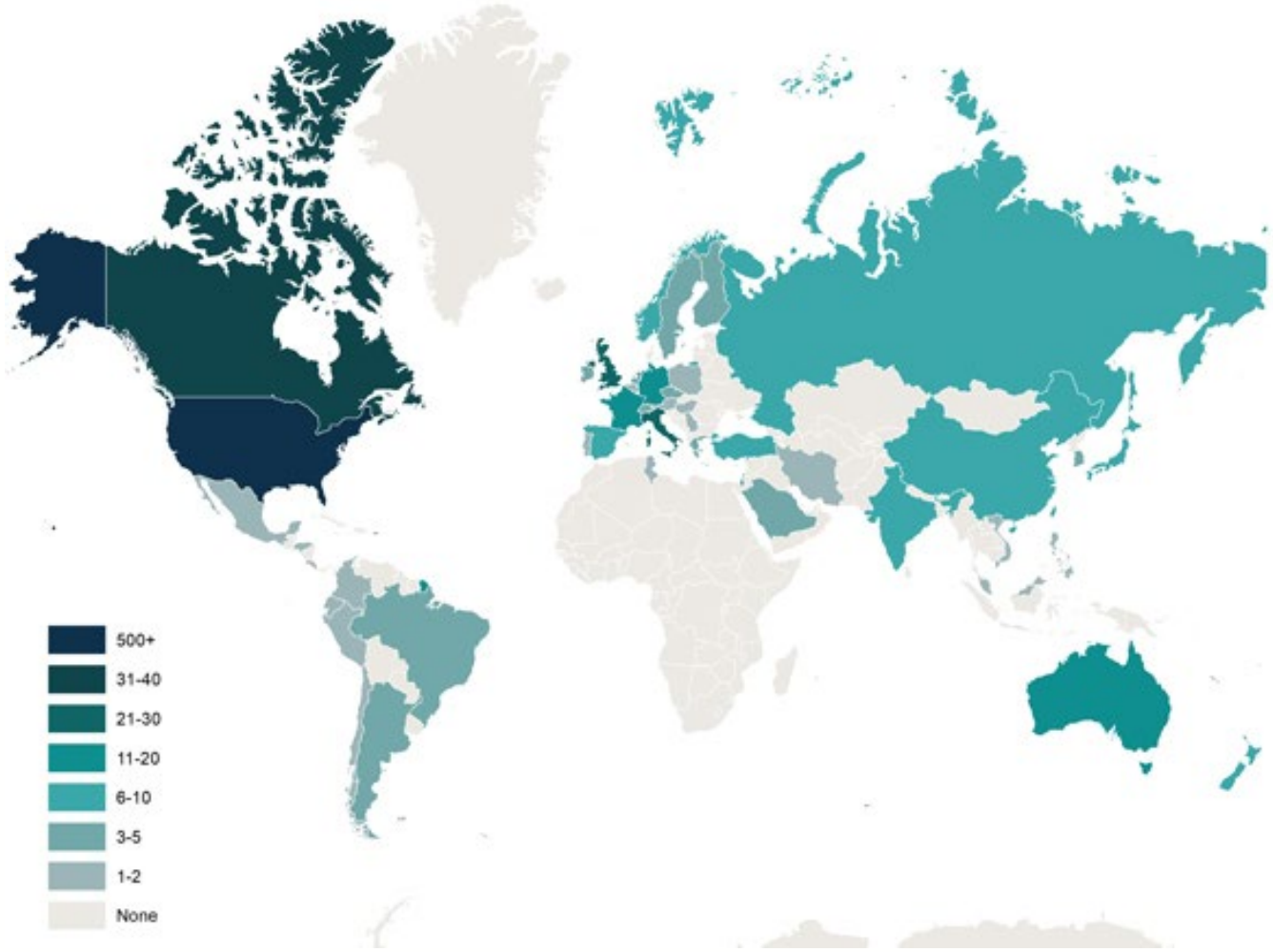
- Currently being validated with COG specimens/data
- If confirmed, plan to propose risk stratification on next COG study

Clay. JCO PO. 2019.

Children's Hospital of Philadelphia® Cancer Center

PPB/DICER1 REGISTRY

- Treatment recommendations
  - Not a clinical trial
- Central review of pathology
- Clinical/treatment/outcome data
- Biospecimen collection
- Imaging collection
- Led to multiple discoveries, proposed COG trial – ARAR2131



EXPERT/PARTNER CONSORTIUM (EUROPE)

Reviews and Therapy Recommendations

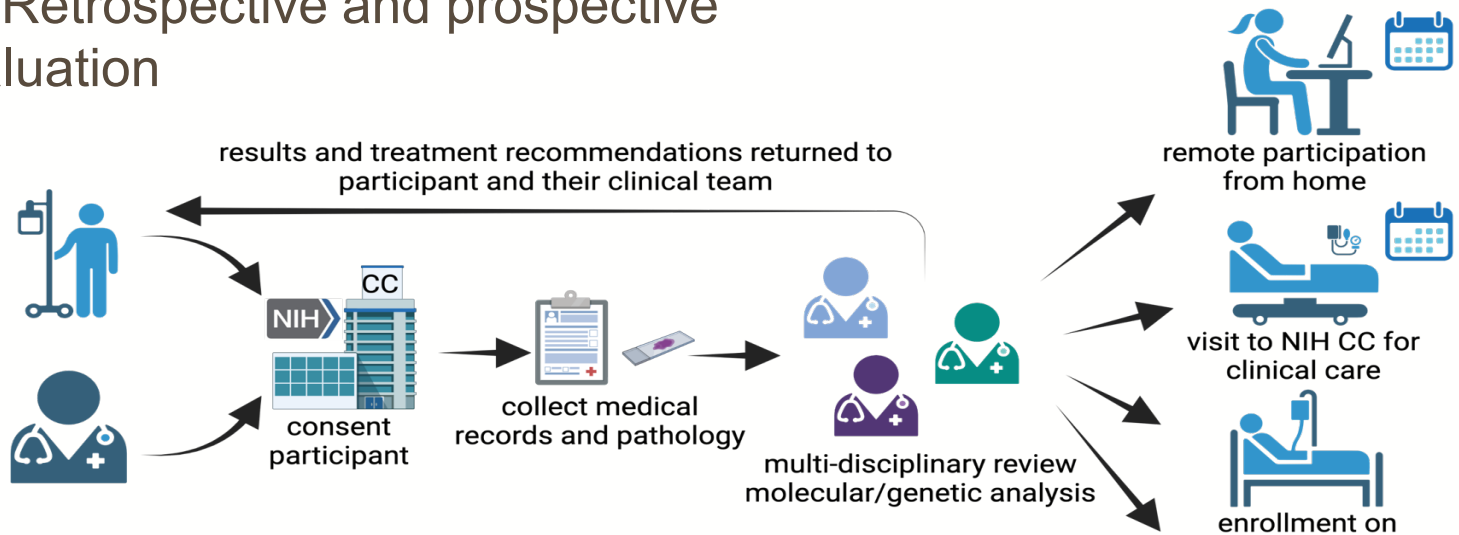
Lemelle, L.; Flaadt, T.; Fr...	2022	NUT Carcinoma in Children and Adolescents: The Expert European Standard Clinical...	J Pediatr Hematol Oncol
Abele, M.; Bajčiová, V.; W...	2022	Primary lung carcinoma in children and adolescents: An analysis of the European Co...	Eur J Cancer
Virgone, C.; Roganovic, J...	2021	Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnos...	Pediatr Blood Cancer
Surun, A.; Schneider, D. T...	2021	Salivary gland carcinoma in children and adolescents: The EXPeRT/PARTNER diagn...	Pediatr Blood Cancer
Stachowicz-Stencel, T.;...	2021	Thymoma and thymic carcinoma in children and adolescents: The EXPeRT/PARTNE...	Pediatr Blood Cancer
Schneider, D. T.; Orbach,...	2021	Consensus recommendations from the EXPeRT/PARTNER groups for the diagnosis...	Pediatr Blood Cancer
Ferrari, A.; Lopez Almara...	2021	Cutaneous melanoma in children and adolescents: The EXPeRT/PARTNER diagnosti...	Pediatr Blood Cancer
Bisogno, G.; Sarnacki, S.;...	2021	Pleuropulmonary blastoma in children and adolescents: The EXPeRT/PARTNER diag...	Pediatr Blood Cancer
Bien, E.; Roganovic, J.; K...	2021	Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recom...	Pediatr Blood Cancer
Ben-Ami, T.; Kontny, U.;...	2021	Nasopharyngeal carcinoma in children and adolescents: The EXPeRT/PARTNER diag...	Pediatr Blood Cancer
Orbach, D.; André, N.; Br...	2020	Mesothelioma in children and adolescents: the European Cooperative Study Group f...	Eur J Cancer
Cecchetto, G.; Ganarin, A...	2017	Outcome and prognostic factors in high-risk childhood adrenocortical carcinomas:...	Pediatr Blood Cancer
Stachowicz-Stencel, T.;...	2015	Thymoma and thymic carcinoma in children and adolescents: a report from the Euro...	Eur J Cancer
Schneider, D. T.; Orbach,...	2015	Ovarian Sertoli Leydig cell tumours in children and adolescents: an analysis of the E...	Eur J Cancer
Bisogno, G.; Brennan, B.;...	2014	Treatment and prognostic factors in pleuropulmonary blastoma: an EXPeRT report	Eur J Cancer
Bien, E.; Godzinski, J.; Da...	2011	Pancreatoblastoma: a report from the European cooperative study group for paediat...	Eur J Cancer

Very Rare Tumor –
Virtual Tumor Board

MYPART: MY PEDIATRIC AND ADULT RARE TUMOR NETWORK

CANCER MOONSHOT

- **Primary objective:** Comprehensively and longitudinally evaluate the natural history of pediatric and young adult rare solid tumors or tumor predisposition syndromes defining the clinical spectrum
- **Eligibility: Children and adults** with rare solid tumors / biological relatives
  - Rare tumor defined as <15 cases per 100,000
  - Off or on site (NIH Clinical Center) participation
  - Treatment recommendations
- **Standardized longitudinal evaluation:** Retrospective and prospective
  - Medical and family history, clinical evaluation
  - Patient reported outcomes
  - Medical record data extraction
- **Comprehensive molecular profiling**
  - Tumor tissue, blood, saliva
- **Molecular tumor board**
- **Genetic counseling**
- **Annotated biospecimen repository**
- **Development of interventional trials**



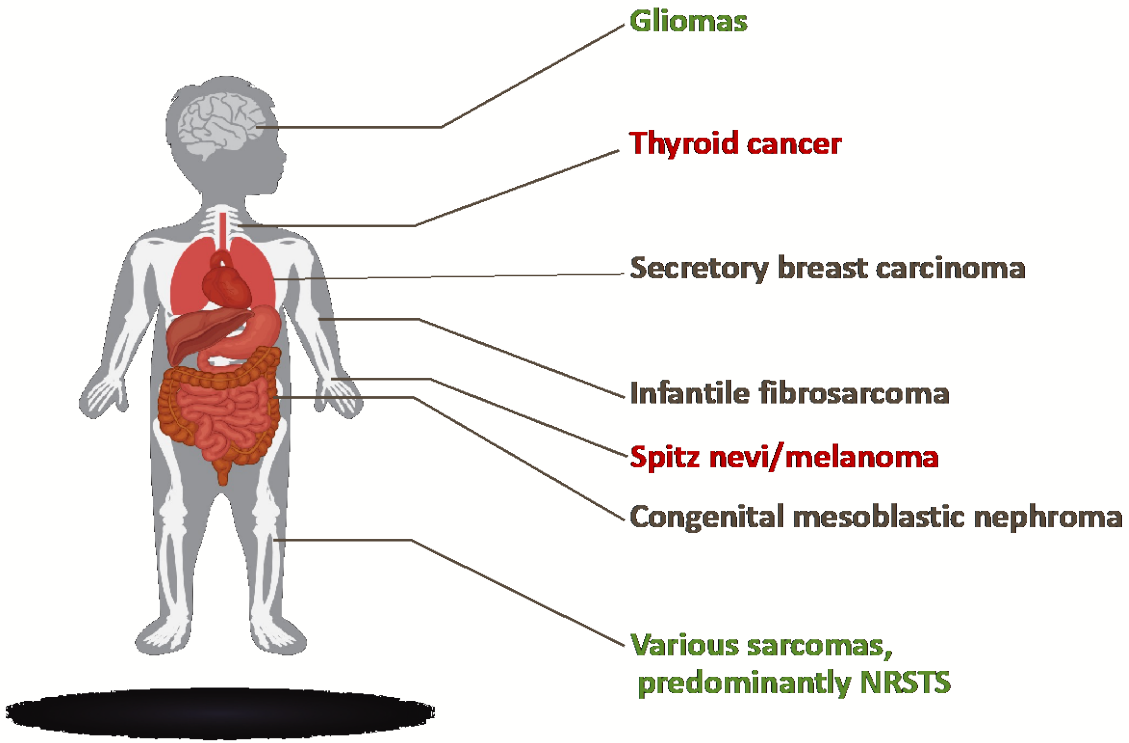
NCI MyPART My Pediatric and Adult Rare Tumor Network

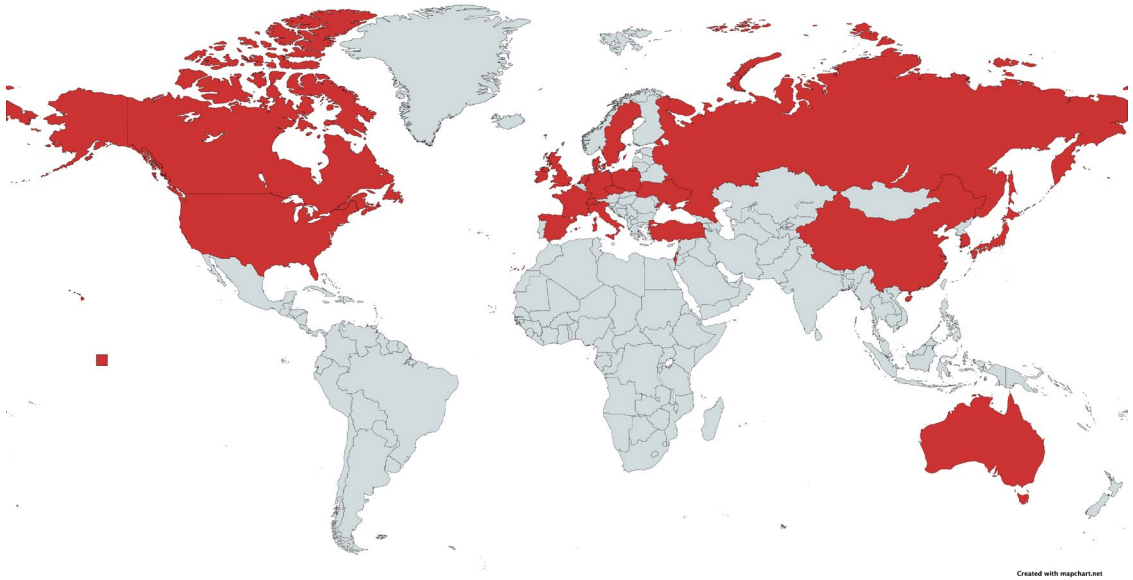
A program of the National Cancer Institute of the National Institutes of Health

https://www.cancer.gov/pediatric-adult-rare-tumor NCT03739827

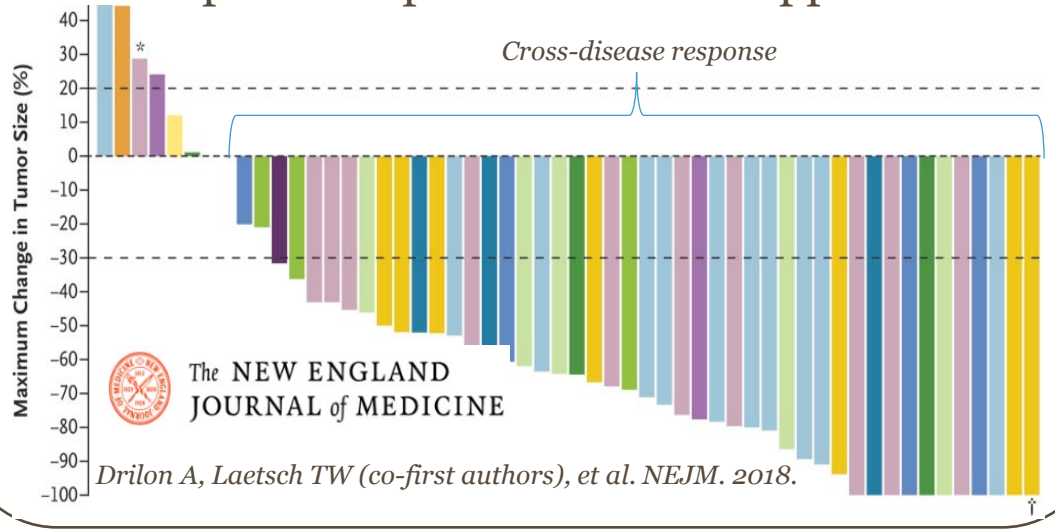
INDUSTRY – LAROTRECTINIB

NTRK Fusions





12 pediatric patients -> FDA approval

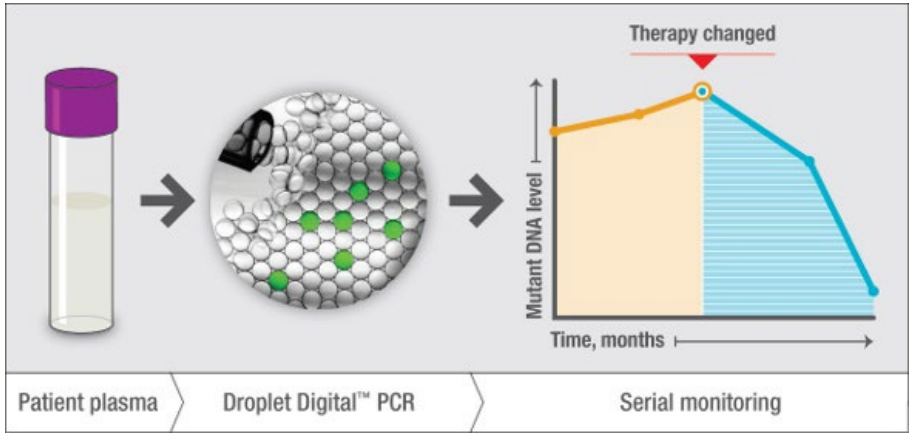


Drilon A, Laetsch TW (co-first authors), et al. NEJM. 2018.

Children's Hospital of Philadelphia®
Cancer Center

ONGOING CLINICAL TRIALS OF FRONTLINE LAROTRECTINIB

- ADVL1823: single agent frontline larotrectinib across histologies
- CONNECT1903: concurrent larotrectinib + chemotherapy for pediatric patients with CNS tumors
- DOD funded study to enhance RAI avidity for patients with thyroid cancer



ADVL1823 biospecimens for correlative studies:
- ctDNA
- Pre-treatment and post-therapy tissue
  - Central sequencing
  - Histology/diagnosis of NTRK fusion
  - Response to therapy

Proposal to gather and study specimens from patients enrolled to industry-sponsored study

Children's Hospital of Philadelphia® Cancer Center

LESSONS FROM SUCCESSFUL APPROACHES TO STUDYING RARE TUMORS

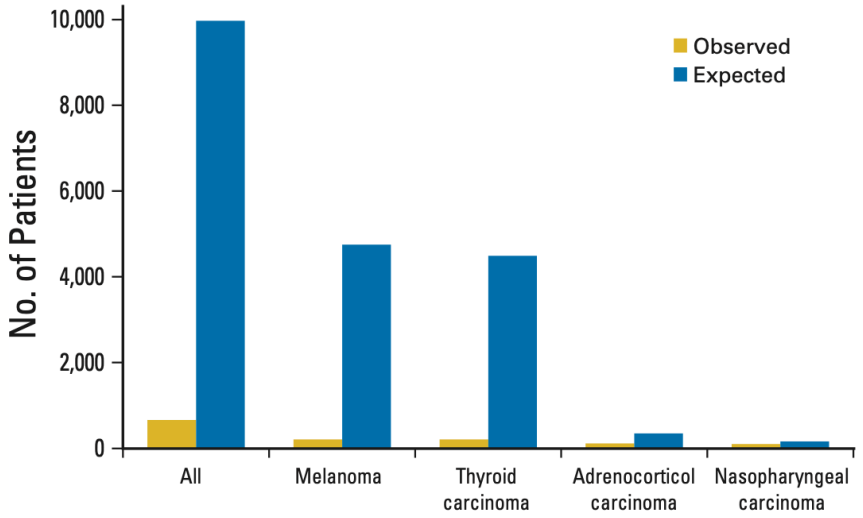
- Small studies can make huge difference
  - Studies of ≤20 patients can be very informative when there is no standard of care
- Collaboration is key!
  - Most successful studies have been international
- Need disease champions

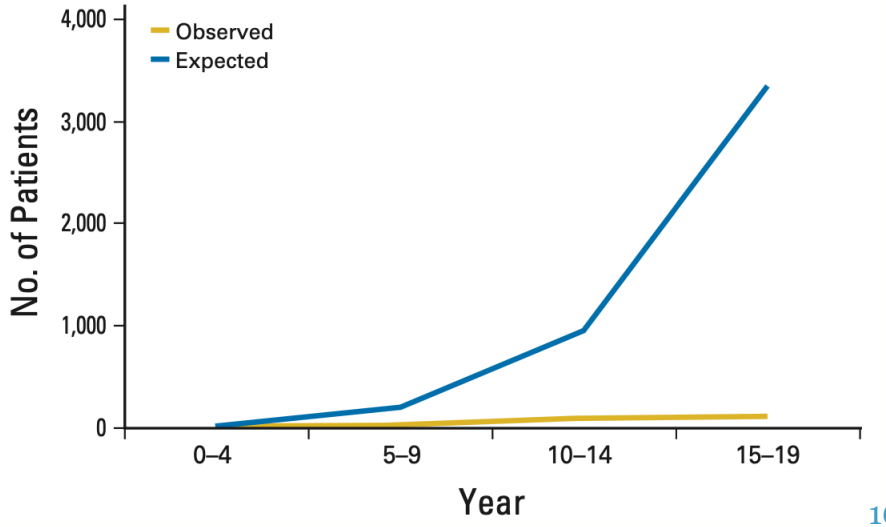
CURRENT CHALLENGES

- Individual efforts have been hugely impactful within a disease, but hard to scale
  - Need for unified framework and resources
- Large number of rare tumors. How to select which to focus on?
  - Pan-rare tumor effort?
  - Targets of opportunity?
  - Greatest unmet need/understudied cancers?
- Project EveryChild
  - Allows capture of biospecimens and some clinical data from all patients with cancer
  - Limited clinical/treatment/outcome data
  - Limited enrollment of rare tumor patients

PROJECT EVERYCHILD

- Ongoing work to evaluate reasons for limited enrollment of patients with rare tumors
  - Lack of therapeutic study/patient benefit
  - Limited reimbursement
  - Patients not seen by oncologists (melanoma, thyroid cancer)
  - AYA patients treated at adult centers
- MCI may increase enrollment
  - Clinical results/increased reimbursement
  - Activated Sept. 2022
- Opportunity to integrate with external registries to incorporate disease specific champions/experts





Pappo. JCO. 2010.

CONCLUSIONS

- Rare tumors comprise a significant proportion of pediatric cancers
- Overall less progress than for common cancers, worse outcomes
- Exceptions have been disease focused efforts led by individuals
- Opportunity to accelerate progress
  - Biospecimen collection (for some tumors we have no models)
  - Robust clinical data
  - Deep molecular profiling (MCI + …)
    - Need to correlate with robust clinical, pathologic, and outcome data

ACKNOWLEDGEMENTS

- Vice-chairs
  - Kris Ann Schultz
  - Murali Chintagumpala
- COG leadership
  - Doug Hawkins
  - Peter Adamson
  - Carlos Rodriguez-Galindo
- Entire rare tumor committee
- Collaborators
- Patients/families

Children's Hospital of Philadelphia
Cancer Center

Morning Session

Kris Ann Schultz, MD

Pediatric Oncologist, Children's Minnesota

PI, International PPB/DICER1 Registry, PI, International Ovarian and Testicular Stromal Tumor Registry

Children's MINNESOTA

PPB/*DICER1*: Bedside to Bench (and Back)

Kris Ann Schultz, MD
Pediatric Oncologist, Children's Minnesota

Children's Minnesota

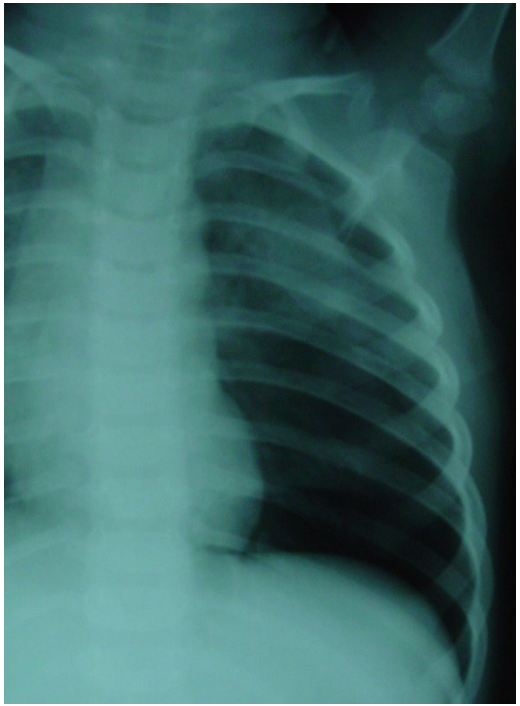
Disclaimers, Disclosures and Confidentiality Protections

- I have no disclosures.
- Children's Minnesota makes no representations or warranties about the accuracy, reliability, or completeness of the content. Content is provided "as is" and is for informational use only. It is not a substitute for professional medical advice, diagnosis, or treatment. Children's disclaims all warranties, express or implied, statutory or otherwise, including without limitation the implied warranties of merchantability, non-infringement of third parties' rights, and fitness for a particular purpose.
- You hold all responsibility for your use or nonuse of the content. Children's shall not be liable for claims, losses, or damages arising from or related to any use or misuse of the content.
- This content and its related discussions are privileged and confidential under Minnesota's peer review statute (Minn. Stat. § 145.61 et. seq.). Do not disclose unless appropriately authorized. Notwithstanding the foregoing, content may be subject to copyright or trademark law; use of such information requires Children's permission.
- **Some of the data presented here has not yet been published or peer-reviewed.**
- Please ask if you have any questions about these disclaimers and/or confidentiality protections.

Bedside (to Registry) to Bench– and back again

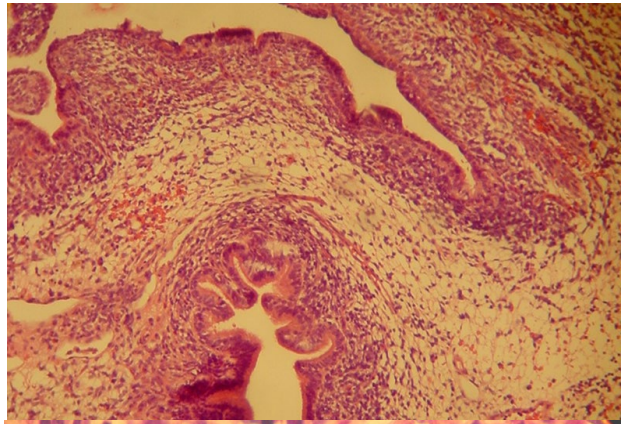
- Overview of PPB/DICER1
- Current research
- Roses and thorns

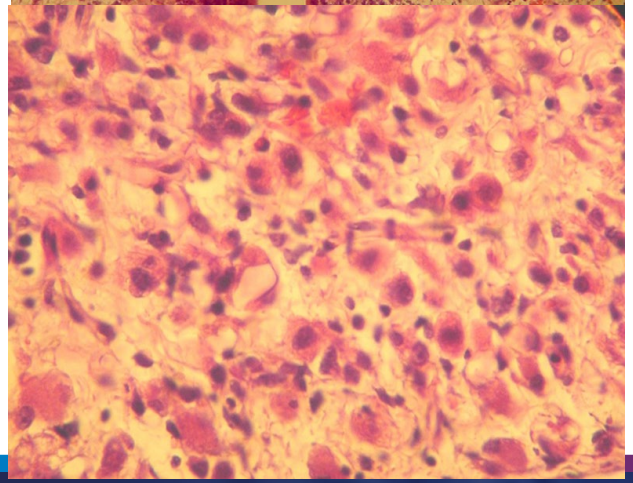
Start at the bedside



2 year old girl

- Presented with respiratory distress
- Chest x-ray showed pneumothorax
- Found to have cystic lung lesion





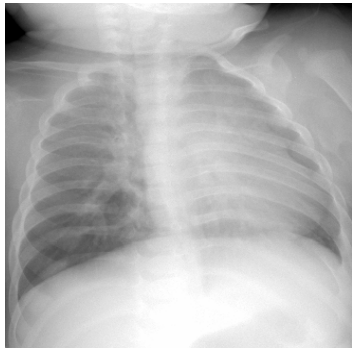
blastema cambium layer and anaplastic stroma in sarcoma botryoides

anaplastic stroma suggestive of rhabdomyosarcoma morphology

Pleuropulmonary blastoma (PPB)

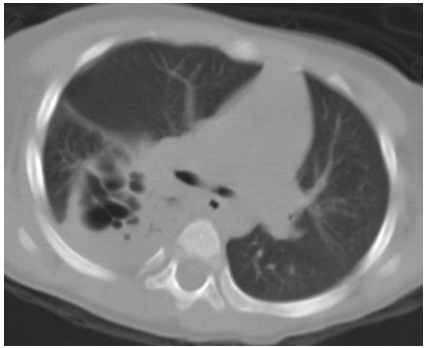
- Most common lung cancer of infancy and childhood
  - 92% of clinically significant PPB diagnosed in children less than 7 years of age
  - Like other sarcomas, the malignant component derives from lung mesenchyme
- 4 main types recognized

PPB Types



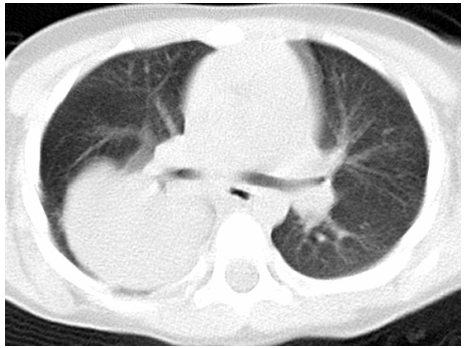
Type I

8 months



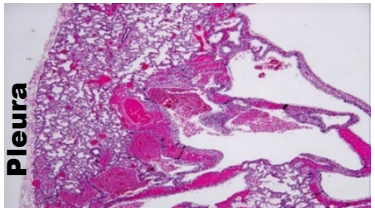
Type II

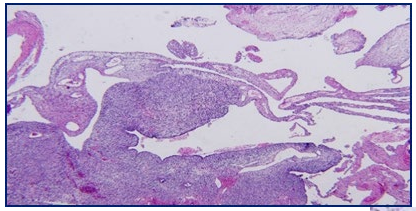
36 months

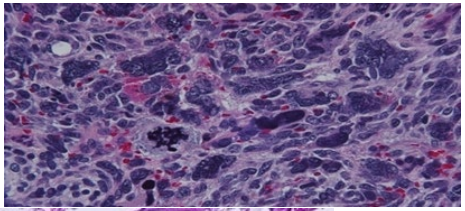


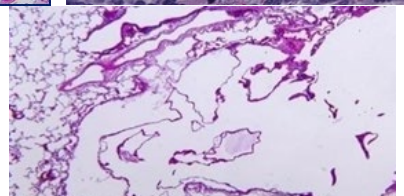
Type III

41 months









Type Ir PPB

Science 2009

DICER1 Mutations in Familial Pleuropulmonary Blastoma

D. Ashley Hill,[1,2]* Jennifer Ivanovich,[1] John R. Priest,[2] Christina A. Gurnett,[1] Louis P. Dehner,[1] David Desruisseau,[1] Jason A. Jarzembowski,[3] Kathryn A. Wikenheiser-Brokamp,[4] Brian K. Suarez,[1] Alison J. Whelan,[1] Gretchen Williams,[2,5] Dawn Bracamontes,[1,2] Yoav Messinger,[2,5] Paul J. Goodfellow[1]

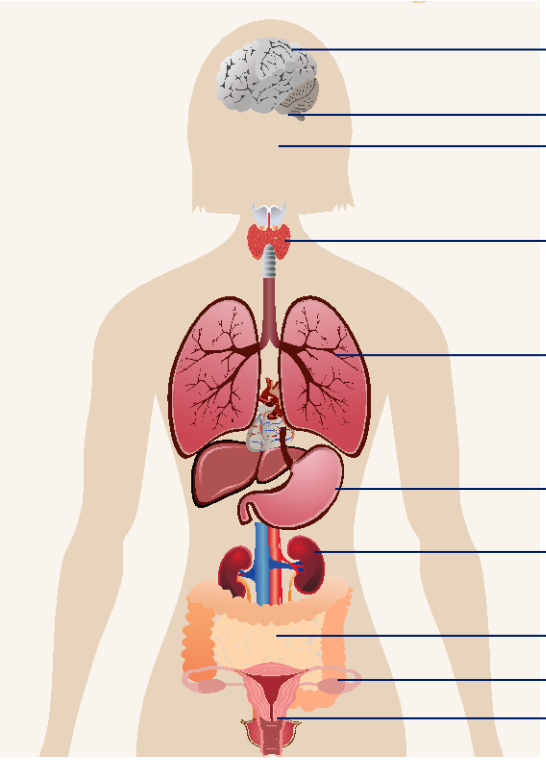
Pleuropulmonary blastoma (PPB) is a rare pediatric tumor of the lung that arises during fetal lung development and is often part of an inherited cancer syndrome [Online Mendelian Inheritance in Man (OMIM) 601200]. PPBs contain both epithelial and mesenchymal cells. Early in tumorigenesis, cysts form in lung airspaces, and these cysts are lined with benign-appearing epithelium. Mesenchymal cells susceptible to malignant transformation reside within the cyst walls and form a dense "cambium" layer beneath the epithelial lining. In a subset of patients, overgrowth of the mesenchymal cells produces a sar-

from affected members in each of 11 families (four included in the linkage study and seven additional families) (Fig. 1A, fig. S3, and table S1). In 10 of these families, the mutations result in proteins truncated proximal to the two carboxy-terminal RNase III functional domains in DICER1 (Fig. 1B) and thus likely cause loss of function. The missense mutation [$Leu^{1583} \rightarrow Arg^{1583}$ (L1583R)] detected in the 11th family (family C) affects an evolutionarily conserved amino acid, and the nonpolar to polar change was neither a previously reported sequence variant [National Center for Biotechnology Information Single

controls tested by Pyrosequencing (QI
Incorporated, Valencia, CA).

Apart from PPB-associated tumors in
of family members, the majority of oblig
riers with *DICER1* mutations are phenot
normal, suggesting that loss of one *DICE*
is compatible with normal development and
cient for tumor formation. Mice haploinsuffi
Dicer1 also show no overt phenotypic abno
(7). DICER1 immunohistochemistry of PPB
suggests expression from the wild-type alle
in tumor-associated epithelium in six of th
families harboring PPBs with a residual e
cystic component but is retained in the me
mal tumor cells (Fig. 1C and fig. S5). DIC
normally present in lung bronchial and
epithelium throughout life. The areas o
staining in the tumor epithelium were se
in most cases but were clearly evident
overlying cambium layers. The genetic b
this altered expression in epithelium is un
but the phenotype recapitulates that see
Dicer1$^{-/-}$ mice. Interestingly, the tumor as

DICER1-related conditions



BRAIN: Pituitary blastoma, Pineoblastoma, CNS sarcoma, ETMR

EYES: CBME

NOSE: NCMH

THYROID: Thyroid nodules, cancer

LUNGS: PPB Type I, II, III, Ir

ABDOMEN: PPB-like peritoneal sarcoma

KIDNEYS: Cystic nephroma, Wilms tumor, renal sarcoma

SMALL INTESTINE: Polyps

OVARIES: SLCT, Gynandroblastoma

GU: Cervical ERMS

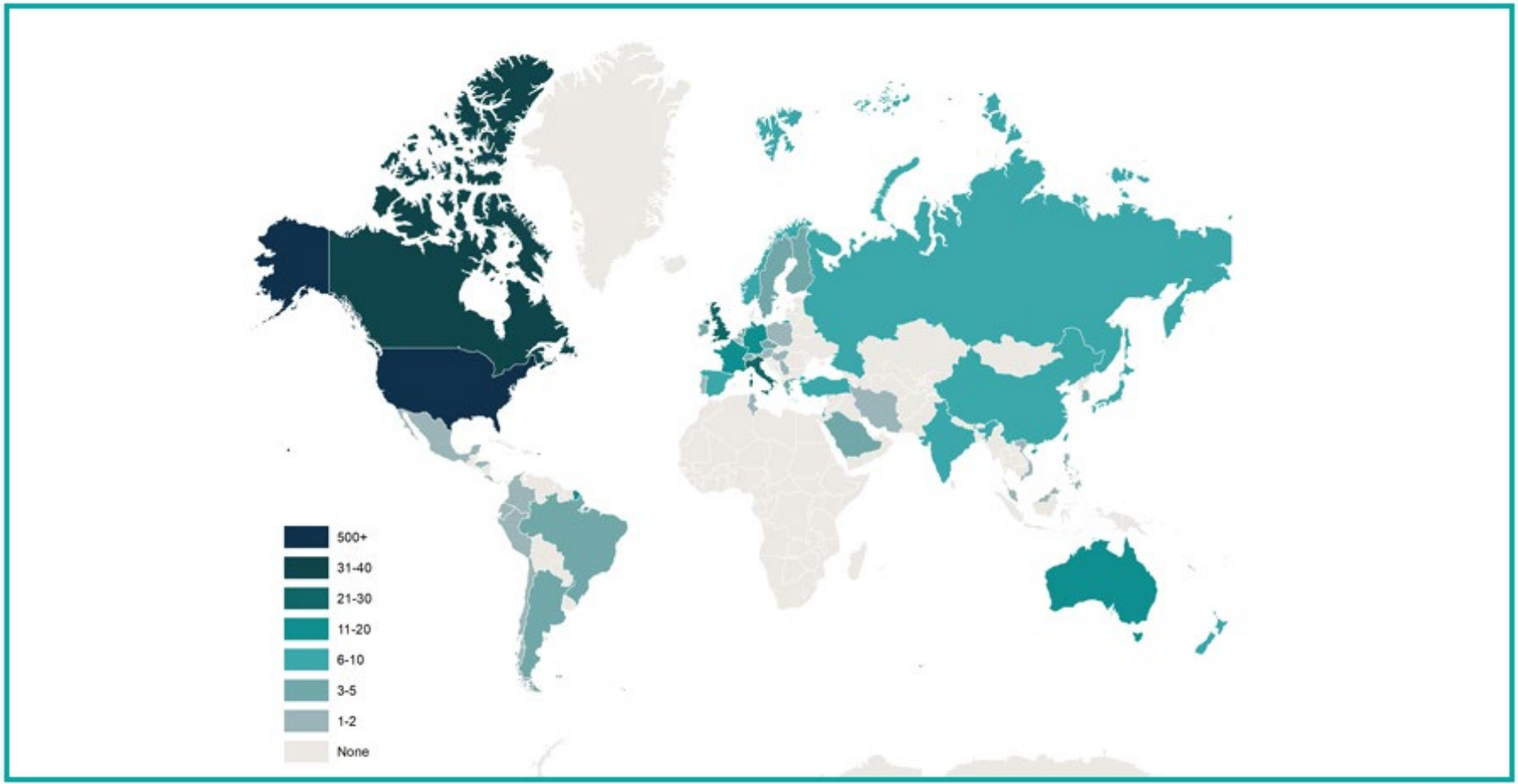
Image credit Junne Kamihara, MD

DICER1

- Fascinating gene, key in human development
- Regulates cell growth and proliferation
- 1 in 3,000 individuals has a germline loss of function P/LP variant
- Many individuals experience healthy lives
- Minor findings such as thyroid nodules and lung cysts are common
- These may serve as an entry point to surveillance
- Power of pattern recognition
- Some DICER1-related tumors arise outside the context of predisposition

International PPB/*DICER1* Registry

- Founded at Children's Minnesota in 1987
- Eligibility
  - Individuals of any age
  - Suspected or known PPB or *DICER1*-related condition
  - Germline pathogenic *DICER1* variant or mosaicism
- Offers free central pathology review
- >800 individuals from 47 states and 49 countries


500+
31-40
21-30
11-20
6-10
3-5
1-2
None

Mission of the PPB/*DICER1* Registry

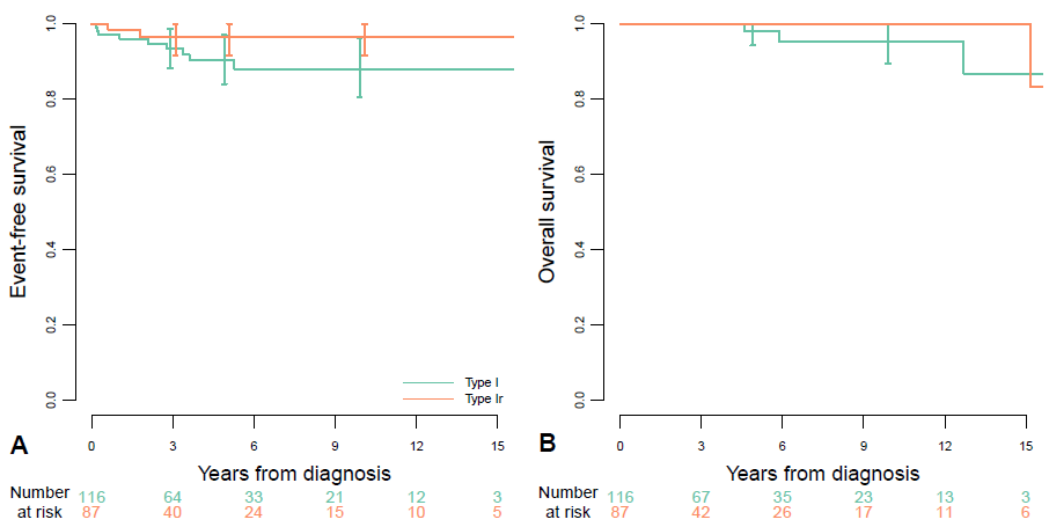
Improve outcomes for children and families affected by PPB and other *DICER1*-related conditions

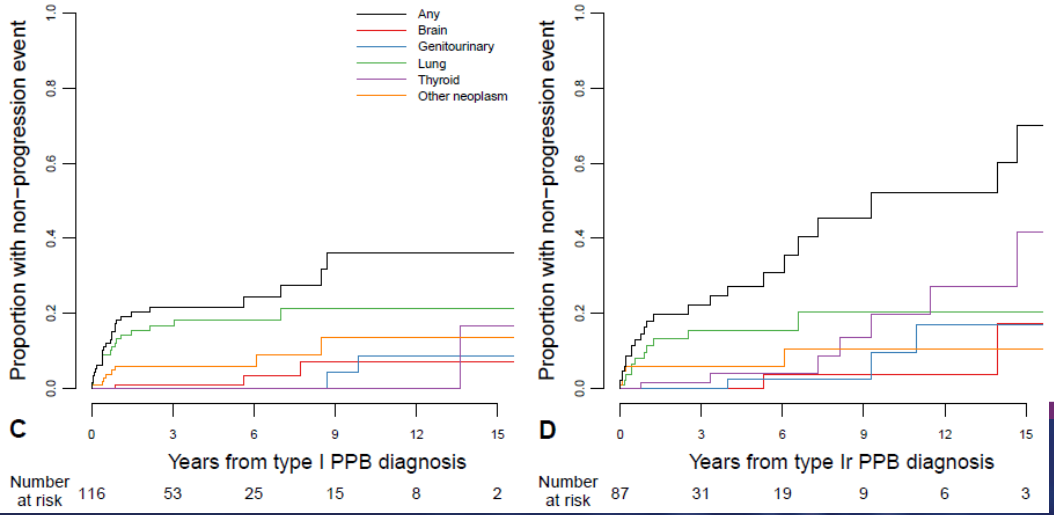
4 Strategic Pillars

- Define **optimal therapy** for PPB, Sertoli-Leydig cell tumor and other *DICER1*-related cancers
- Validate **testing and surveillance** guidelines
- Develop **new ways to diagnose and follow** children with *DICER1*-related cancers
- Discover **new therapies** for *DICER1*-related cancers

Strategic Pillar #1: Define optimal therapy

- Role of chemotherapy in Type I PPB
- Which lung cysts in individuals with *DICER1* require surgery?
- Treatment of Types II and III PPB
- Optimal treatment regimens for other *DICER1*-related cancers
- Treatment options for recurrence





Children's MINNESOTA

INTERNATIONAL PPB/DICER1 REGISTRY

Type I

Type Ir

A: EFS

B: OS

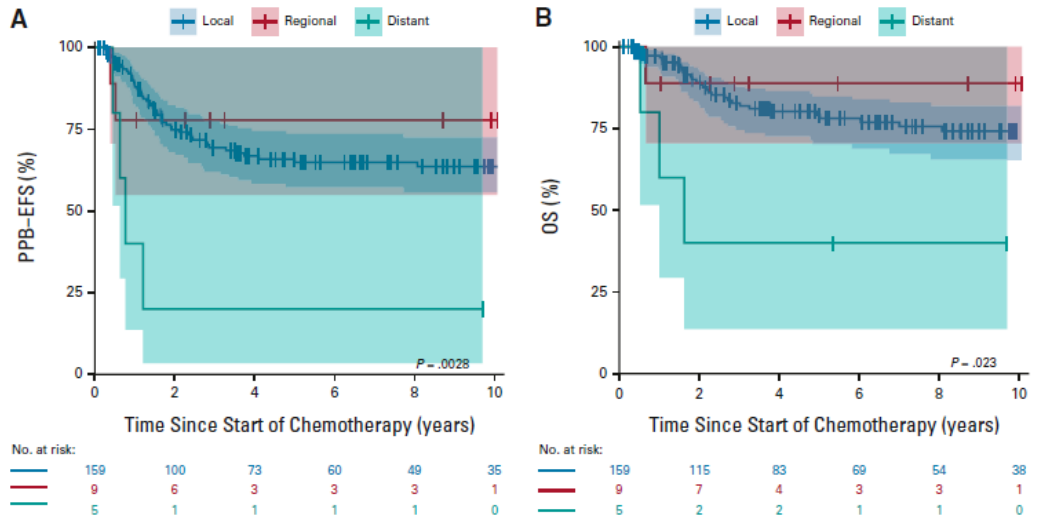
C/D: Proportion with non-progression event by system

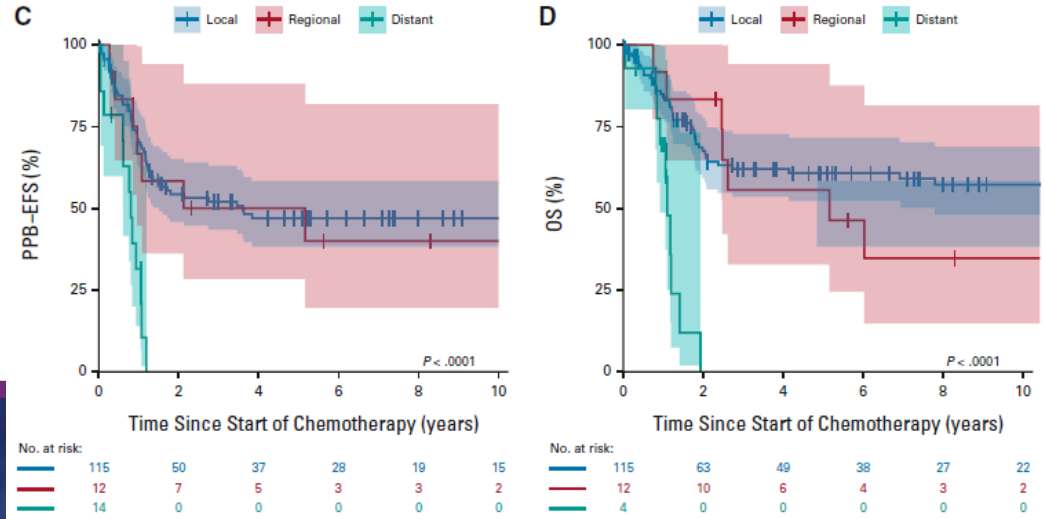
JCO 2022

Outcome by PPB type and extent of disease

Local Regional Distant

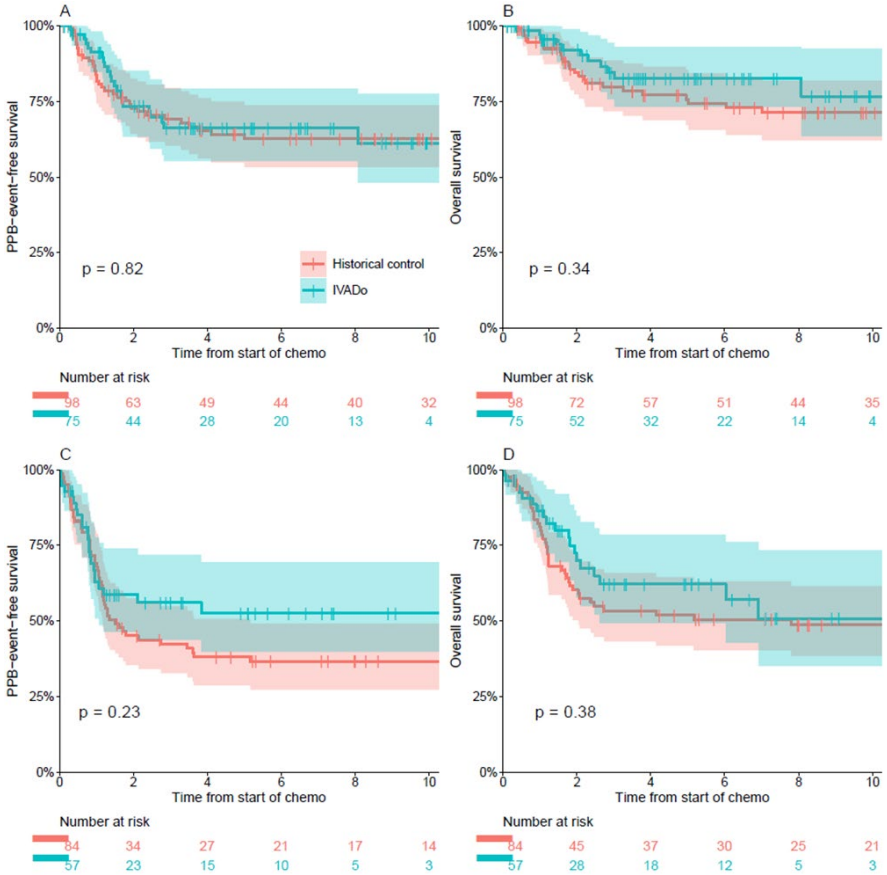
- **A**: Type II PPB-EFS
- **B**: Type II OS
- **C**: Type III PPB-EFS
- **D**: Type III OS





JCO 2022

Types II and III: Outcomes after IVADo



IVADo 3 year PPB-EFS

Type II 66.2% (CI: 55.3, 79.3)

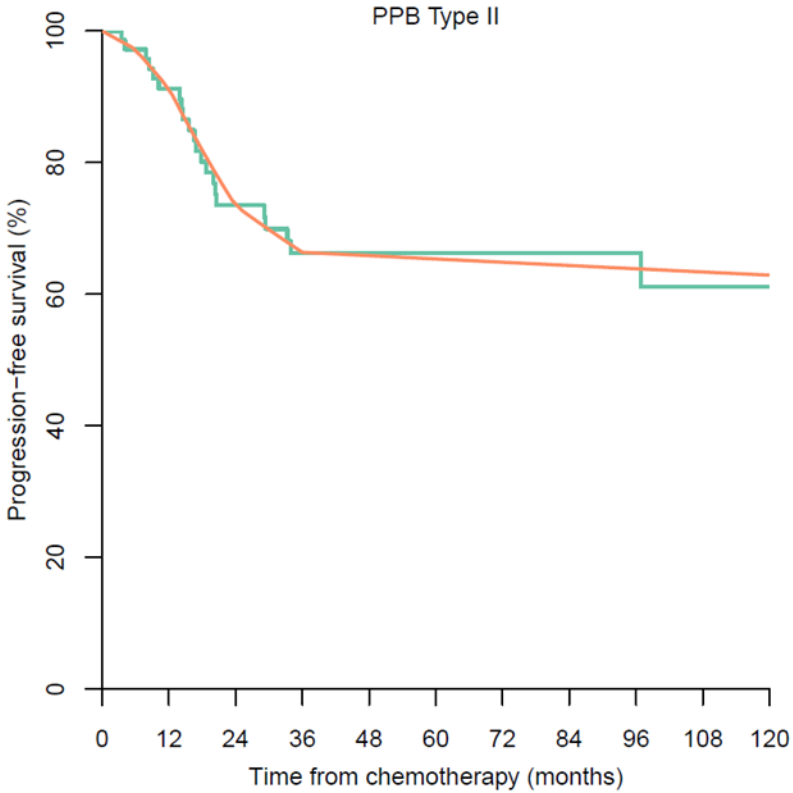
Type III 56.1% (CI: 43.7, 71.9)

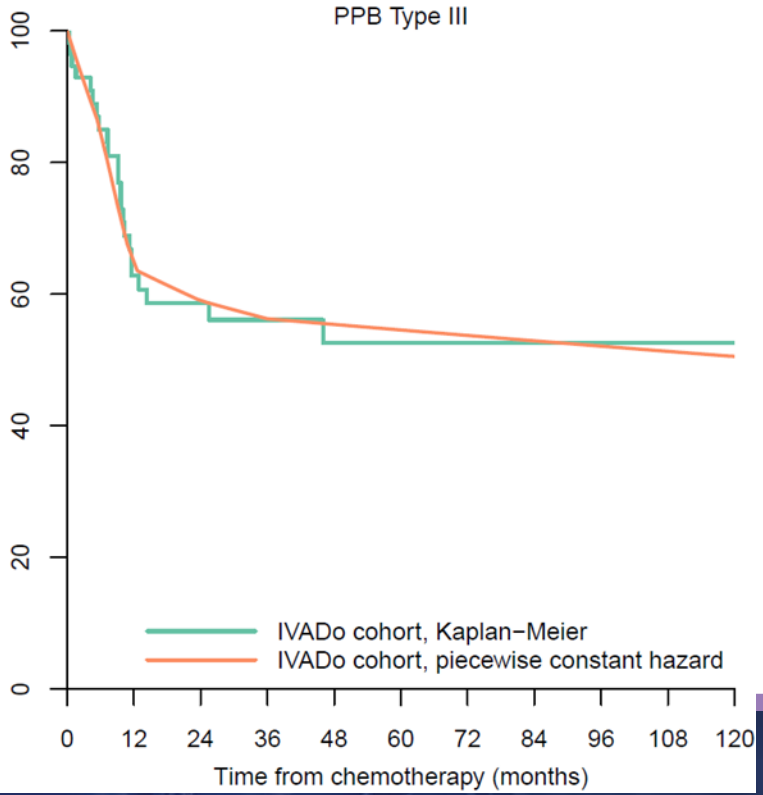
Historical control

IVADo

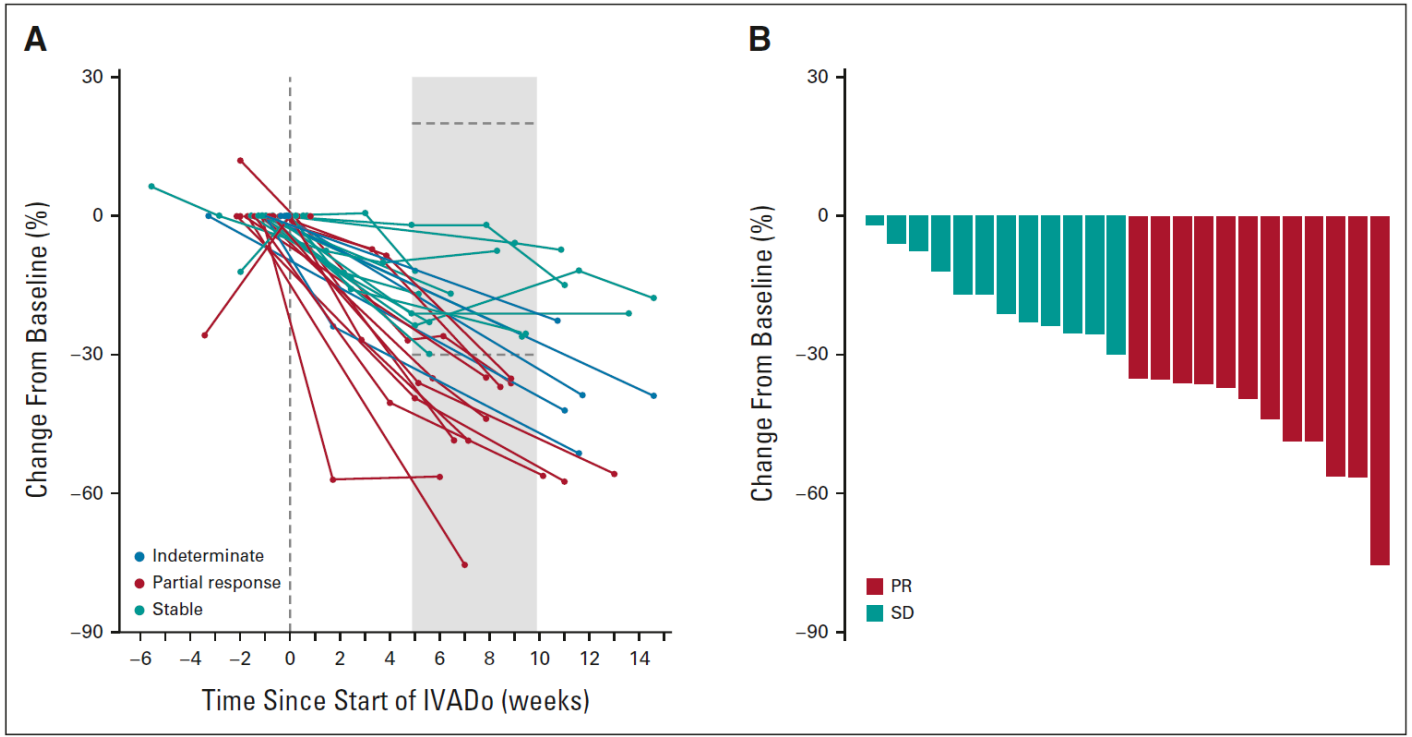
JCO 2022

Benchmark survival curves





Response to first cycles of IVADo



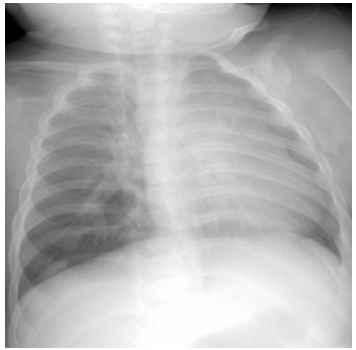
JCO 2022

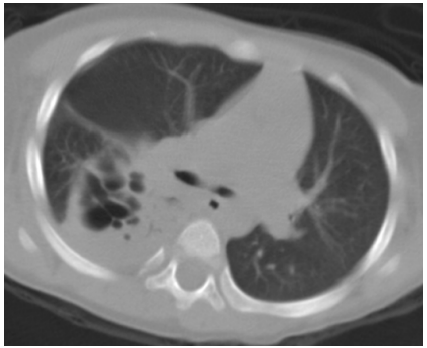
- 24 children with baseline measurements prior to initiation of chemotherapy and subsequent measurements between weeks 5 and 9 post initiation of chemotherapy or after cycle 2 and prior to cycle 4 chemotherapy
- 50% (12/24) children had partial responses and 50% (12/24) had stable disease

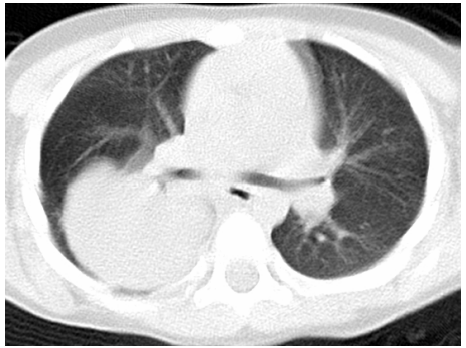
Key goals in Types II and III PPB

- Development of prospective treatment trial
- For Type II and III
  - Optimize upfront tumor reduction
  - Reduce risk of local **and CNS** metastases
- For Type I PPB
  - Standardize approach to chemotherapy
- Optimize translational opportunities

Pillar #2: Optimize testing and surveillance



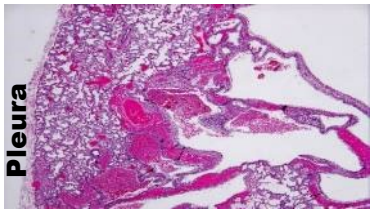


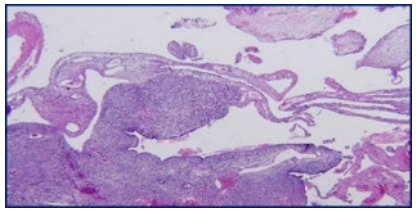


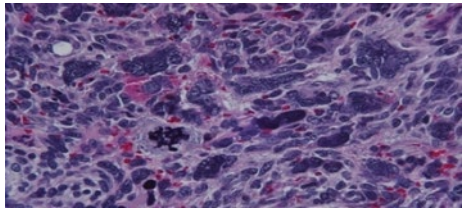
Type I

Type II

Type III



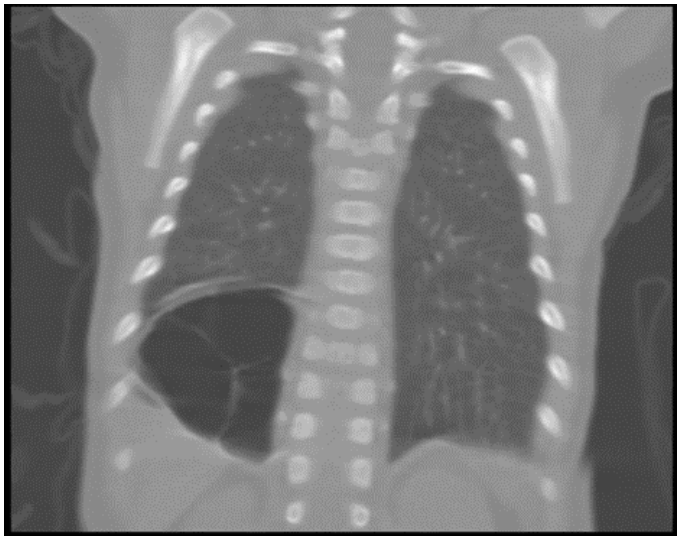




Pillar #2: Early diagnosis

- 33 year old self referred to Registry
- History of Sertoli-Leydig cell tumor at age 17
  - Wanted to help others
  - “If my tumor sitting in a jar somewhere could help someone…”
- Research germline testing showed *DICER1*
- Pregnant with 3rd child

Pillar #2 Early diagnosis



- Carefully resected with no spillage
- Type I PPB with features of transition to Type II
- Treated with surgery alone
- No chemotherapy

- Knowledge is Power!

Testing and surveillance are key to early diagnosis

Table 1. Indications for *DICER1* testing

Major:

- Individuals with PPB (all types)
- Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral
- Thoracic ERMS[a]
- Cystic nephroma
- Genitourinary sarcomas including undifferentiated sarcoma[a]
- Ovarian SLCT
- Gynandroblastoma
- Uterine cervical or ovarian ERMS[a]
- Genitourinary/gynecologic neuroendocrine tumors
- Multinodular goiter or thyroid cancer in two or more first-degree relatives or in an index patient with a family history consistent with *DICER1* syndrome[a]
- Childhood-onset multinodular goiter[a] or differentiated thyroid cancer[a]
- CBME
- NCMH
- Pineoblastoma
- Pituitary blastoma

Consider testing if two of the following

Minor:

- Lung cyst(s) in adults
- Renal cyst(s)[a]
- Wilms tumor
- Multinodular goiter or differentiated thyroid cancer
- ERMS other than thoracic or gynecologic[a]
- Poorly differentiated neuroendocrine tumor
- Undifferentiated sarcoma[a]
- Macrocephaly[a]
- Consider testing for any childhood cancer in constellation with any other minor criteria

Established guidelines for surveillance

Table 2. Suggested signs and symptoms and imaging surveillance by system for individuals with *DICER1* pathogenic variants

System	Signs/symptoms to consider	Condition of interest	Screening: clinical and radiographic
Lung	Tachypnea, cough, fever, and pain; pneumothorax	– PPB – Lung cysts – Pulmonary blastoma	CXR at birth and every 4–6 months until 8 years of age, every 12 months 8–12 years of age; consider a CT of chest at 3–6 months of age.[a] Toddlers: if initial CT normal: repeat between 2.5 and 3 years of age.[a] If mutation detected at >12 years of age, consider baseline CXR or chest CT.
Thyroid	Visible or palpable thyroid nodule(s) Persistent cervical lymphadenopathy Hoarseness Dysphagia Neck pain Cough	– Multinodular goiter – Differentiated thyroid cancer	Baseline thyroid US by 8 years of age, then every 3 years or with symptoms/findings on physical exam. With anticipated chemotherapy or radiotherapy: baseline US and then annually for 5 years, decreasing to every 2–3 years if no nodules are detected.
Female reproductive tract	Hirsutism Virilization Abdominal distension, pain, or mass	– SLCT – Gynandroblastoma – Cervical ERMS	For females beginning at 8–10 years of age: pelvic and abdominal US every 6–12 months at least until age 40. End of interval is undetermined, but current oldest patient with *DICER1*-associated SLCT was 61 years of age. Education regarding symptoms strongly recommended.
Renal	Abdominal or flank mass and/or pain, hematuria	– Wilms tumor – Renal sarcoma – Cystic nephroma	Abdominal US every 6 months until 8 years of age, then every 12 months until 12 years of age. If mutation detected at >12 years of age, consider baseline abdominal US.
Gastrointestinal	Signs of intestinal obstruction	– Small intestine polyps	Education regarding symptoms recommended.
Central nervous system and head and neck (excluding thyroid)	Headache, emesis, diplopia, decreased ability for upward gaze, altered gait (pineoblastoma); precocious puberty; Cushing syndrome (pituitary blastoma); decreased visual acuity and leukocoria (CBME); nasal obstruction (NCMH)	– Macrocephaly – Pineoblastoma – Pituitary blastoma – CBME – NCMH	Physical exam. Annual routine dilated ophthalmologic exam (generally unsedated) with visual acuity screening from 3 years of age through at least 10 years of age. Further testing if clinically indicated. Recommend urgent MRI for any symptoms of intracranial pathology.

We continue to hear more stories like that of our young friend

Still need to revise over time

Still need novel strategies

International Ovarian and Testicular Stromal Tumor (OTST) Registry founded in 2011 in parallel to PPB/DICER1 Registry

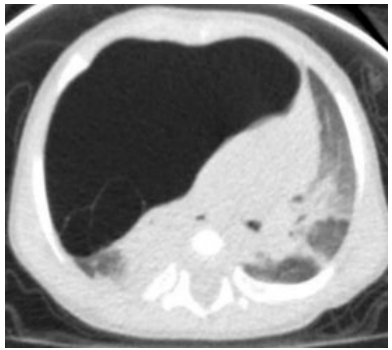
Established Guidelines for Surveillance

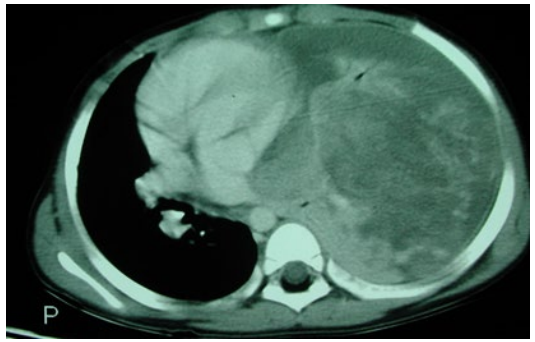
Table 2. Suggested signs and symptoms and imaging surveillance by system for individuals with *DICER1* pathogenic variants

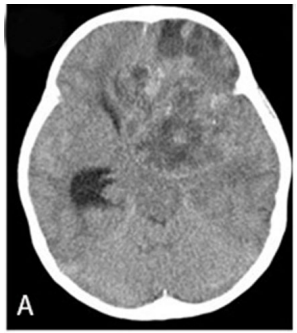
System	Signs/symptoms to consider	Condition of interest	Screening: clinical and radiographic
Lung	Tachypnea, cough, fever, and pain; pneumothorax	– PPB – Lung cysts – Pulmonary blastoma	CXR at birth and every 4–6 months until 8 years of age, every 12 months 8–12 years of age; consider a CT of chest at 3–6 months of age.[a] Toddlers: if initial CT normal: repeat between 2.5 and 3 years of age.[a] If mutation detected at >12 years of age, consider baseline CXR or chest CT.
Thyroid	Visible or palpable thyroid nodule(s) Persistent cervical lymphadenopathy Hoarseness Dysphagia Neck pain Cough	– Multinodular goiter – Differentiated thyroid cancer	Baseline thyroid US by 8 years of age, then every 3 years or with symptoms/findings on physical exam. With anticipated chemotherapy or radiotherapy: baseline US and then annually for 5 years, decreasing to every 2–3 years if no nodules are detected.
Female reproductive tract	Hirsutism Virilization Abdominal distension, pain, or mass	– SLCT – Gynandroblastoma – Cervical ERMS	For females beginning at 8–10 years of age: pelvic and abdominal US every 6–12 months at least until age 40. End of interval is undetermined, but current oldest patient with *DICER1*-associated SLCT was 61 years of age. Education regarding symptoms strongly recommended.

Pillar #3: Novel diagnostics

- We need better ways to diagnose and follow individuals with *DICER1*- cancers
- Type I: Role of chemotherapy
- Type II/III: Assessment of response
- All DICER1 cancers: Detect recurrence at earliest possible time point







Pillar #4: Novel therapeutics

- Early detection efforts underway
- Some tumors will not be amenable to early detection including those not related to germline variation
- Few curative options for children with recurrent *DICER1*-related cancers
- Need for more effective, less toxic treatments
- PDX program testing conventional and novel therapeutics
- *DICER1* Registry Laboratory Consortium founded in 2022

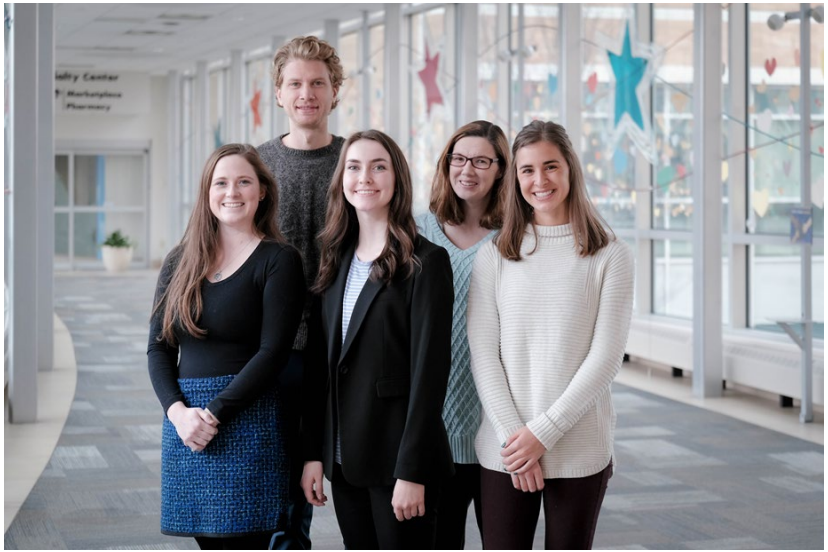
“If you study common tumors, run randomized, blinded, placebo-controlled trials. If you study rare tumors, find friends.”

- EXPeRT consortium

Importance of outreach

- Registry hosts annual family meetings
- Annual scientific symposia
  - Next scientific meeting: May 2023
  - Email DICER1@childrensmn.org for invitation
- Websites (PPBregistry.org/OTSTregistry.org)
- Facebook/Twitter
  - #everyjourneymatters
  - #earliestandmostcurableform
- Parent/Patient Advisory Board

Cancer research is a team sport

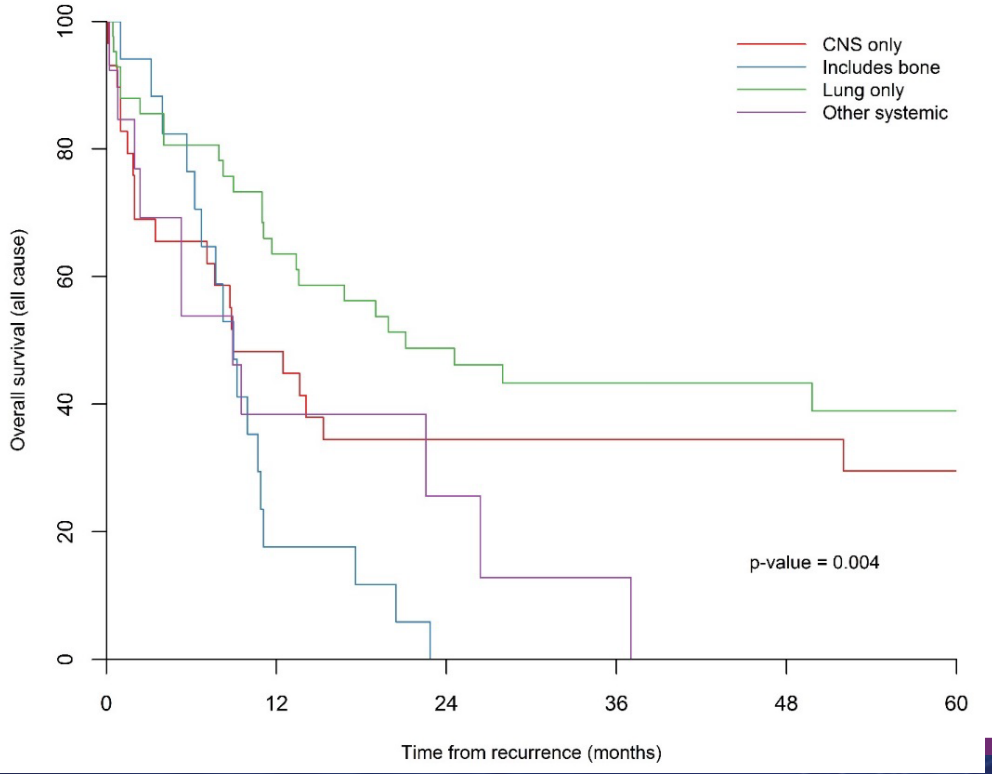


- Anne Harris
- Paige Mallinger
- Alexander Nelson
- Nicole Frederickson
- Anna Dybvik
- Melissa Abraham

Roses and Thorns

- Very rare and heterogeneous rare tumors
- Requires multidisciplinary approach
- Start with the end in mind
  - Where is the need greatest?
  - What questions are most critical to answer?
  - What data is needed to answer them?
- Collaborate not duplicate

Interesting is not enough!



Collaborators

Children's MINNESOTA

Children's National Medical Center

Washington University in St. Louis

EXPeRT

DANA-FARBER Boston Children's

CANCER AND BLOOD DISORDERS CENTER

NIH

National Institutes of Health

Centre of Pediatric Hematology Oncology Immunology named after D. Rogachev

T.C. İSTANBUL ÜNİVERSİTESİ 1453

İSTANBUL ÜNİVERSİTESİ ONKOLOJİ ENSTİTÜSÜ İstanbul - 1982

Beijing Children's Hospital

RESOURCEPATH

Thank you

International PPB/*DICER1* Registry
Yoav Messinger
Anne Harris
Paige Mallinger
Alex Nelson
Nicole Frederickson
Anna Dybvik
Melissa Abraham

***DICER1* Genetics**
D. Ashley Hill
Mandy Field
Weiying Yu
Chenyu Xu

PPB/DICER1/OTST Central Review
Louis (Pepper) Dehner
D. Ashley Hill

NIH Collaborators
Doug Stewart
Laura Harney
Ann Carr

Thanks to the many kids, families and clinicians who support PPB/*DICER1* research!

Pine Tree Apple Tennis Classic
Childhood cancer has met its match!

REIN IN SARCOMA
Increase awareness. Increase survivors.

Thank you!

DICER1@childrensmn.org
KrisAnn.Schultz@childrensmn.org
612-813-7121
www.PPBregistry.org
www.OTSTregistry.org

Morning Session

Mary Frances Wedekind, DO

Staff Clinician and Research Assistant,
Pediatric Oncology Branch

National Cancer Institute

Framework for a National Rare Tumor Study: Initial Thoughts

Mary Frances Wedekind, DO

POB/CCR/NCI/NIH

NIH NATIONAL CANCER INSTITUTE

Pediatric ONCOLOGY BRANCH

November 18, 2022

Background: Rare Pediatric and AYA Tumors

- Rare tumor: 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 tumors
  - Insufficient patient numbers for most tumors
  - Data collection not standardized/structured

Diagnosis and Treatment Odyssey Example

12y F presenting with neck stiffness

Progressive symptoms

6 months before imaging performed
8 months before diagnosis

Diagnosed with nasopharyngeal carcinoma

Started standard therapy
After 3 cycles, no response

Diagnosis changed to poorly differentiated chordoma

Surgery
Proton RT

Follow up included only imaging the primary site

4 years later

Presented with diffusely metastatic relapse

Clinical trial

No response to treatment

Referral to specialized center

Diagnosis and Treatment Odyssey Example

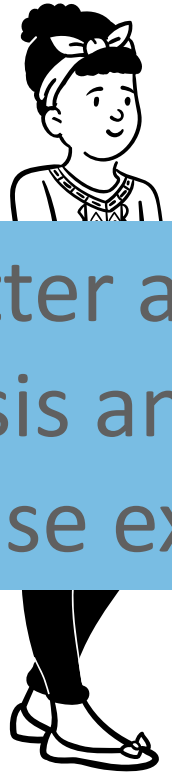
12y F presenting with neck stiffness

Progressive symptoms

6 m

8 m

Diagnc



Referral to specialized center

ose

4 years later

Started standard therapy
After 3 cycles, no response

Diagnosis changed to poorly differentiated chordoma

Surgery
Proton RT

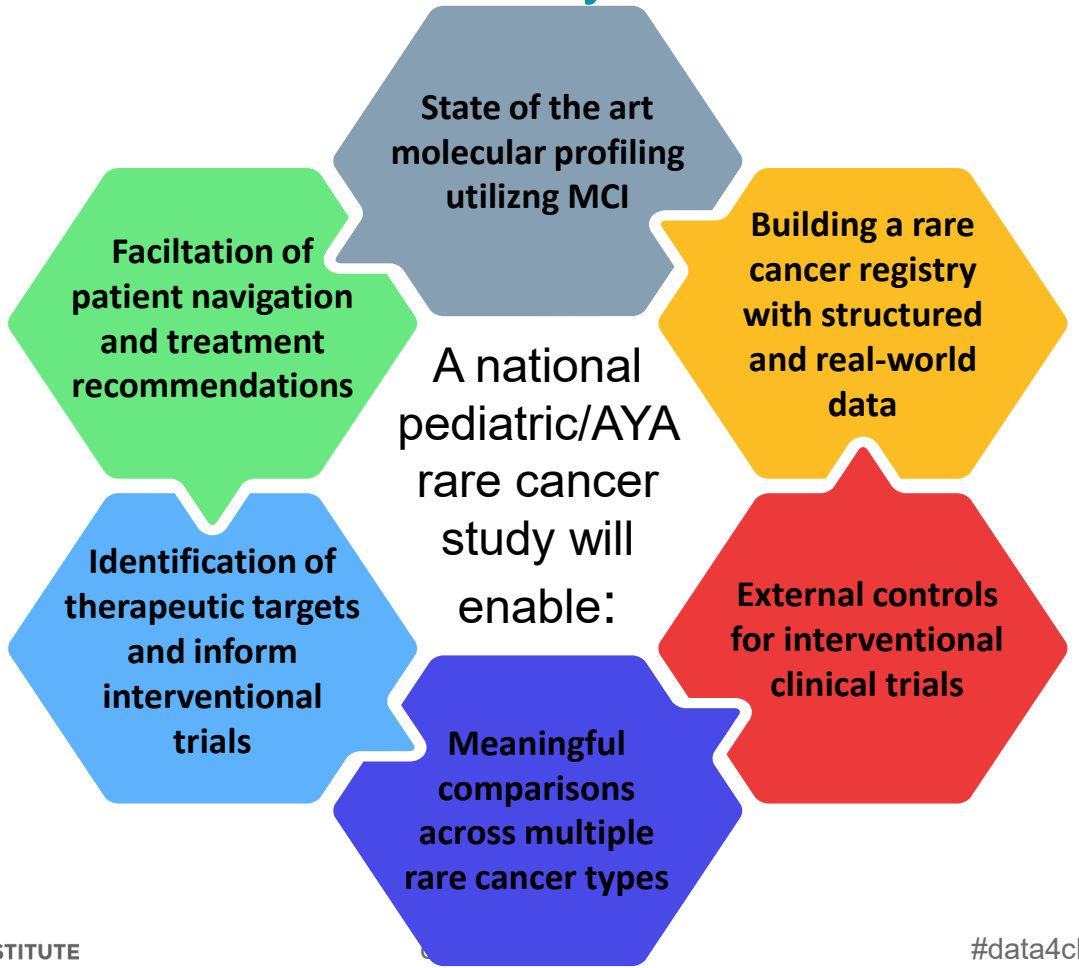
Follow up included only imaging the primary site

How can we better achieve timely and accurate diagnosis and connection with disease experts?

Lessons Learned: Rare Pediatric and AYA Tumor 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
    - Collection of core clinical information on the 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

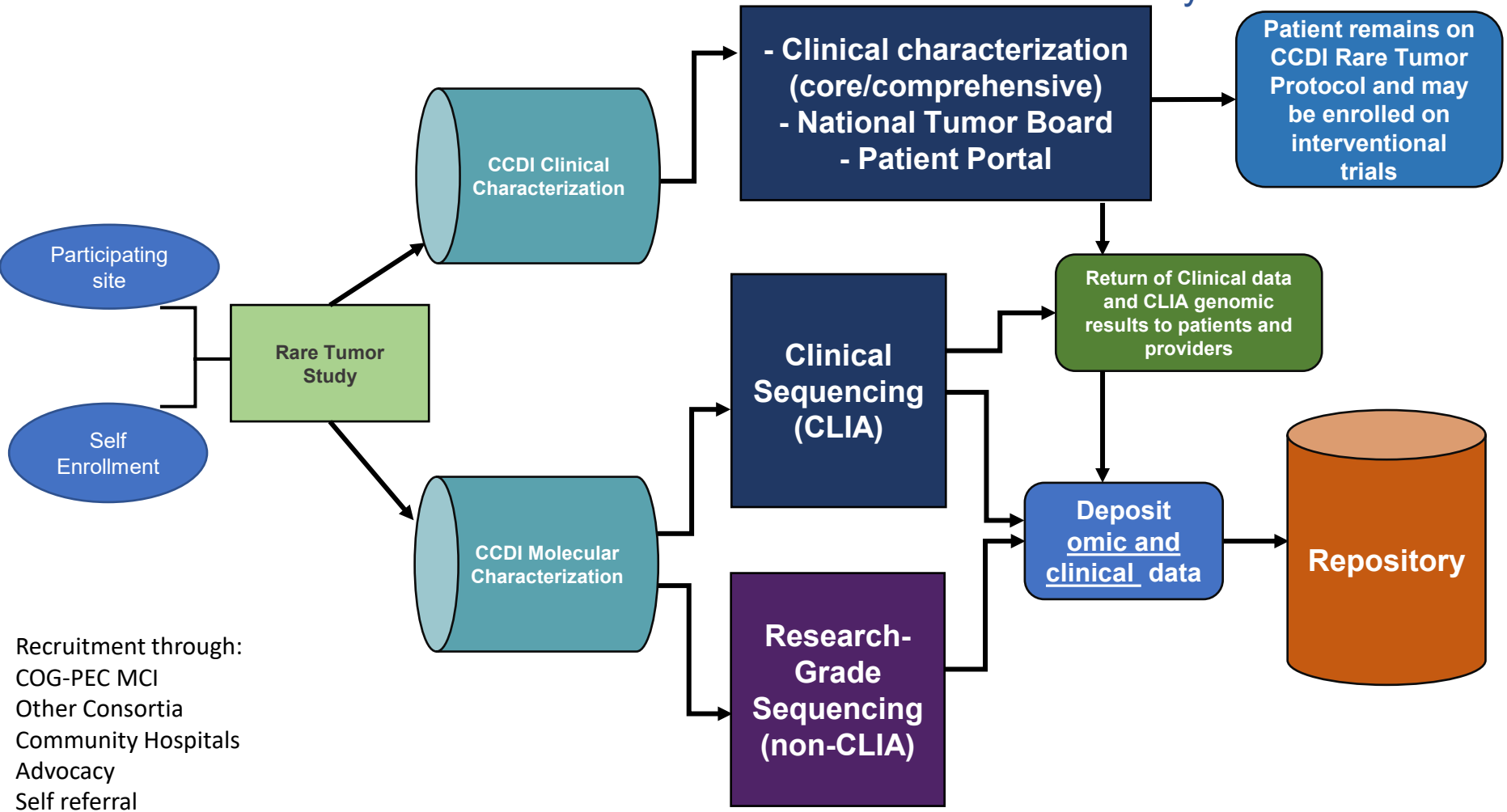
Objectives:

- Determine feasibility of a national observational protocol for all known 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 Tumor Study



Recruitment through:
COG-PEC MCI
Other Consortia
Community Hospitals
Advocacy
Self referral

Recruitment

- 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 tumor study
  - Other consortia, such as PBTC, CBTN, CONNECT, PNOC, TACL etc.
- Community hospitals/physician/advocacy
- Self-referral

Study Design

- Coordination:
  - CCDI coordinated national collaboration
  - Overall Study PIs
  - Rare tumor cohort PIs (rare tumor experts/champions)
- Trial sites:
  - Multi-site with select participating sites (open call)
  - 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 (enrollment at participating sites)
  - Biospecimen analysis offered through the CCDI MCI for clinical molecular characterization
  - Research molecular characterization conducted by the disease experts
  - Data for patients enrolled through PEC-MCI, will be accessible to the national rare cancer study
  - Data sharing with other rare tumor 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:

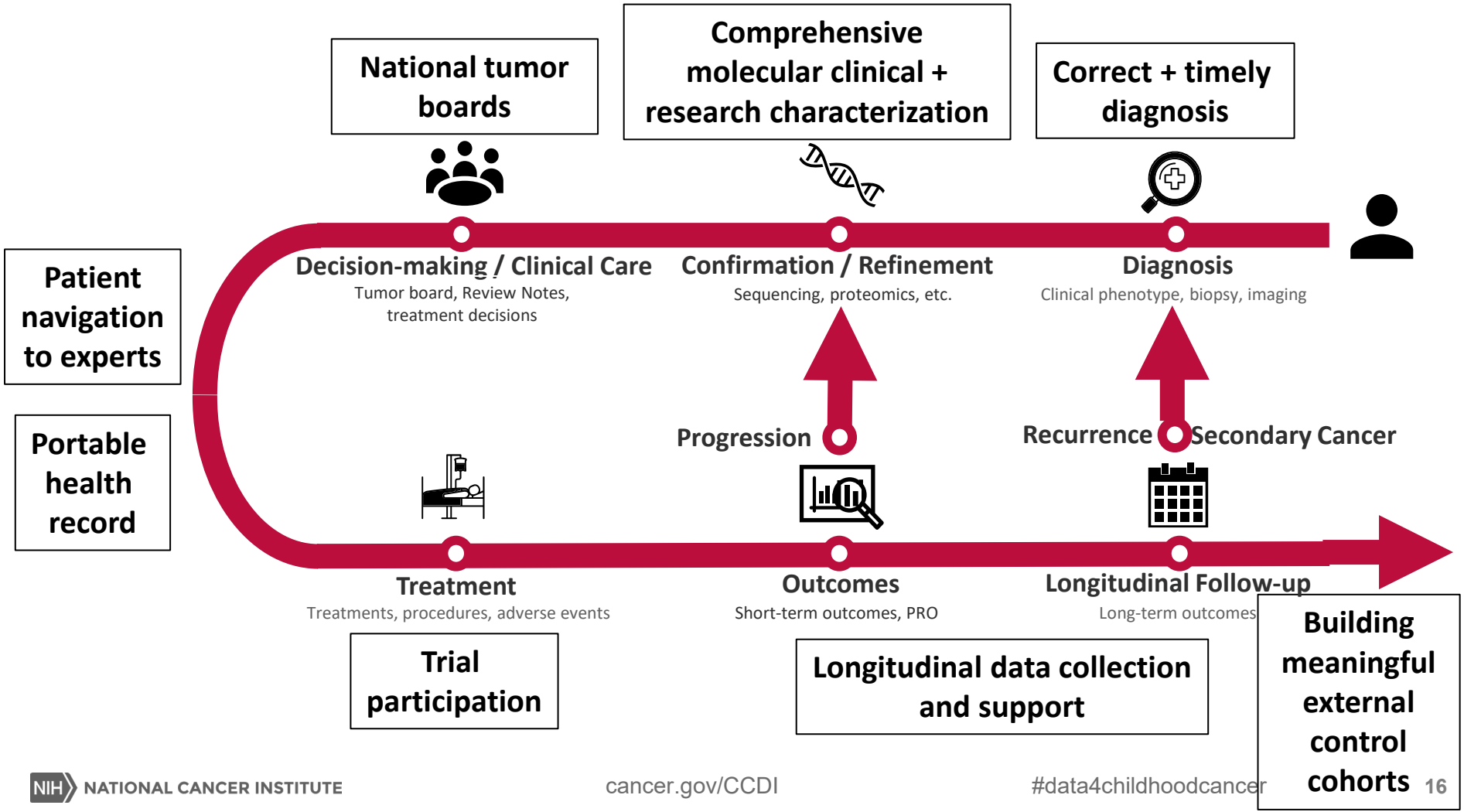
- Clinicians and researchers with specific interest and experience in the rare tumor presented
- Genetic counselor to provide treatment recommendations for patients and build upon the collective knowledge base of treating clinicians
- Learn from and collaborate with already established molecular and 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

Implications for Future Patients

12y F presenting with neck stiffness

Progressive symptoms

2 months before imaging performed
3 months before diagnosis

Shorten time to diagnosis

Diagnosed with Nasopharyngeal Carcinoma

Enrolled on National Longitudinal Study

Molecular profiling

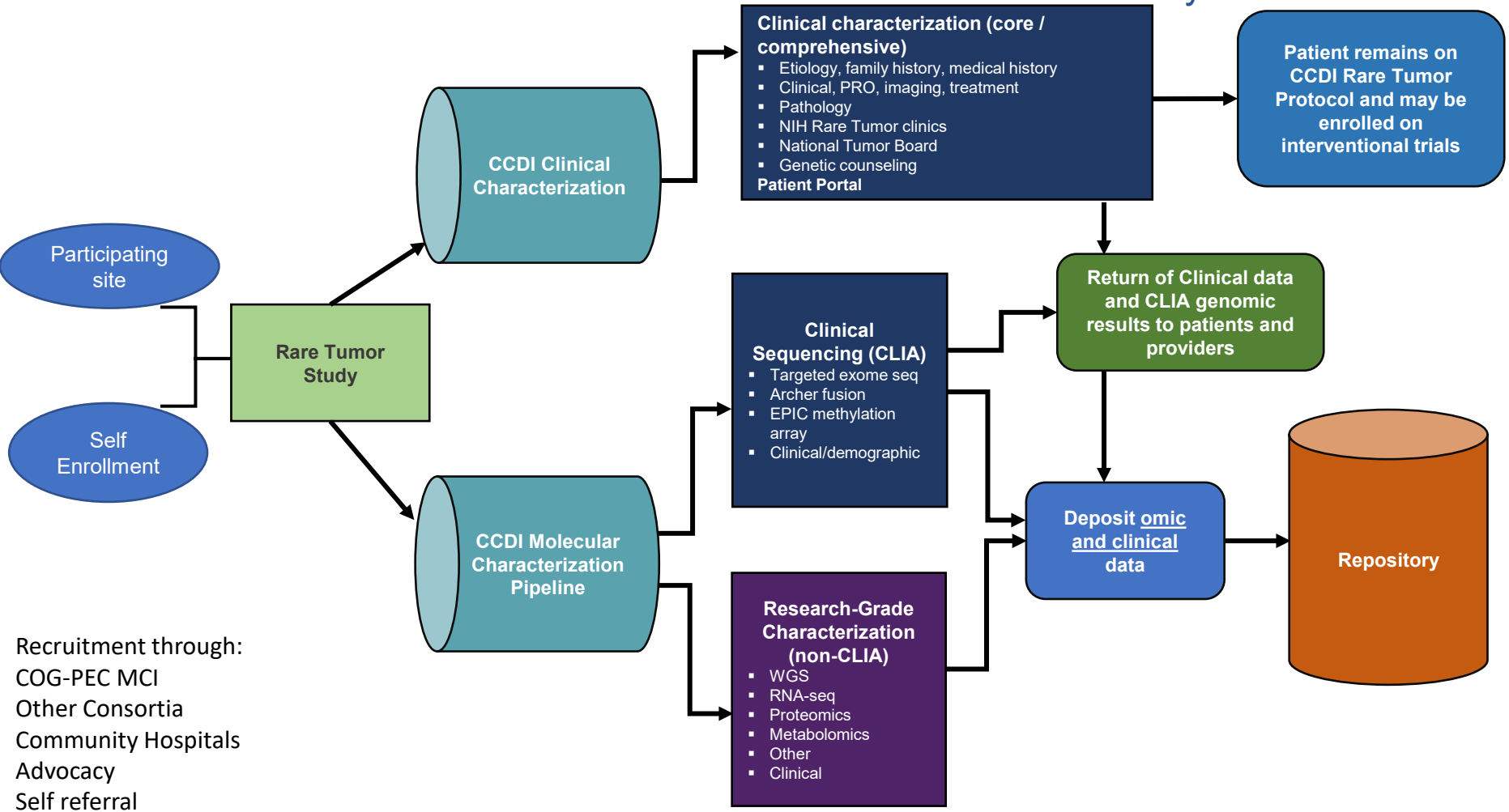
Diagnosis changed to poorly differentiated chordoma

Clinical data & biospecimens collected, national tumor board discussion, etc

Relapse

Treatment plan formed, follow up plan determined, connection with advocacy

CCDI Coordinated Rare Pediatric / AYA Tumor Study



Recruitment through:
COG-PEC MCI
Other Consortia
Community Hospitals
Advocacy
Self referral

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!**

www.cancer.gov

www.cancer.gov/espanol

Panel Discussion: Need for a National Initiative

Tom Badgett, MD, PhD
Associate Professor of Pediatrics
Kentucky Children's Hospital,
Markey Cancer Center

Wendy Baskins
Patient Advocate

Ted Laetsch, MD
Pediatric Oncologist
Cancer Center at Children's
Hospital of Philadelphia

Mignon Loh, MD
Chief, Division of Pediatric
Hematology, Oncology, Bone
Marrow Transplant and Cellular
Therapy Seattle Children's Hospital

Troy McEachron, PhD
Investigator, Pediatric
Oncology Branch
National Cancer Institute

Ann Ramer, MPH
Patient Advocate

Adam Resnick, PhD
Center for Data Driven
Discovery in Biomedicine
(D3b), Children's Hospital
of Philadelphia

Kris Ann Schultz, MD
Pediatric Oncologist, Children's
Minnesota PI, International PPB/DICER1
Registry, PI, International Ovarian and
Testicular Stromal Tumor Registry

Mary Frances Wedekind, DO
Staff Clinician and Research
Assistant, Pediatric
Oncology Branch
National Cancer Institute

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

Childhood Cancer Data Initiative (CCDI)

NIH NATIONAL CANCER INSTITUTE

November 18, 2022

Afternoon Session

Katherine Janeway, MD, MMSc

Associate Professor of Pediatrics, Harvard Medical School,

Senior Physician, Dana-Farber / Boston Children's Cancer and Blood Disorders Center,

Director, Clinical Genomics, Dana-Farber Cancer Institute

Core Data Elements: Lessons Learned From Genomic Projects

Katherine A. Janeway, MD, MMSc

CCDI Workshop Rare Cancers

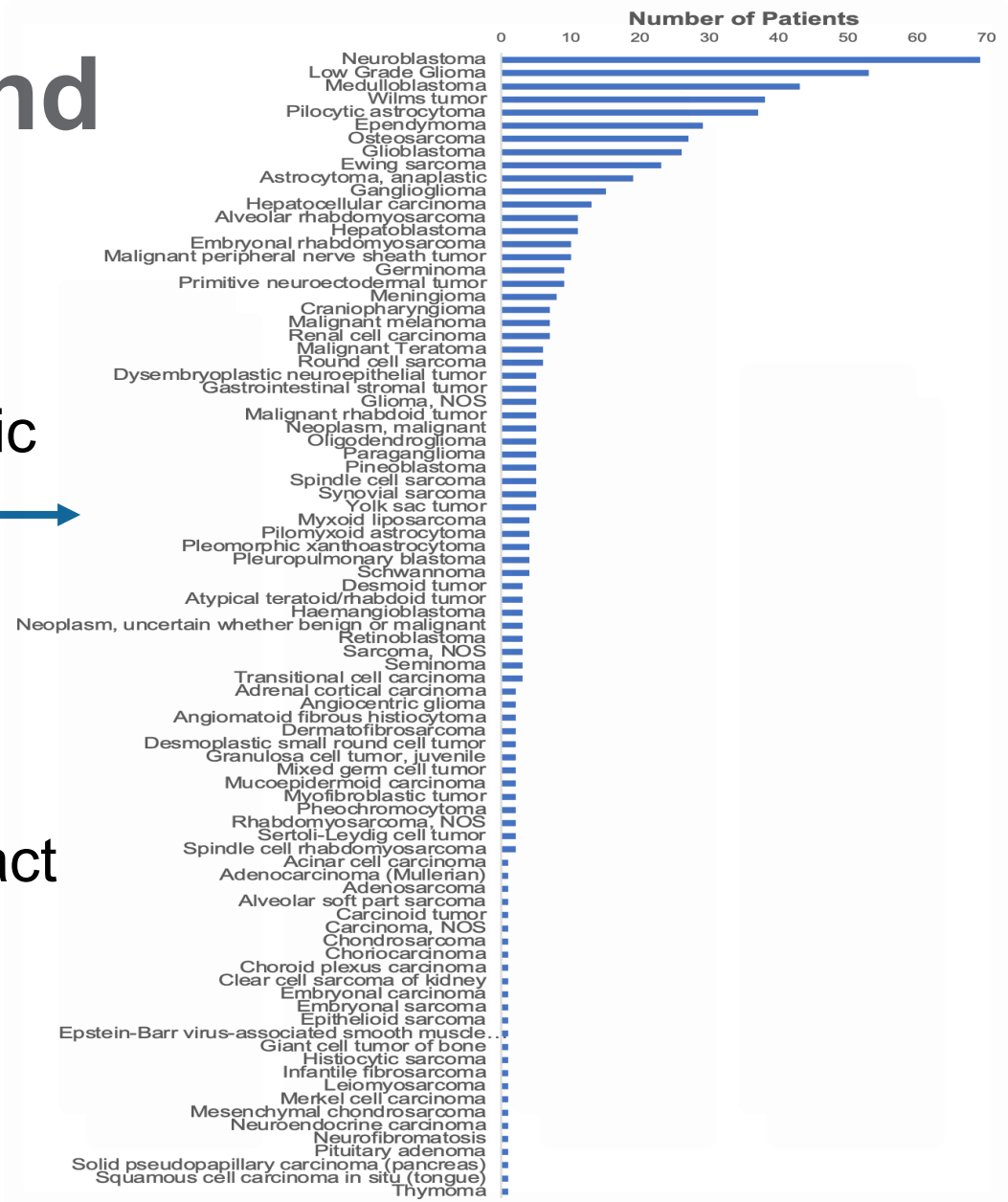
November 18, 2022

Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Background

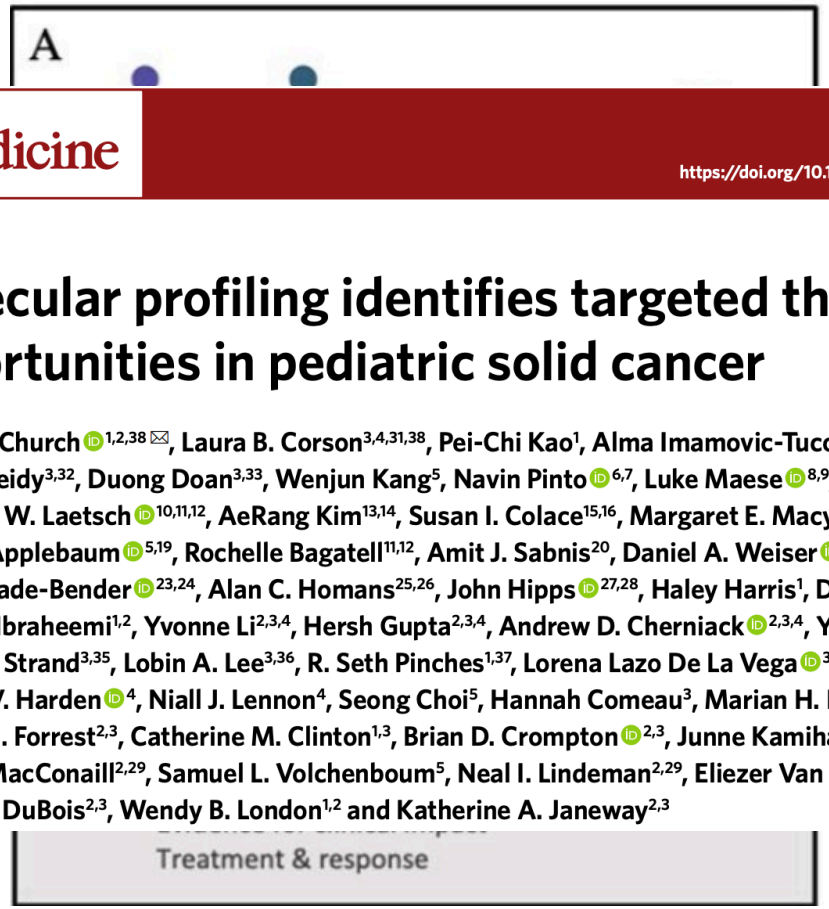
PROFILE Cancer Research Study

- Prospective cohort study
  - 50,000 sequenced patients, 1,000 pediatric patients
- Intervention: panel sequencing
- Example outcomes of interest
  - Responders to matched targeted therapy
  - Molecular subgroups with prognostic impact
- Requires longitudinal treatment and response data from the EMR



DATA SHARING INITIATIVES

GAIN/iCat2 Study



nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01856-6

Check for updates

Molecular profiling identifies targeted therapy opportunities in pediatric solid cancer

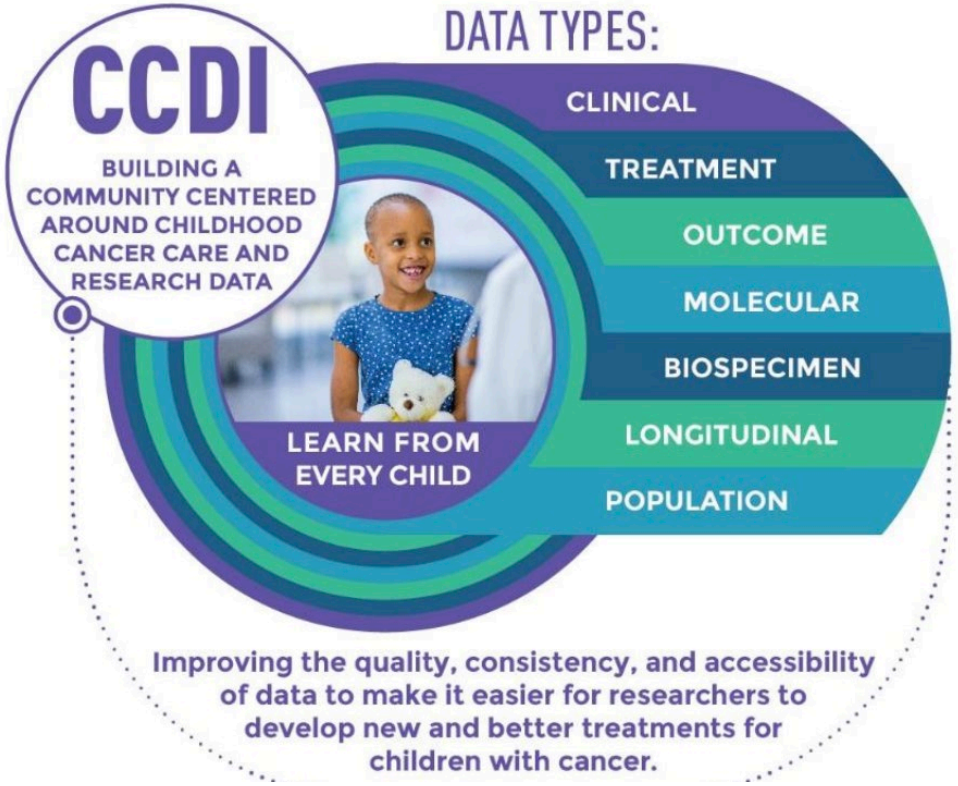
Alanna J. Church[1,2,38] ✉, Laura B. Corson[3,4,31,38], Pei-Chi Kao[1], Alma Imamovic-Tuco[3,4], Deirdre Reidy[3,32], Duong Doan[3,33], Wenjun Kang[5], Navin Pinto[6,7], Luke Maese[8,9], Theodore W. Laetsch[10,11,12], AeRang Kim[13,14], Susan I. Colace[15,16], Margaret E. Macy[17,18], Mark A. Applebaum[5,19], Rochelle Bagatell[11,12], Amit J. Sabnis[20], Daniel A. Weiser[21,22], Julia L. Glade-Bender[23,24], Alan C. Homans[25,26], John Hipps[27,28], Haley Harris[1], Danielle Manning[29], Alyaa Al-Ibraheemi[1,2], Yvonne Li[2,3,4], Hersh Gupta[2,3,4], Andrew D. Cherniack[2,3,4], Ying-Chun Lo[1,29,34], Gianna R. Strand[3,35], Lobin A. Lee[3,36], R. Seth Pinches[1,37], Lorena Lazo De La Vega[3], Maegan V. Harden[4], Niall J. Lennon[4], Seong Choi[5], Hannah Comeau[3], Marian H. Harris[1,2], Suzanne J. Forrest[2,3], Catherine M. Clinton[1,3], Brian D. Crompton[2,3], Junne Kamihara[2,3], Laura E. MacConaill[2,29], Samuel L. Volchenboum[5], Neal I. Lindeman[2,29], Eliezer Van Allen[2,4,30], Steven G. DuBois[2,3], Wendy B. London[1,2] and Katherine A. Janeway[2,3]

AACR American Association for Cancer Research

FINDING CURES TOGETHER™

PROJECTGENIE

Genomics Evidence Neoplasia Information Exchange



Dana-Farber Cancer Institute | Boston Children's

Dana-Farber/Boston Children's Cancer and Blood Disorders Center

NIH NATIONAL CANCER INSTITUTE

Childhood Cancer Data Initiative

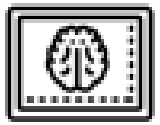
National Childhood Cancer Registry Explorer

PRISSMM

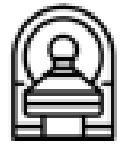
Characteristic	Clinical Trial Data	Real World EMR Data	PRISSMM Solution
Treatment and duration	Defined by trial	Variability in schedule & drugs	Definition treatment regimen
Response endpoint	Standards	No standards Inability to use RECIST	Creates standard
Data collection	Prospective	Retrospective	Consistent directives Methods facilitate QC
Proportion of cancer journeys	Minority	Majority	Capture each treatment course
Future goal	Share & harmonize	Natural language processing	Provides gold standard for training dataset

PRISSMM™:
A Taxonomy for Defining Cancer Outcomes

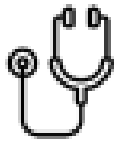
Pathologic evidence of locoregional or distant evidence of tumor



Radiographic evidence of locoregional recurrent or persistent tumor

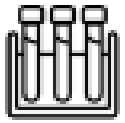


Imaging evidence of distant/disseminated tumor beyond the primary site



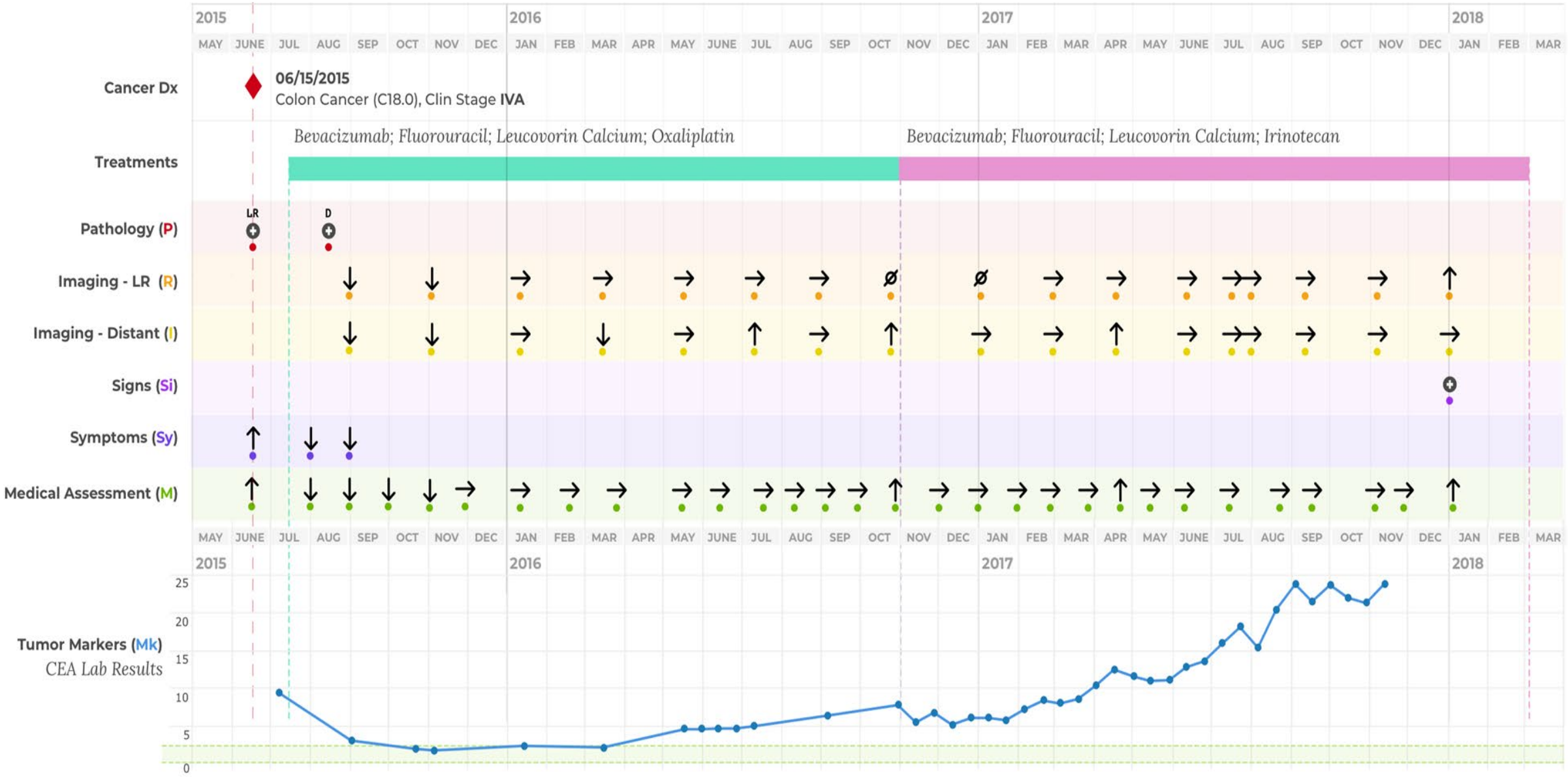
Symptoms of tumor on physical exam or symptoms that can be attributed to tumor

Signs of cancer on physical exam or symptoms that can be attributed to tumor



Tumor **M**arker evidence of persistent or recurrent tumor

Oncology **M**edical Provider assessment


2015
2016
2017
2018
MAY JUNE JUL AUG SEP OCT NOV DEC JAN FEB MAR APR MAY JUNE JUL AUG SEP OCT NOV DEC JAN FEB MAR APR MAY JUNE JUL AUG SEP OCT NOV DEC JAN FEB MAR
Cancer Dx
06/15/2015
Colon Cancer (C18.0), Clin Stage IVA
Treatments
Bevacizumab; Fluorouracil; Leucovorin Calcium; Oxaliplatin
Bevacizumab; Fluorouracil; Leucovorin Calcium; Irinotecan
Pathology (P)
LR
D
Imaging - LR (R)
Imaging - Distant (I)
Signs (Si)
Symptoms (Sy)
Medical Assessment (M)
Tumor Markers (Mk)
CEA Lab Results
25
20
15
10
5
0

What Does PRISSMM Include?

REDCAP databases to support curation

Training guide

Common model that is largely tumor site agnostic

Specific additions for particular tumor sites

QA procedures and guidance

Relies on common ontologies

Detailed variable and data dictionary

Pediatric Adaptation PRISSMM

Selected pediatric cancers

With 2 other pediatric cancer centers
- UCSF and MSKCC
- Select data elements, sources

Incorporated existing or emerging data standards
- Toronto staging guidelines
- PCDC for overlapping diseases (neuroblastoma)

Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines

Sumit Gupta, Joanne Aitken*, Ute Bartels, Nickhill Bhakta, Mihaela Bucurenci, James D Brierley, Beatriz De Camargo, Eric Chokunonga, Jessica Clymer, Dana Coza, Chris Fraser, Soad Fuentes-Alabi, Gemma Gatta, Thomas Gross, Zsuzsanna Jakab, Betsy Kohler, Tezer Kutluk, Florencia Moreno, Kayo Nakata, Sari Nur, D M Parkin, Lynne Penberthy, Jason Pole, Jenny N Poynter, Kathy Pritchard-Jones, Oscar Ramirez, Lorna Renner, Eva Steliarova-Foucher, Michael Sullivan, Rajaraman Swaminathan, Liesbet Van Eycken, Tushar Vora, A L Frazier*

Lancet Oncology, 2020

Pediatric Adaptation PRISSMM

Osteosarcoma – Janeway, Shukla, Sweet-Cordero

Pathology:
- Tumor Necrosis, Margins from Local Control procedures, Tumor Grade

Staging:
- Disease specific definitions for metastatic disease

Prognostic Factors:
- Size of primary tumor

Ewing Sarcoma – Janeway, Shukla, Sweet-Cordero

Pathology:
- Fusions Identified from Clinical Testing, CD 99 Expression, Tumor Necrosis, Margins from Local Control procedures

Staging:
- Disease specific definitions for metastatic disease

Prognostic Factors:
- Size of primary tumor

Wilms Tumor– Mullen, Ortiz

Diagnosis:
- Nephroblastomatosis and Nephrogenic Rests, Number and Size of lesions

Pathology:
- Histology (e.g. Anaplasia)

Staging:
- Kidney and overall

Neuroblastoma– Shusterman

Staging:
- INRG Staging

Prognostic Factors:
- COG Risk Classification
- MYNC Status and Ploidy
- Revised INPC Prognostic Group
- Mitosis Karyorrhexis Index (MKI)

9 of11 added fields equivalent to PCDC

DFCI PRISSMM DATA

250 Patients

4 Pediatric solid tumors (OS, EWS, WT, NBL)

Average **18** curated imaging reports per patient (range 1-87)

Average **4** curated pathology reports per patient (range 0-24)

Median follow-up **27** months (range 0-263)

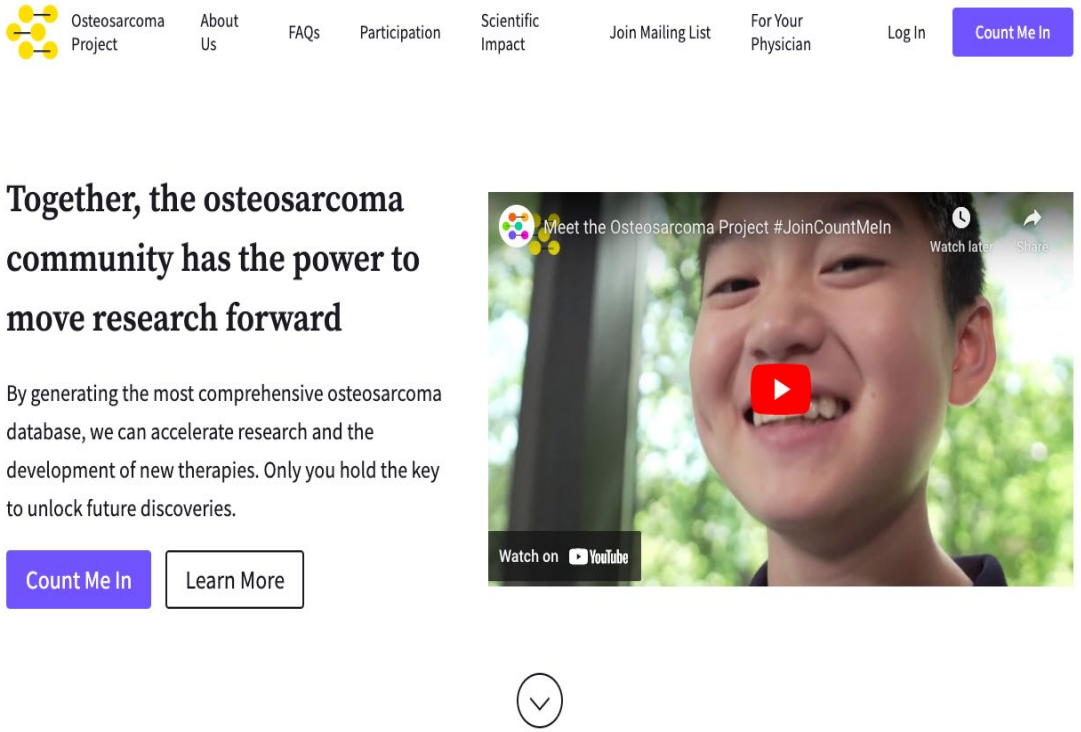
DFCI data contributed to CCDI NCCR

These & additional 350 will be submitted by MSKCC to GENIE

Lessons Learned

- In rare pediatric cancers diagnosis classification is a problem
  - Can not be derived from billing codes
  - Requires pathology report and molecular data
- Need to capture pediatric-specific staging and biomarkers (prognostic factors)
  - Can be abstracted or derived
- Important to record key dates
  - Local control
  - First recurrence
- Treatment regimens can also be used as a proxy for progression
- Abstract radiology reports to train NLP
- Abstract pathology reports to identify samples for research

Cancer Moonshot PE-CGS OSproject.org



200 patients enrolled; >50 institutions
Modified Pedi PRISSMM

Acknowledgements

Alanna Church
Brian Crompton
Steven Dubois
Lindsay Frazier
Suzanne Forrest
Jaclyn Scheinda
Jenny Mack
Eli VanAllen
Nick Wagle
Neal Lindeman
Catherine Clinton
Giana Strand
Lorena Lazo De La Vega
Neal Shukla
Andrew Kung
Alejandro Sweet-Cordero
Deborah Schrag

Evelina Ceca
Sidney Benich
Wendy London
Madhu Sidharan
Ellen Sukharevsky
Hannah Comeau
Sam Volchenbaum
Stephanie suser

PATIENTS AND FAMILIES!

Funders:

Division Hematology-Oncology Consortium Funding
Medel Fund
C&S Grocers

Afternoon Session

Subhashini Jagu, PhD

Scientific Policy and Program Branch A
Chief, Supervisory Health Scientist Administrator

Center for Biomedical Informatics & Information Technology, National Cancer Institute

Connecting the Data: CCDI Data Ecosystem

Summary of Activities

NIH NATIONAL CANCER INSTITUTE

11/18/2022

Outline

- CCDI Data Ecosystem Objectives
- Infrastructure & Components
- General Data Flow

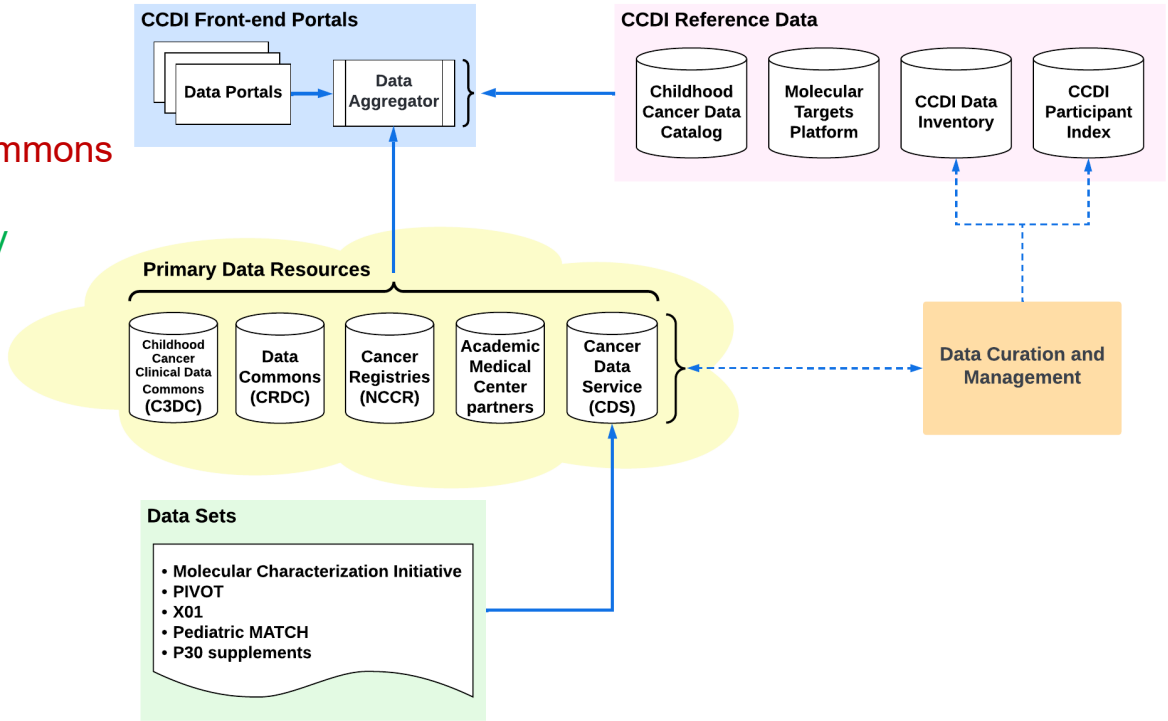
CCDI Data Ecosystem: Objectives

Create a platform that:

- Supports 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
- Supports broad sharing of results
- Creates a central view/portal to facilitate discovery and analysis

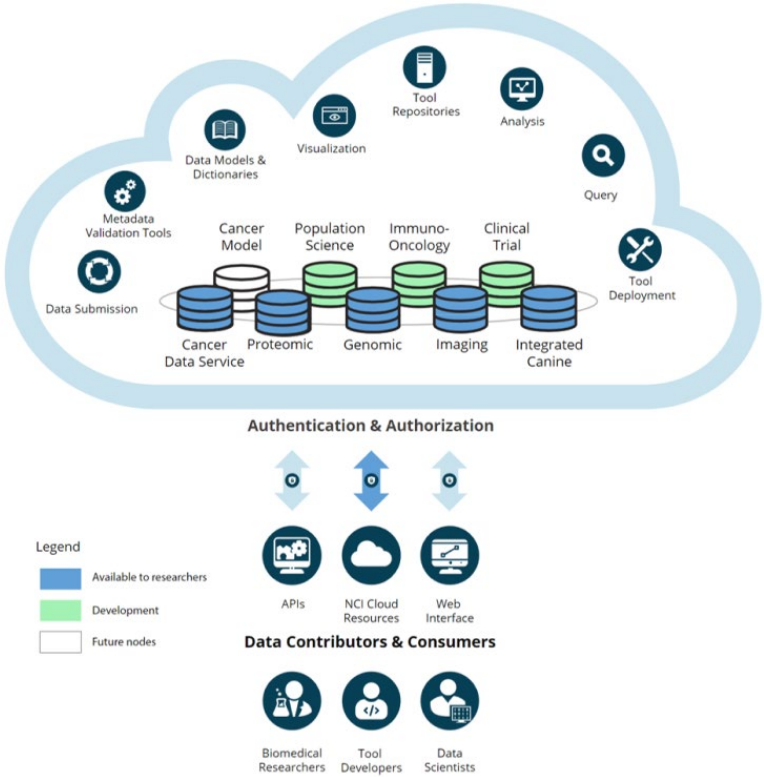
CCDI Data Ecosystem: Components Connecting the Data

- Data access portal
- Primary data sources
  - Childhood Cancer Clinical Data Commons
  - Cancer Research Data Commons
  - National Childhood Cancer Registry
  - Academic Medical Centers
- Reference Databases
  - Data Catalog
  - Molecular Targets Platform
  - Data Inventory
  - Participant Index



NCI Cancer Research Data Commons

- Provides state-of-the-art visualization, analysis, and interoperability tools in a flexible, cloud-based computational environment
- Data are stored in domain-specific Data Commons (DC)
  - Clinical, Genomics, Proteomics, Imaging
- Long-term preservation of NCI-funded data

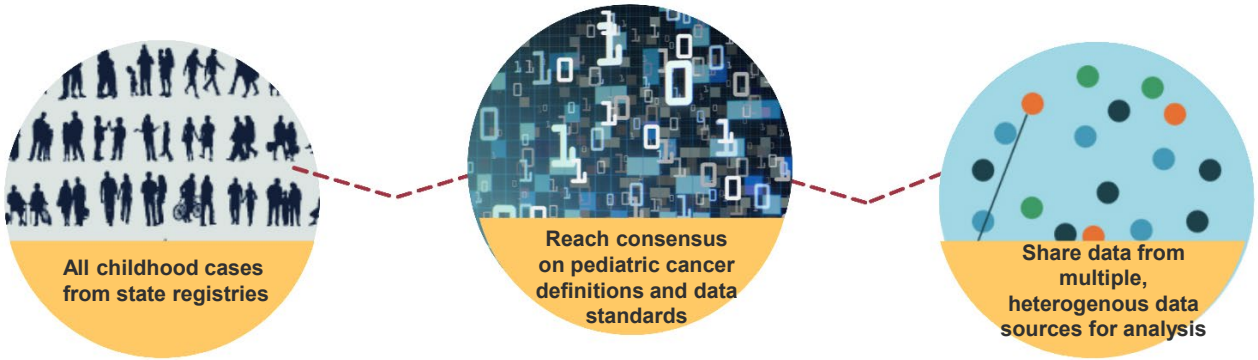


https://datascience.cancer.gov/data-commons

National Childhood Cancer Registry (NCCR)

Leverage and link data from registries and other sources:

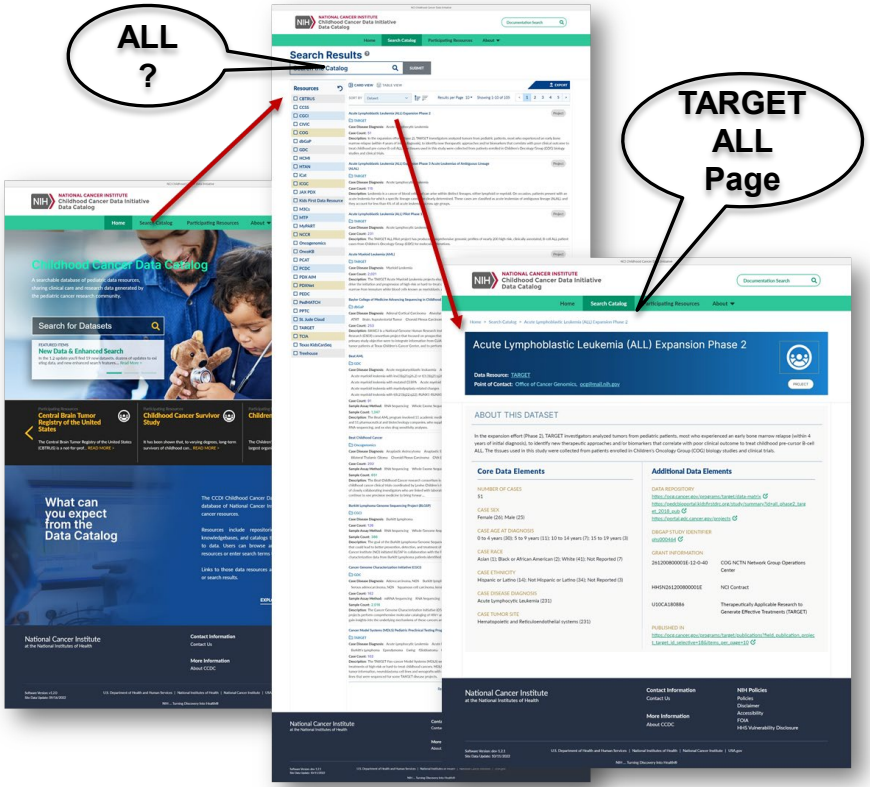
- Longitudinal treatment, procedures, outcomes
- Social determinants of health
- Clinical trials, survivorship studies, biospecimen or tissue location
- Tumor and germline molecular characterization



https://cancercontrol.cancer.gov/research-emphasis/supplement/childhood-cancer-registry

Childhood Cancer Data Catalog

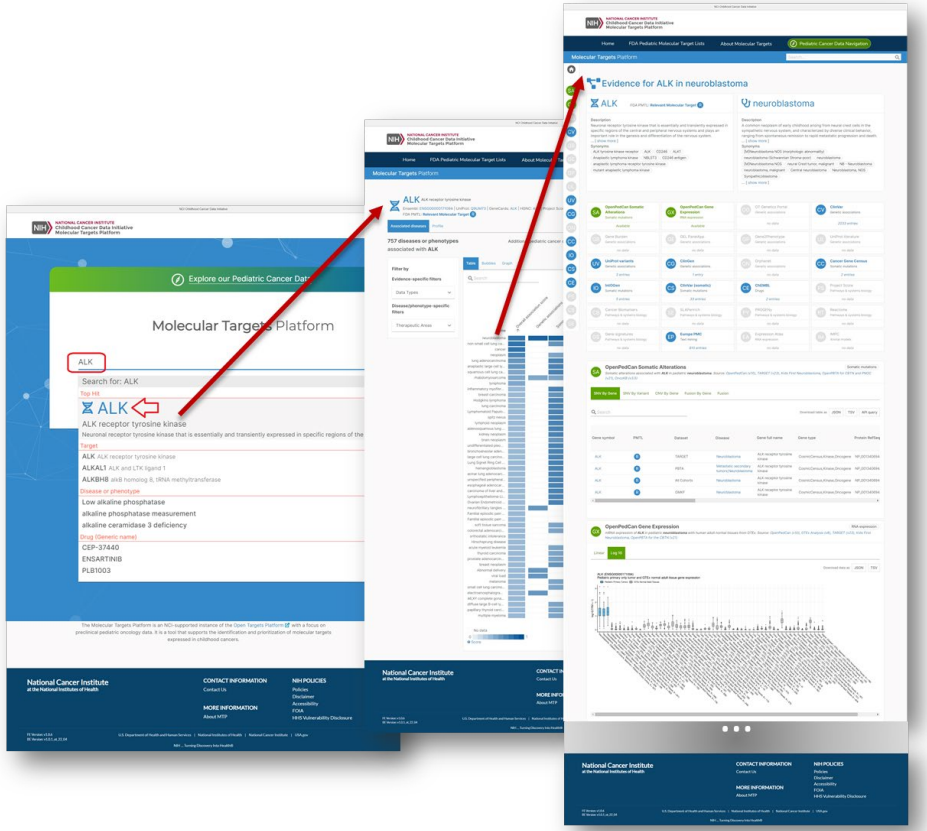
- An inventory of pediatric oncology data resources, including childhood cancer repositories, registries, knowledgebases, and catalogs that either manage or refer to data.
- 31 Resources, 105 Datasets



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

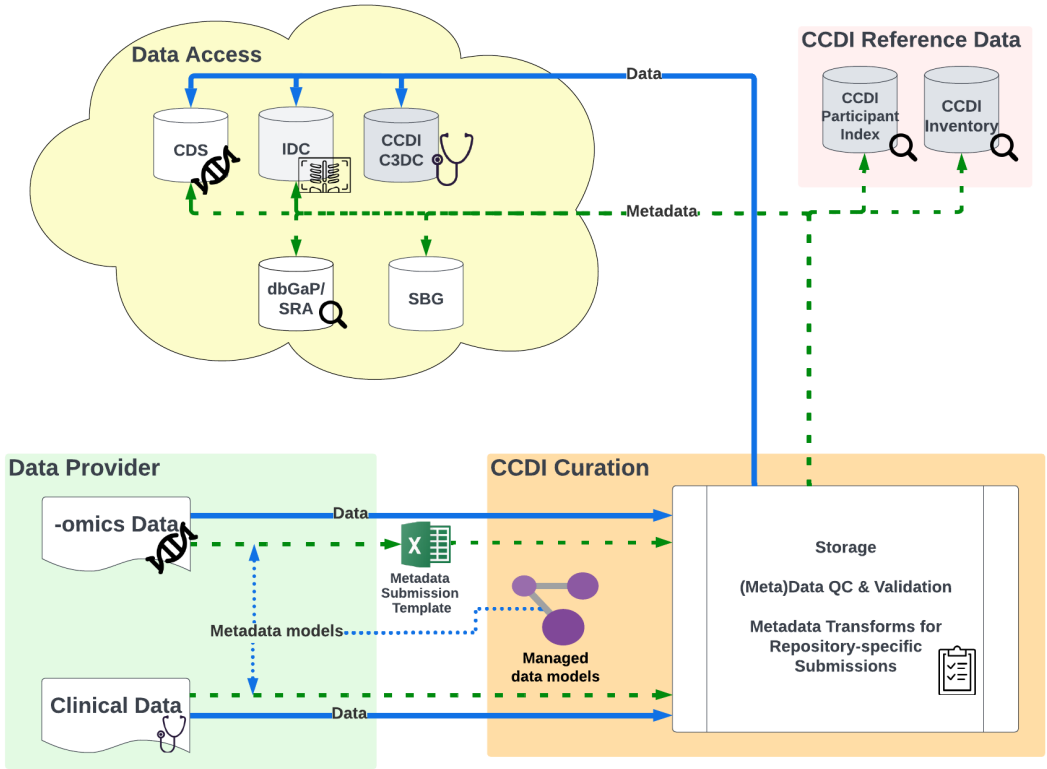
Molecular Targets Platform (MTP)

- An instance of the Open Targets Platform with a focus on pediatric cancer data.
- MTP allows users to browse and identify associations between molecular targets, diseases, and drugs.
- Includes the FDA Pediatric Molecular Target Lists (FDA PMTL)



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

CCDI Data Flow Overview



CDS: Cancer Data Service

IDC: Imaging Data Commons

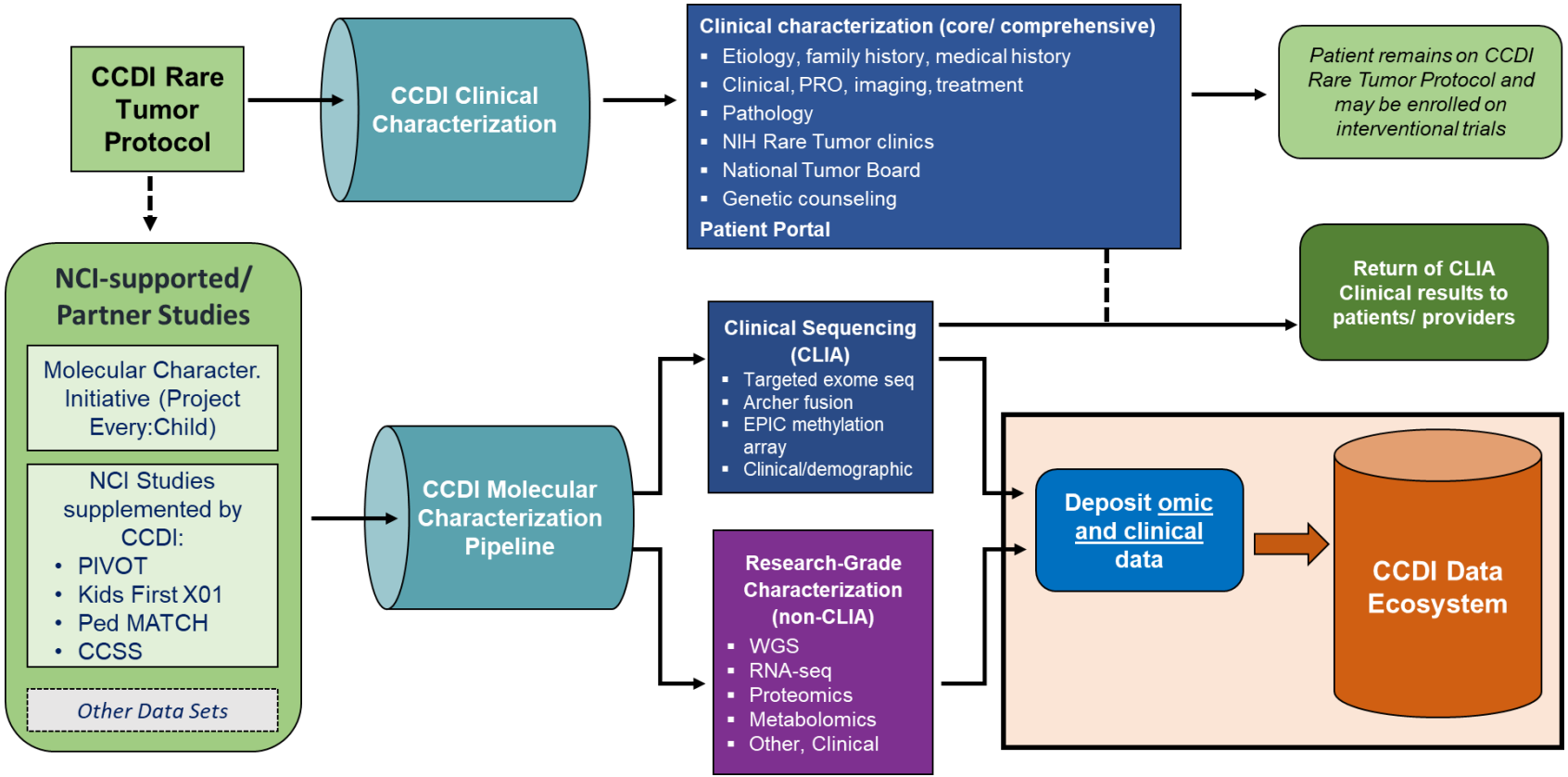
dbGaP: database of Genotypes and Phenotypes

SRA: Sequence Read Archive

SBG: Seven Bridges Genomics

C3DC: Childhood Cancer Clinical Data Commons

CCDI Data Generation Pipeline/Overview



CCDI: Data Generation & Sharing Projects

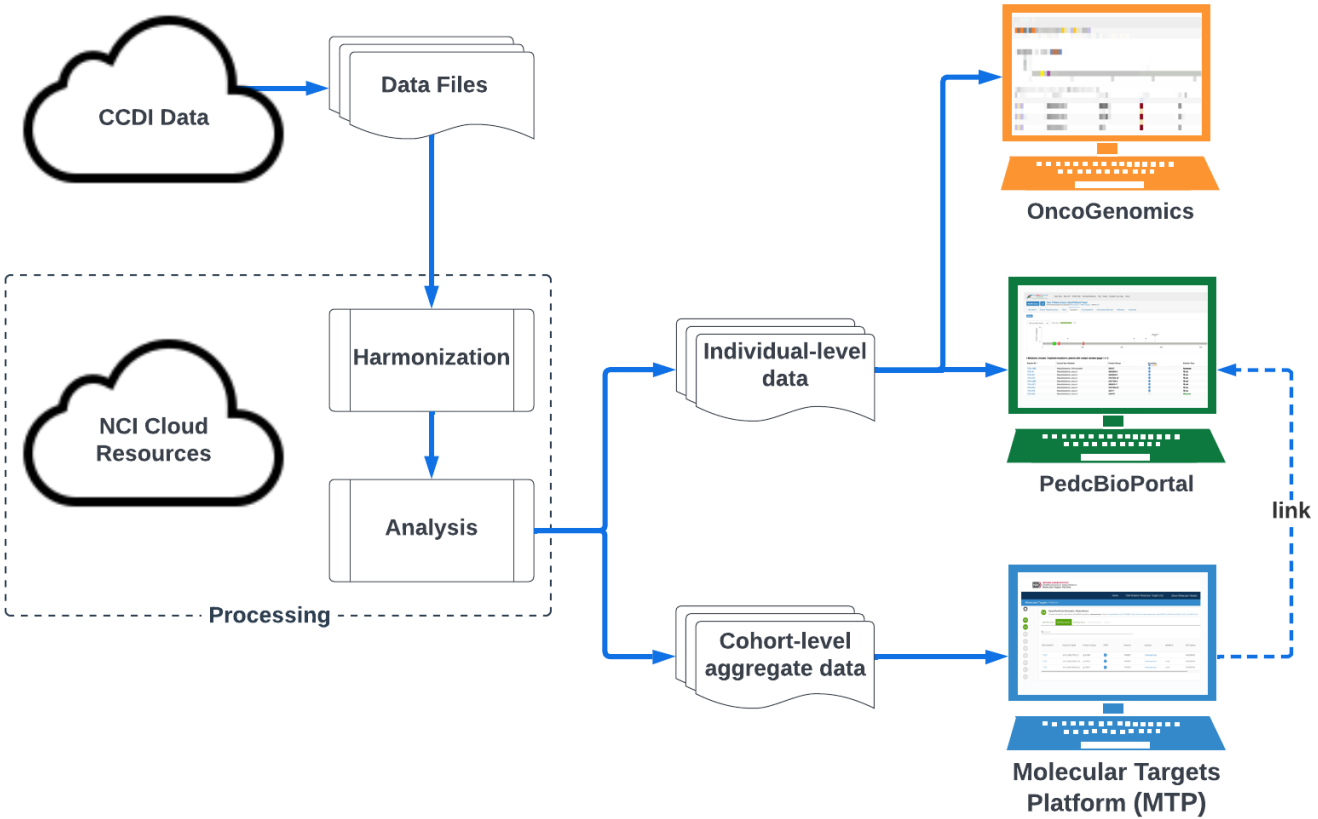
Available Individual-level Genomics Data (dbGaP)

- phs002790.v1.p1 (CNS, STS, Rare tumors - MCI)
- phs002599.v1.p1 (Acute Myeloid Leukemia - OHSU)
- phs002504.v1.p1 (Juvenile myelomonocytic leukemia - UCSF)
- phs002620.v1.p1 (Solid tumors - MSKCC)

Coming soon

- phs002518.v1.p1 (all cancer types – USC) ; phs002431.v1.p1 (Pediatric/AYA Cancer Touchstone data - Univ. Michigan); phs002517.v1.p1 (CBTN - CHOP); phs002827.v1.p1 (Bone & Soft Tissue Cancers – SickKids)
- Molecular characterization data from patient derived models
- Correlative studies data (Solid tumors – Pediatric MATCH)

Downstream Applications: An Example



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

www.cancer.gov

www.cancer.gov/espanol

Afternoon Session

Gwen Nichols, MD

Chief Medical Officer, The Leukemia & Lymphoma Society (LLS)

The Leukemia & Lymphoma Society Patient Portals Research – Past, Present and Future

Gwen L. Nichols, MD

Chief Medical Officer

NIH NATIONAL CANCER INSTITUTE

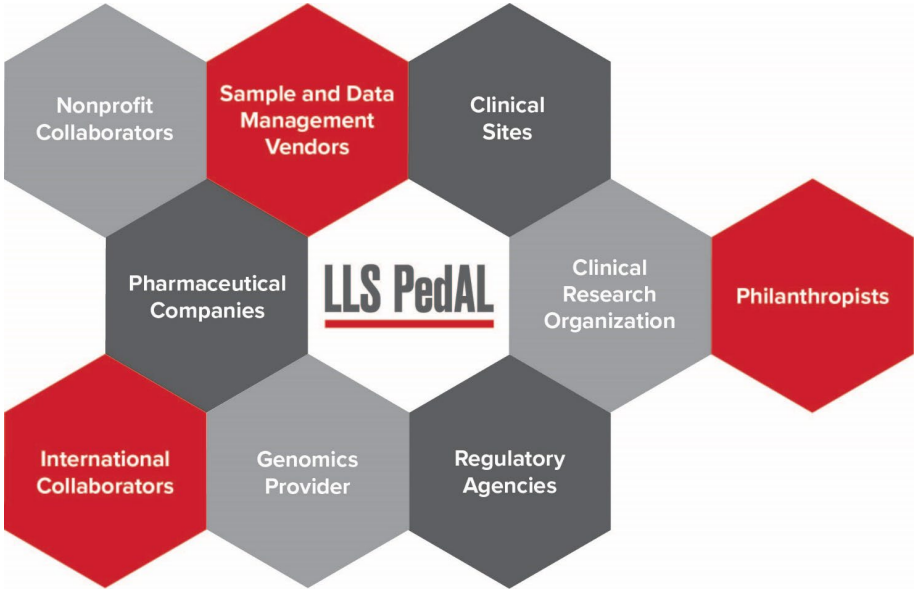
November 2022

LLS PedAL

The LLS PedAL (Pediatric Acute Leukemia) Master Trial

askpedal@lls.org

- International collaboration to bring precision medicine (genomics and other biomarkers) to acute leukemia treatment for children
- Matching children with innovative new treatment
- Creating clinical trial efficiency with multiple partners vs. one drug at a time
- Collecting data TOGETHER using agreed endpoints and dictionary
- Working with multiple partners: NCI, Pharma, COG, ITCC



- Available at many sites - Bringing the drugs to the kids, not the kids to the drugs

LEUKEMIA & LYMPHOMA SOCIETY®

PEDAL GOALS

- **SCREEN** - Screen all children with relapsed AML and a subset of children with ALL for sub-trial eligibility based on clinical data, flow cytometry and genomic sequencing.

- **ACCESS** - To partner with pharmaceutical companies, the NCI, and European Study Groups (via the EuPAL Foundation) to support a drug development platform for children with relapsed leukemia that: aligns and achieves regulatory and scientific objectives and ensures that children have early access to effective therapies.

- **CHANGE** - Improve post-relapse data collection to inform changes in primary outcome measures and toxicity definitions that better reflect the realities of routine care for children with relapsed leukemia.

The PedAL Screening Trial is available to all COG sites in N.A. , Australia, New Zealand with a parallel Registry in Europe

- Leukemia blast enumeration and cell surface biomarker detection
- Foundation Medicine Sequencing

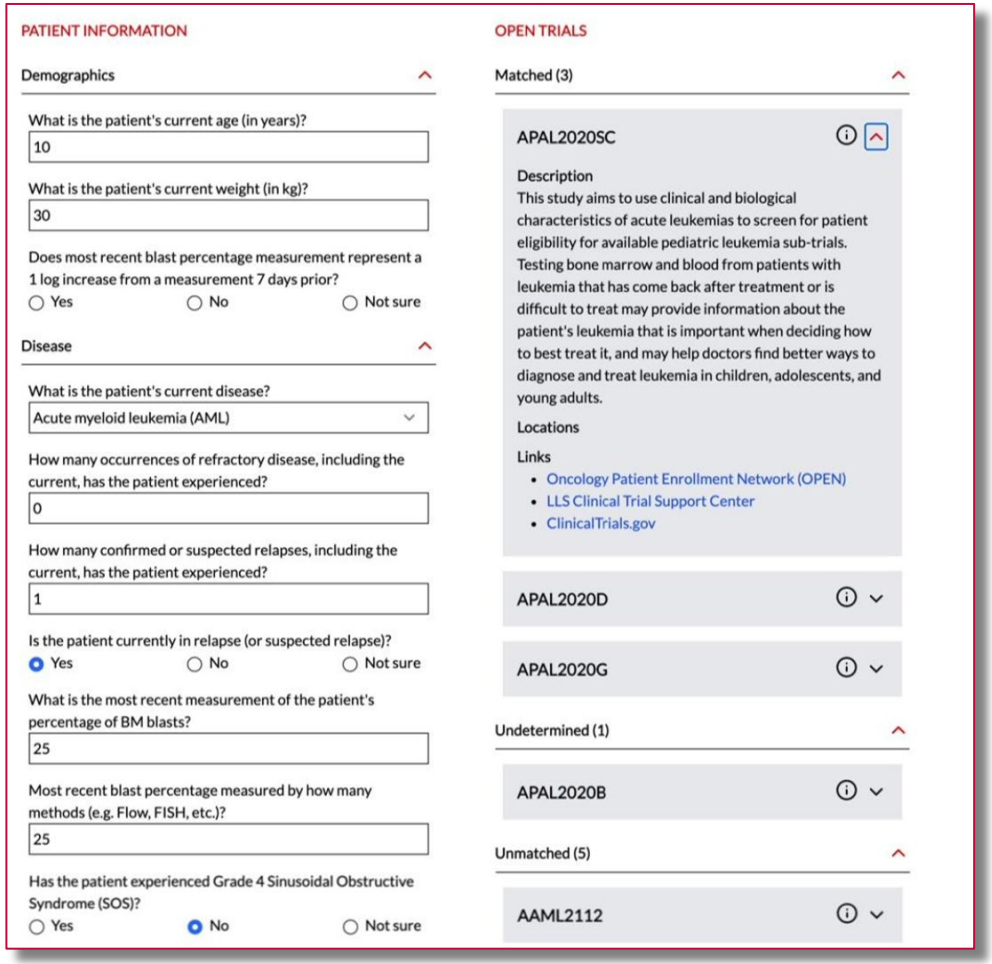
} **Available to enrolling physician and family**

GEARBOx

Genomic **E**ligibility **A**lgorithm at **R**elapse for **B**etter **O**utcomes

http://gearbox.pedscommons.org

- LLS-funded initiative with the U. of Chicago Pediatric Data Commons, to have children with relapsed/refractory AML access to a clinical trial within 72 hours
- Information sourced from clinicaltrials.gov
- GEARBOx tool rolled out nationwide Q2 2022
- Helps patients and clinicians navigate the complex process of trial enrollment
- Complemented by LLS clinical trial navigation nurses who can help with ALL the support needed for HCPs, patients and families to participate in clinical trials



Additional resources

- **Information Resource Specialists:** Highly trained oncology social workers and nurses provide one-on-one information & support on treatment, financial & psychosocial resources www.LLS.org/IRC
- **Clinical Trial Nurse Navigators:** Nurses with expertise in blood cancers work one-on-one with patients, caregivers or HCPs, or you can refer a patient www.LLS.org/CTSCreferral
- **Nutrition Consultation:** Patients and caregivers may receive free one-on-one phone and email consultations with a registered dietitian with expertise in oncology nutrition. This service is available for all cancer diagnoses.
- *An extension of your team, providing support to you & your patients*
- Phone: (800) 955-4572, M-F, 9 am to 9 pm ET
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists

www.cancer.gov

www.cancer.gov/espanol

Afternoon Session

Corrie Painter, PhD

VP, External Research & Partnerships - Precede Biosciences, Strategic Advisor - Broad Institute

Count Me In; Patient Partnered Research to Accelerate Discoveries in Cancer

Corrie Painter, PhD

Strategic Advisor, Count Me In

NIH NATIONAL CANCER INSTITUTE

Disclosures

Precede Biosciences

One Health

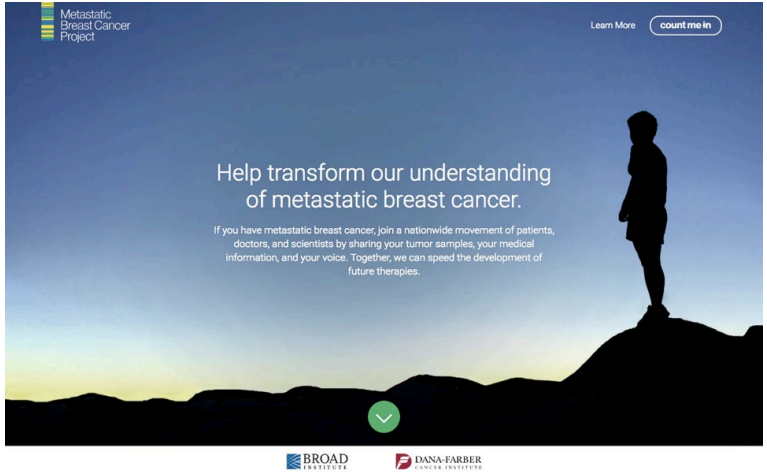
Building clinico-genomics datasets to fuel discoveries

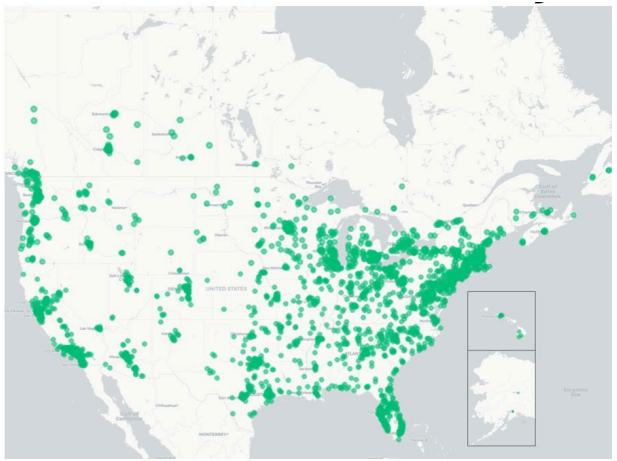
Generation of publicly available database of clinical, genomic, molecular, and patient reported data in cancer to enable researchers to find patterns in the data – and help accelerate discoveries and the development of new treatment strategies

- Build in lockstep with patient communities
- Identify & build portals to house de-identified data
- Communicate progress to participants at regular intervals
- Evolve with participant feedback

The Metastatic Breast Cancer Project

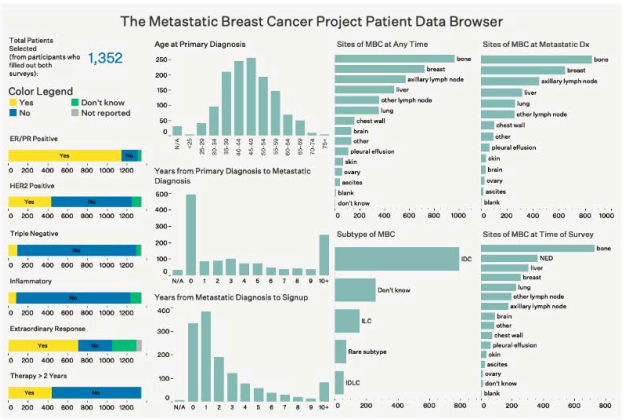
MBCproject.org





*Over **6000 women and men** with metastatic breast cancer from all 50 states have joined the MBCproject since our launch in October 2015*

Data Availability and Portals



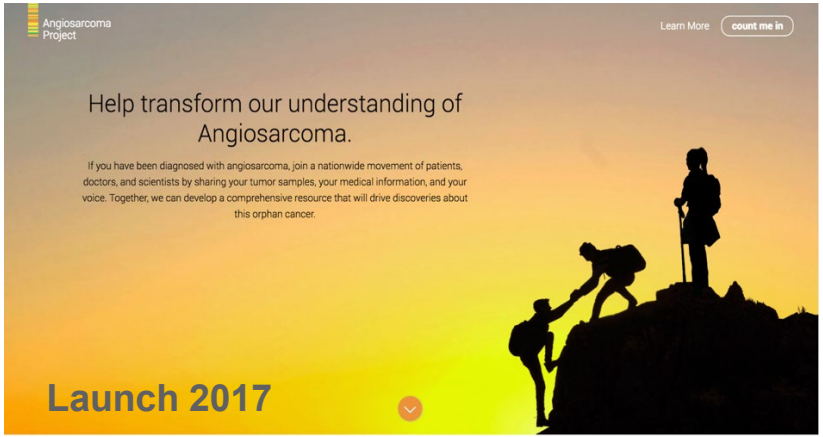
cBioPortal for Cancer Genomics

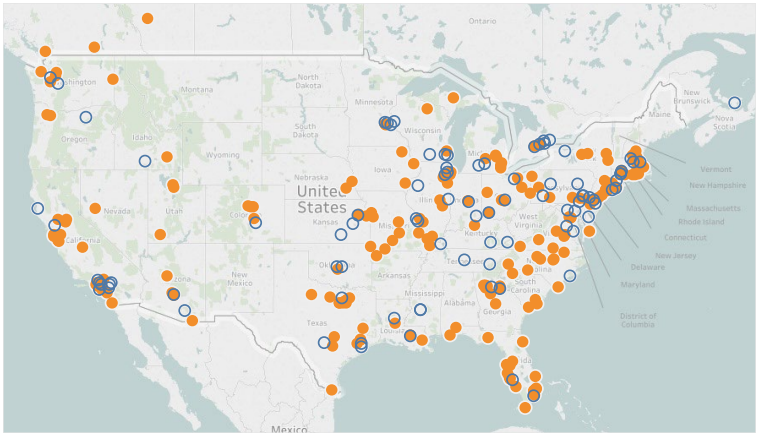
NIH NATIONAL CANCER INSTITUTE Genomic Data Commons

MBCPROJECT.ORG
PATIENT DATA BROWSER

- De-identified, clinically annotated WES and RNA-seq data (cBioPortal.org) ~ 400 WES tumor/normal
- WES and RNA-seq BAM files with accompanying clinical data - DBGaP and the NCI Genomic Data Commons.
- Patient reported data portal – MBCProject.org
- To date, the MBCproject has been cited in more than 30 peer reviewed publications

Open source data led to rapid impact in angiosarcoma





nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0749-z

The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research

Corrie A. Painter[1,2,15], Esha Jain[1,2,3,15], Brett N. Tomson[1,2,15], Michael Dunphy[1,2], Rachel E. Stoddard[1,2], Beena S. Thomas[1,2], Alyssa L. Damon[1,2], Shahrayz Shah[1,2], Dewey Kim[1,2,3], Jorge Gómez Tejeda Zañudo[2,3], Jason L. Hornick[4], Yen-Lin Chen[5], Priscilla Merriam[3,6], Chandrajit P. Raut[6,7], George D. Demetri[3,6,8], Brian A. Van Tine[9], Eric S. Lander[1,2,10,11], Todd R. Golub[1,2,12] and Nikhil Wagle[1,2,3,13,14*]

Primary Publication Feb 2020

Clinical/translational cancer immunotherapy
Original research

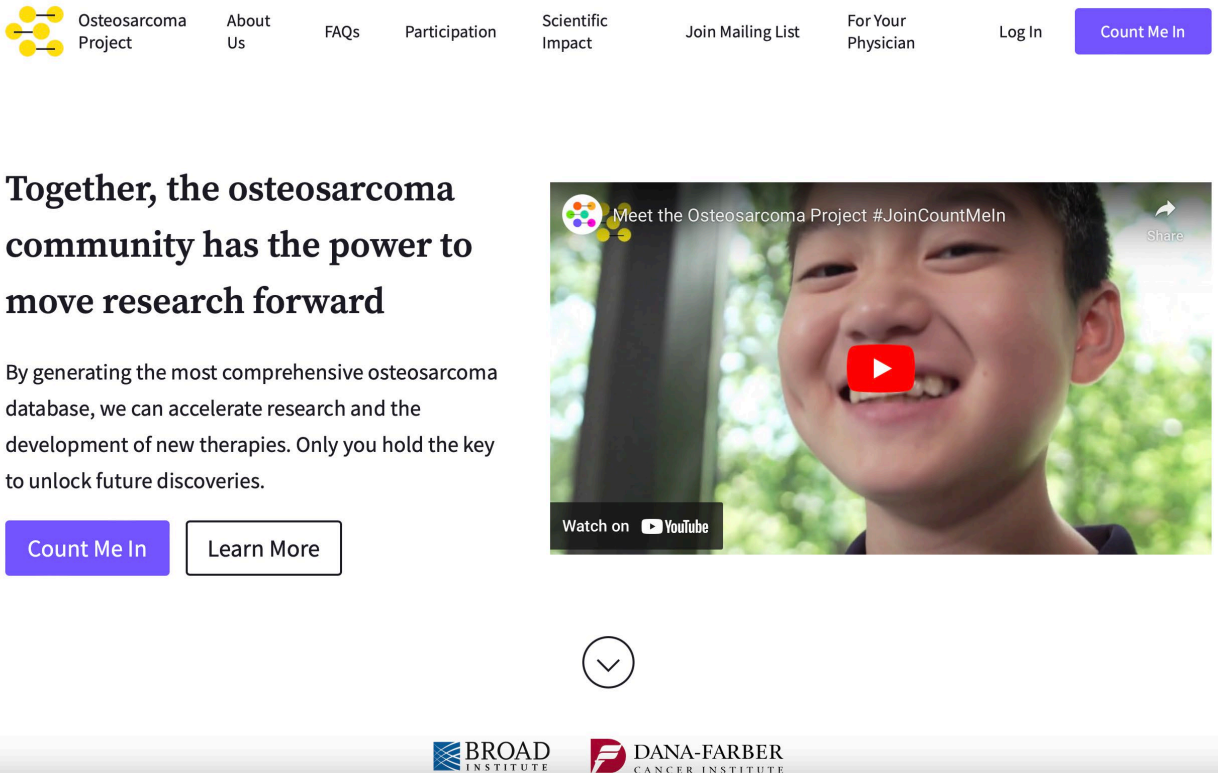
Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART)

Michael J Wagner [1, 2], Megan Othus [3], Sandip P Patel [4], Chris Ryan [5], Ashish Sangal [6], Benjamin Powers [7], G Thomas Budd [8], Adrienne I Victor [9], Chung-Tsen Hsueh [10], Rashmi Chugh [11], Suresh Nair [12], Kirsten M Leu [13], Mark Agulnik [14, 15], Elad Sharon [16], Edward Mayerson [3], Melissa Plets [3], Charles Blanke [5, 17], Howard Streicher [16], Young Kwang Chae [15] and Razelle Kurzrock [4]

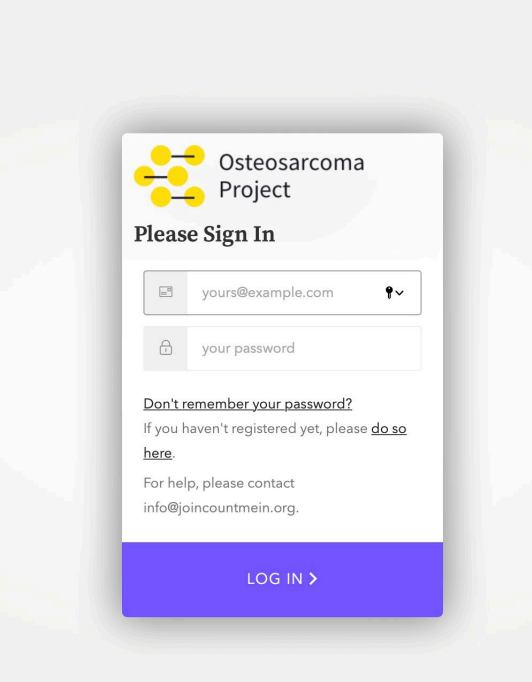
Correspondence to Dr Michael J Wagner; wagnermj@uw.edu

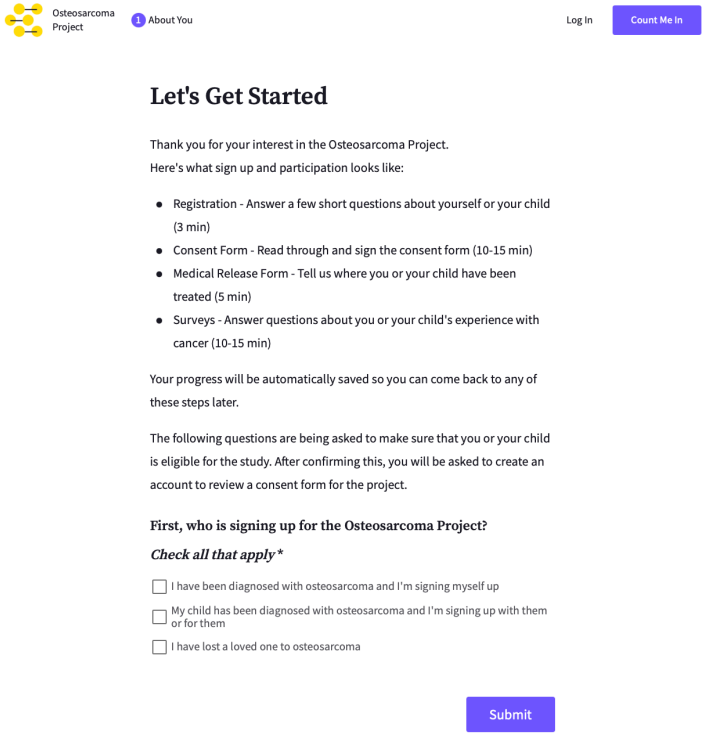
Trial results published Aug 2021

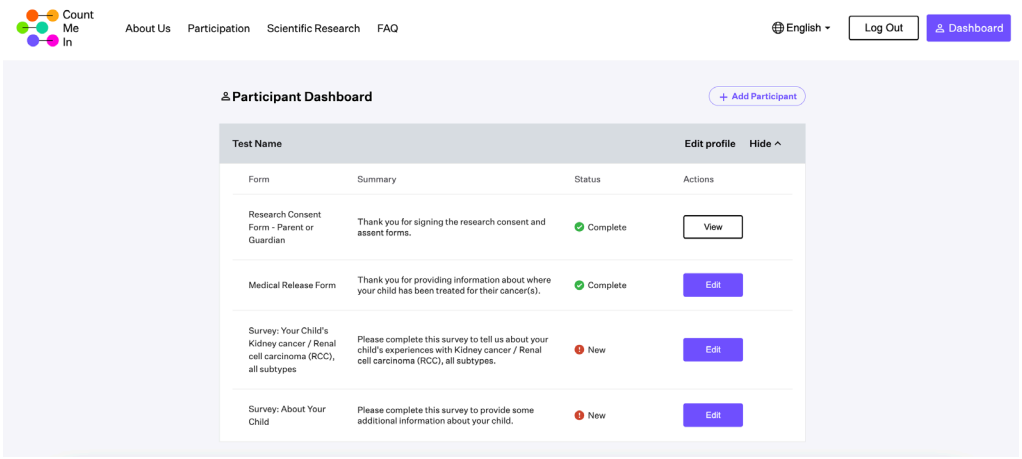
Counting Pediatrics In

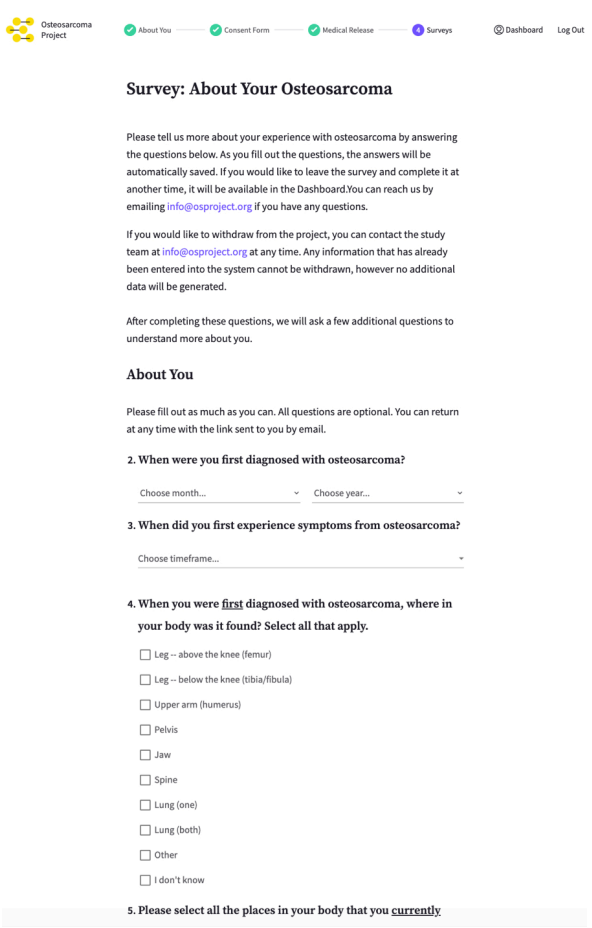


Osteosarcoma project portal









Survey's, consent and medical release forms are available on the project website: OSproject.org

Next steps

Deliver tumor and germline specific information back to participants

Launch additional high impact cohorts

Continue to drive awareness of projects for patient enrollment and data for scientific discoveries

www.cancer.gov

www.cancer.gov/espanol

Afternoon Session

Rajkumar Venkatramani, MD, MS, MBA, FAAP

Baylor College of Medicine

Role for national rare cancer tumor boards

Rajkumar Venkatramani, MD, MS, MBA

November 18, 2022

Texas Children's Cancer and Hematology Centers

Rare Cancer Tumor Boards (examples)

- Desmoid Tumor (sponsored by Desmoid Tumor Research Foundation)
- Pediatric brain tumors (Sponsored by Society of NeuroOncology)
- Rare tumor board (Sponsored by Texas Children's Hospital)
- Liver tumor board (UCSF)

Texas Children's Cancer and Hematology Centers

Texas Children's Rare Tumor Board

- Started April 2018
- Initially conceived as including institutions in Texas
- Gradually expanded to an open forum for all institutions

Texas Children's Cancer and Hematology Centers

Texas Children's Rare Tumor Board

- First Thursday of every month at 1 pm CST
- 60 minutes
- 2-4 cases per session
- Literature review (optional)

Texas Children's Cancer and Hematology Centers

Participants

- Pediatric oncologists/surgeons/pathologists
- Invited specialists depending on cases presented
- Approximately 20 attendees per tumor board
- Approximately 190 people are on the email list (grew organically)

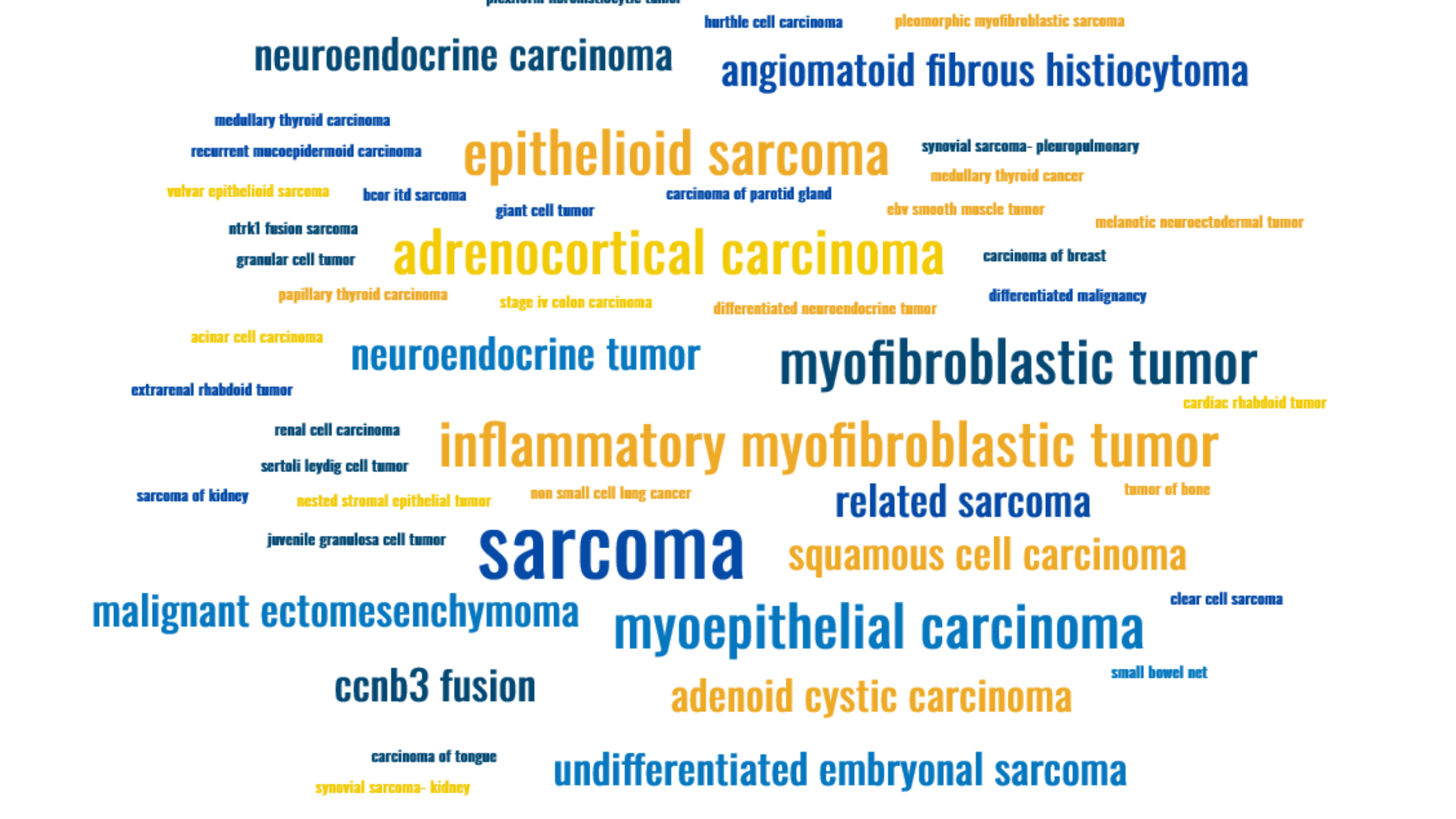
Texas Children's Cancer and Hematology Centers

Cases

- 113 different cases presented in 4.5 years
- 58 institutions from 43 cities
- 99 different tumors

Texas Children's Cancer and Hematology Centers


MONTANA
NORTH DAKOTA
MINNESOTA
SOUTH DAKOTA
WISCONSIN
MICHIGAN
IDAHO
WYOMING
IOWA
NEBRASKA
ILLINOIS
NEVADA
UTAH
COLORADO
KANSAS
PA
WEST VIRGINIA
KENTUCKY
VIRGINIA
CALIFORNIA
OKLAHOMA
TENNESSEE
NC
ARKANSAS
NEW MEXICO
Birmingham, Alabama
MISSISSIPPI
NB
PRINCE EDWARD ISLAND
NOVA SCOTIA
MAINE
VT.
Gulf of Mexico
Sargasso Sea
Nassau
Havana
CUBA
George Town
MEXICO


hurthle cell carcinoma
pleomorphic myofibroblastic sarcoma
neuroendocrine carcinoma
angiomatoid fibrous histiocytoma
medullary thyroid carcinoma
recurrent mucoepidermoid carcinoma
epithelioid sarcoma
synovial sarcoma- pleuropulmonary
medullary thyroid cancer
vulvar epithelioid sarcoma
bcor itd sarcoma
carcinoma of parotid gland
giant cell tumor
ebv smooth muscle tumor
melanotic neuroectodermal tumor
ntrk1 fusion sarcoma
granular cell tumor
adrenocortical carcinoma
carcinoma of breast
papillary thyroid carcinoma
stage iv colon carcinoma
differentiated neuroendocrine tumor
differentiated malignancy
acinar cell carcinoma
neuroendocrine tumor
myofibroblastic tumor
extrarenal rhabdoid tumor
cardiac rhabdoid tumor
renal cell carcinoma
inflammatory myofibroblastic tumor
sertoli leydig cell tumor
sarcoma of kidney
nested stromal epithelial tumor
non small cell lung cancer
related sarcoma
tumor of bone
juvenile granulosa cell tumor
sarcoma
squamous cell carcinoma
malignant ectomesenchymoma
clear cell sarcoma
myoepithelial carcinoma
small bowel net
ccnb3 fusion
adenoid cystic carcinoma
carcinoma of tongue
undifferentiated embryonal sarcoma
synovial sarcoma- kidney

box

Search Files and Folders

RV

All Files

Recents

Synced

Notes

Apps

Trash

My Collections

Favorites

Rare Tumors Tumo...

All Files > Rare Tumors Tumor Board

1

New +

Share

NAME ↑	UPDATED	SIZE
Acinar Cell Carcinoma (Pancreas) 05-07-2020.pdf	May 7, 2020 by Rajkumar Venk...	3 MB
Adamantinoma 02-03-2022.pdf	Feb 4, 2022 by Rajkumar Venk...	382.1 KB
Adenocarcinoma (salivary gland) 03-03-2022.pdf	Mar 9, 2022 by Rajkumar Venk...	992.3 KB
Adenoid Cystic Carcinoma 7-1-2021.pdf	Jul 1, 2021 by Rajkumar Venkat...	790.3 KB
Adenoid Cystic Carcinoma (Lacrimal Gland) 05-07-202...	May 7, 2020 by Rajkumar Venk...	816.3 KB
Adrenocortical Carcinoma 12-6-18.pdf V2	Jan 9, 2021 by Rajkumar Venka...	1 MB
Adrenocortical carcinoma recurrent 5-6-2021.pdf	May 6, 2021 by Rajkumar Venk...	1.5 MB
Agenda Rare Tumors Tumor Board.xlsx V101	Yesterday by Rajkumar Venkatr...	20.1 KB
Alveolar Soft Part Sarcoma 5-10-18.pdf	May 27, 2019 by Rajkumar Ven...	1.5 MB
Ameloblastic Carcinoma 12-03-2020.pdf	Dec 3, 2020 by Rajkumar Venk...	337.3 KB
Anaplastic Sarcoma of Kidney 02-03-2022.pdf	Feb 4, 2022 by Rajkumar Venk...	601.1 KB
Angiomatoid Fibrous Histiocytoma (CNS) 11-05-2020....	Nov 5, 2020 by Rajkumar Venk...	248.1 KB

Sharing | Details

Collaborators
Invite People

Shared Link
Public and accessible to anyone with the link

File Request
Create Link

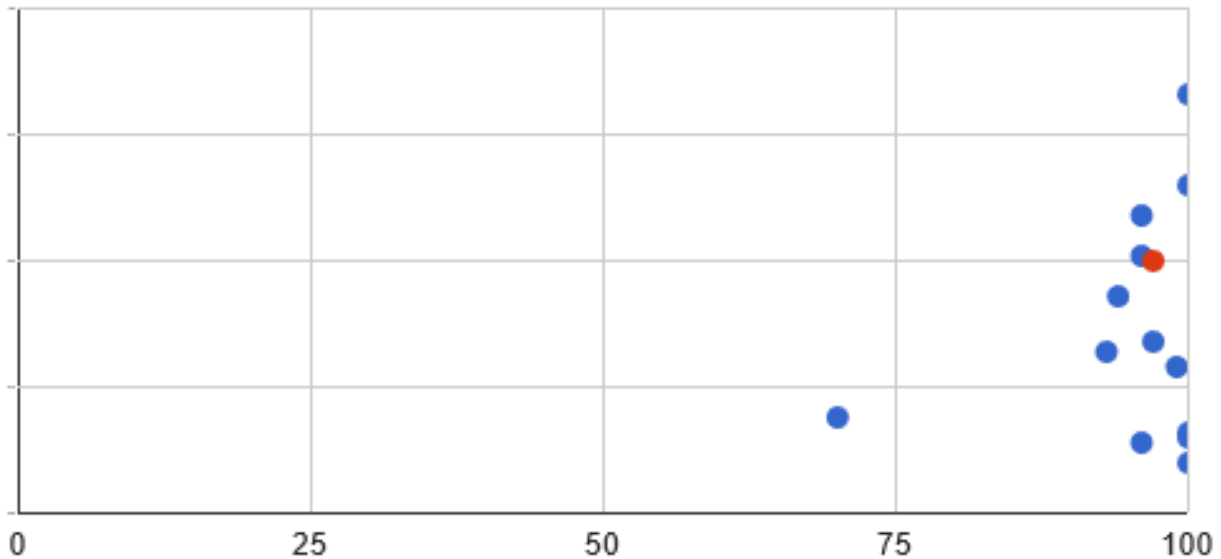
Survey of participants

- N=24

Texas Children's Cancer and Hematology Centers

Presenting my patient in the tumor board was helpful *(presenting_my_patient_in_t)*

Total Count (N)	Missing*	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
13	11 (45.8%)	7	70	100	95.46	8.04	1,241	83.80	93.20	96	97	100	100	100

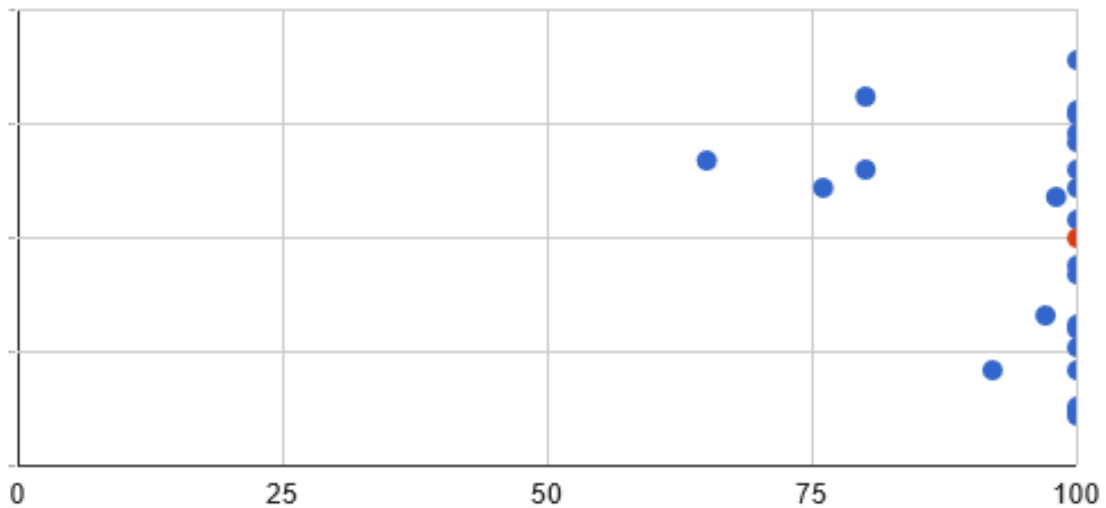


Texas Children's Cancer and Hematology Centers

The tumor board helped increase my knowledge of rare tumors in children

(the_tumor_board_has_helped) Refresh Plot

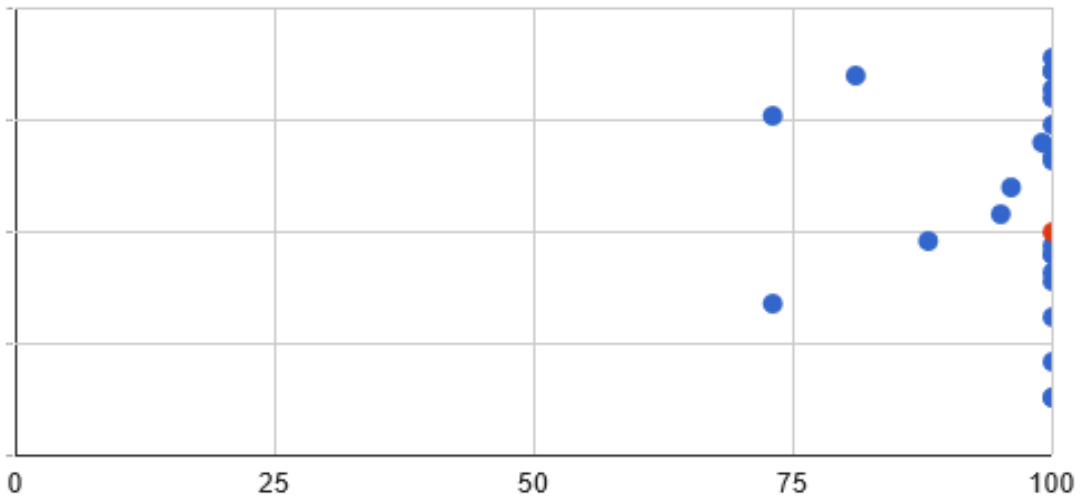
Total Count (N)	Missing*	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
24	0 (0.0%)	7	65	100	95.33	9.68	2,288	76.60	80	97.75	100	100	100	100



Texas Children's Cancer and Hematology Centers

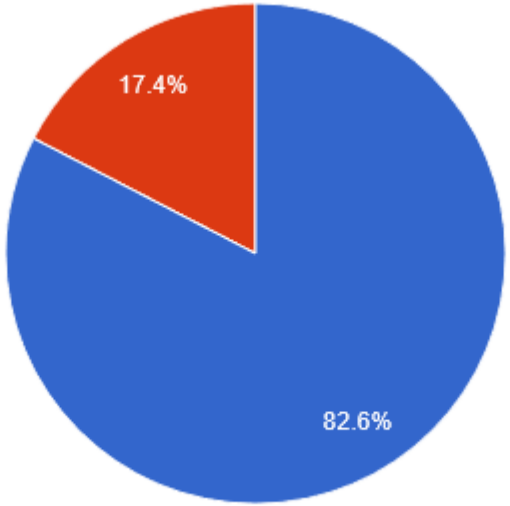
I am likely to recommend this tumor board to a colleague if they have a patient with a rare tumor *(i_am_likely_to_recommend_t)* Refresh Plot

Total Count (N)	Missing*	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
24	0 (0.0%)	7	73	100	96.04	8.42	2,305	74.20	83.10	98.25	100	100	100	100



Texas Children's Cancer and Hematology Centers

I have used the online link to the presentations



Counts/frequency: Yes (19, 82.6%), No (4, 17.4%)

Texas Children's Cancer and Hematology Centers

My Thoughts…

- There is a need for multi-institutional tumor board for rare tumors
- Useful for participants
- Anecdotal evidence is better than no evidence
- Can lead to new collaborations
- Helpful even if there is no recommendation from tumor board (for both patients and physicians)

Texas Children's Cancer and Hematology Centers

Challenges

- Need dedicated resources (administrative, literature review)
- Multidisciplinary participation
- Patient confidentiality/legal implications
- Dedicated website/storage for future access
- Integrating research
- Creating a non real time online tumor board infrastructure

Texas Children's Cancer and Hematology Centers

Panel Discussion: Requirements for a National Initiative

Subhashini Jagu, PhD
Scientific Policy and Program Branch A Chief, Supervisory Health Scientist Administrator
Center for Biomedical Informatics & Information Technology, National Cancer Institute

Katherine Janeway, MD, MMSc
Associate Professor of Pediatrics, Harvard Medical School, Senior Physician, Dana-Farber / Boston Children's Cancer and Blood Disorders Center, Director, Clinical Genomics, Dana-Farber Cancer Institute

Razelle Kurzock, MD, FACP
Center Associate Director, Professor
Medical College of Wisconsin

Robin Lockridge, PhD
Clinical Neuropsychologist
Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc.

Gwen Nichols, MD
Chief Medical Officer, The Leukemia & Lymphoma Society (LLS)

Corrie Painter, PhD
VP, External Research & Partnerships - Precede Biosciences, Strategic Advisor - Broad Institute

Alberto Pappo, MD
Director, Solid Tumor Division
St. Jude Children's Research Hospital

Jack Shern, MD
Physician Scientist, Pediatric Oncology Branch
National Cancer Institute

Rajkumar Venkatramani, MD, MS, MBA, FAAP
Baylor College of Medicine

Samuel Volchenboum, MD, PhD
Pediatric Cancer Data Commons
University of Chicago

U.S. Department of Health & Human Services

National Institutes of Health | National Cancer Institute

cancer.gov

1-800-4-CANCER