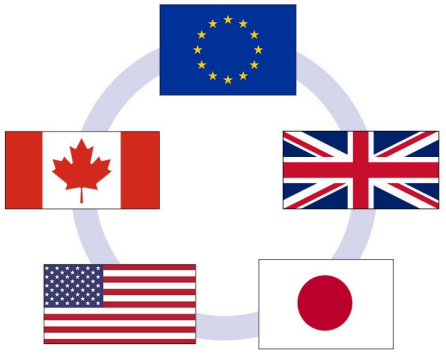
INRG
International Neuroblastoma Risk Group
TASK FORCE

ANR 2020123
MAY 15-18 2023
AMSTERDAM



INRG Task Force
Report of the Meeting
Sunday, May 14, 2023
Amsterdam

INRG Task Force Meeting Agenda

CET	LENGTH	TOPIC	SPEAKER
17:30	15 min	Welcome, History, Accomplishments, Work-in-Progress	Andy Pearson, Sue Cohn
17:45	30 min	INRG Data Commons Research Studies – experience • The application process and perspectives from a YI • Using the INRG Data Commons to analyze a rare patient cohort	Boris Decarolis Steve DuBois
18:15	5 min	BORNEO (BiOmarkers in high Risk NEurOblastoma)	Lucas Moreno, Wendy London
18:20	15 min	Strategy Committee Update: Opportunities for YIs	Meredith Irwin, Lucas Moreno
18:35	15 min	Updates from the INRG Data Commons	Sam Volchenboum
18:50	10 min	Governance Update	Suzi Birz
19:00	20 min	• ALK data addition to the INRG • Future genomic data linking beyond ALK • Links to genomic data – SIOPEN BioPortal	Gudrun Schleiermacher, Matthias Fischer, Meredith Irwin
19:20	10 min	Relapse and Response Patient Data	Lucas Moreno, Julie Park, Wendy London
19:30	10 min	INRG Risk Classification 2.0	Mathias Fischer, Meredith Irwin, Wendy London, Gudrun Schleiermacher, Julie Park, Sue Cohn and Andy Pearson
19:40	20 min	Discussion and Next Steps	Sue Cohn / Andy Pearson
20:00		Adjourn.	

Executive Summary

Attended by more than 70 researchers from 14 countries.

The 2.5 hour meeting included:

- Updates on current activities
- Sharing experiences from INRG Data Commons Research Studies
- Update from the Strategy Committee
- Report on new INRG data efforts
- Discussion about coordinating efforts across groups
- New INRG data efforts
- Update on INRG risk stratification version 2
- Update from the Data Commons

This report provides a summary of the meeting and the discussions.

Follow-up activities:

- ❑ Continue to look for more groups that want to bring data into INRG
- ❑ Ensure project proposals for data from a singloe cooperative group are reviewed by the cooperative group chair
- ❑ Continue to add early career investigators to new projects and identify projects and mentors for these investigators
- ❑ Continue efforts to link clinical and genomic data using available public identifiers
- ❑ Continue work to define new data elements
- ❑ For the relapse studies, explore ways to link the relapse study to the primary data
- ❑ Continue work on INRG risk stratification version 2

Quick links

Data Portal

INRG website

NBL data dictionary

Past and ongoing projects

INRG publications

Publication policy

Project request form

In Amsterdam from around the world

Welcome St. Jude

- Addition of St. Jude data to the INRG Data Commons
- Welcome Sara Federico to the INRG Executive Committee

St. Jude Children's Research Hospital®

Objectives

INRG Task Force September 13, 2022

- Highlight recent research
  - a new investigator
  - an experienced investigator
- Become familiar with new features of the INRG Data Commons
- Highlight new data elements being defined and the governance to add the data
  - genomics
  - relapse and response
- Highlight the direction and plans for the INRG Data Commons and the INRG Risk Classification System (V2.0)
- Demonstrate opportunities for new investigators to INRG
- Seek your feedback

INRG Executive Committee and Leadership

Co-Chairs

Susan Cohn

Andrew Pearson

Gudrun Schleiermacher

Julie Park

Subcommittee Chairs

Genomics: Gudrun Schleiermacher/Mathias Fischer /Meredith Irwin

Metastatic Disease: Kate Matthay

Relapse Data: Julie Park/ Lucas Moreno/Wendy London

Statistical: Wendy London

Strategy Development: Meredith Irwin/Lucas Moreno

Cooperative Group Chairs

Ro Bagatell, COG

Sara Federico, St. Jude

Maja Beck Popovic, SIOPEN

Angelika Eggert, GPOH/ SIOPEN

Akira Nakagawara, JCCG

Takehiko Kamijo, JCCG

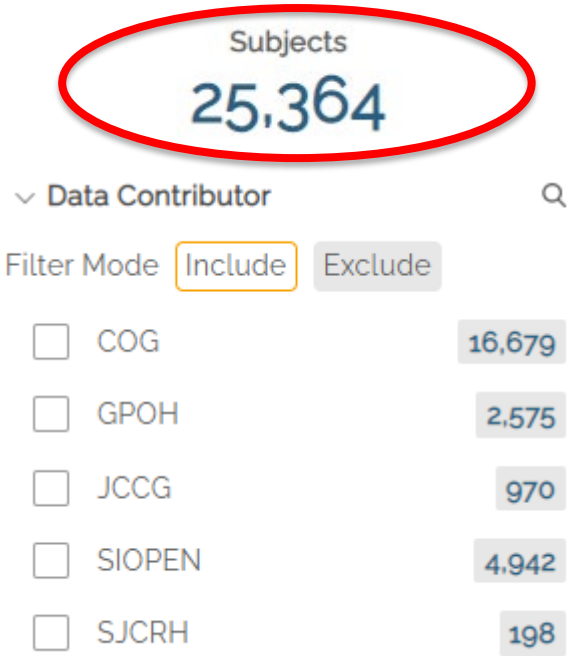
Chief Informatics Officer

Samuel Volchenboum

Executive Administrator

Suzi Birz

Current Data INRG Data Commons (https://portal.pedscommons.org)



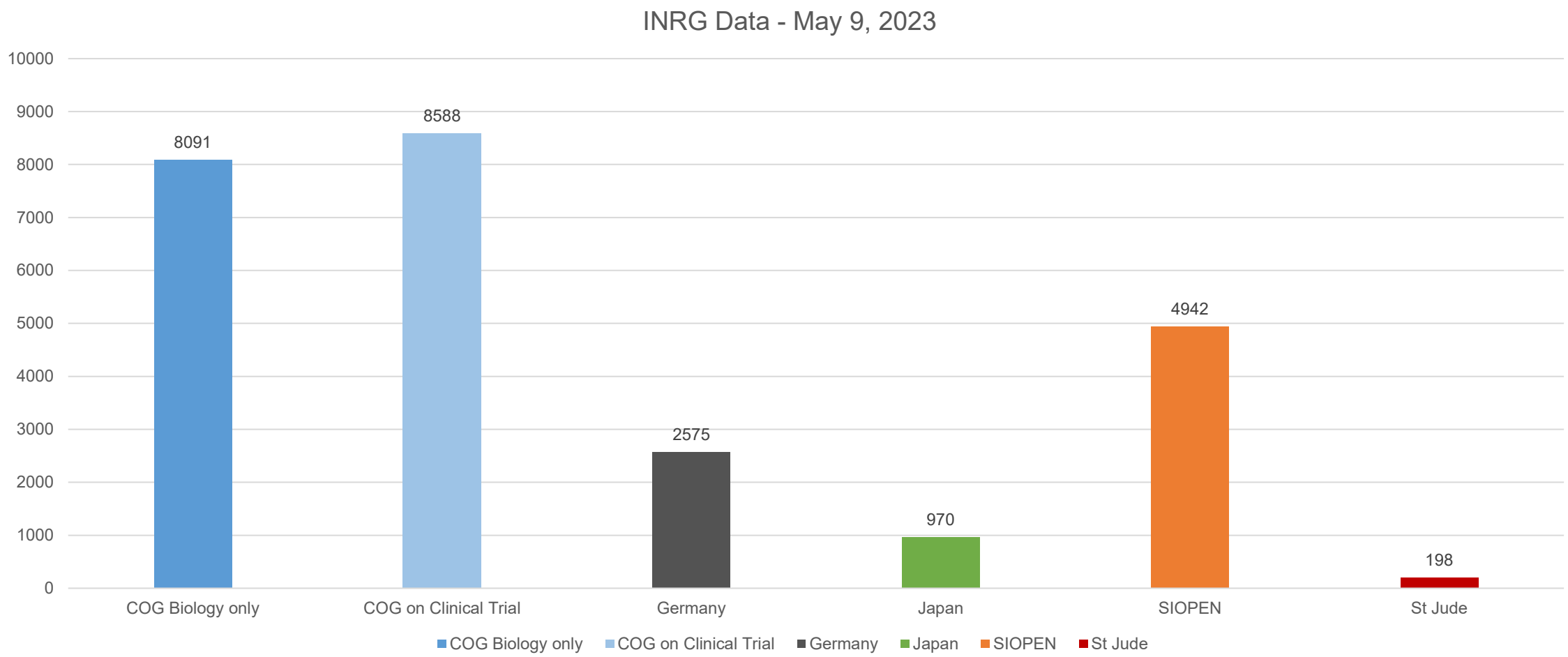
>25,000 patients

- All data elements initially collected to establish the INRG Classification
- Race/Ethnicity
- Clinical Trial Study Number and Assigned Treatment Arm
- Second Cancers
- Imaging Data

Living Database

- New SIOPEN patient data provided once primary trial is published
- New COG patient data; every 6 months
- Outcome on COG patients not on active clinical trials updated every 2 years

INRG Data Include COG Patients Only Enrolled on Biology Studies



Recent data updates to INRG data commons

Cooperative Group	Recent data
COG	• 484 new patients
ST. JUDE	• 198 unique patients added • Planned: updates to 66 participants in the INRG data commons from COG
PREVIOUSLY HIGHLIGHTED	
SIOPEN	• 1,200 new participants (R3 randomization, ALK, mIBG) • 1,092 participants (R0, R1, R2 randomizations) with updated outcomes • 360 participants (R0, R1, R2 randomizations) with updated values for 'rel_site_gen'
GPOH	421 new participants
JAPAN	528 new participants

New data will be available on https://portal.pedscommons.org/ on May 23, 2023

INRG Neuroblastoma Research Studies 2023 Highlights to-date

Pediatric Blood & Cancer

RESEARCH ARTICLE

Clinical and biological features prognostic of survival after relapse or progression of INRGSS stage MS pattern neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project

Kevin Campbell, Pei-Chi Kao, Arlene Naranjo, Takehiko Kamijo, Ramya Ramanujachar, Wendy B. London, Steven G. DuBois

See INRG at ANR

MONDAY	TUESDAY
10:45 Session O2.1 **Outcomes for patients aged 12-18 months with metastatic MYCN non-amplified neuroblastoma and unfavorable biologic features ('Mixed Biology Toddlers')** MR Taylor, PC Kao, JR Park, MS Irwin, MA Applebaum, NR Pinto, WB London, T Cash	**11:39 Rapid Fire session 1B** **Persistence of Racial and Ethnic Disparities in Risk and Survival for Patients with Neuroblastoma: An International Neuroblastoma Risk Group Project** M Chennakesavalu, C Pudela, MA Applebaum, SM Lee, Y Che, A Naranjo, JR Park, SL Volchenboum, TO Henderson, SL Cohn, AV Desai
15:54 Session O4.3 **Building a REDCap on FHIR Tool to Abstract Neuroblastoma Data from Electronic Health Records (EHRs): A Proof-of-Concept Study** B Furner, A Cheng, AV Desai, DJ Benedetti, DL Friedman, KD Wyatt, M Watkins, SL Volchenboum, SL Cohn	

INRG Research Projects – By the numbers

Published	Underway	Recently Approved
24	9	2

Read more at https://inrgdb.org/research/ and https://commons.cri.uchicago.edu/inrg/

The application process and perspectives from a “YI”

Boris Decarolis

Disclosures

ALEXION
AstraZeneca Rare Disease

The application process and perspectives from a “YI”

- January 2022

  eMail from Lucas Moreno and Meredith Irwin

  - “looking for a young & enthusiastic investigator that would like to work with INRG investigators who would serve as mentors”
  - project in low and intermediate risk neuroblastoma

The application process and perspectives from a “YI”

- February 25th 2022

  Kick-Off Meeting (Zoom)

  - Wendy London
  - Sue Cohn
  - Andy Pearson
  - Suzi Birz

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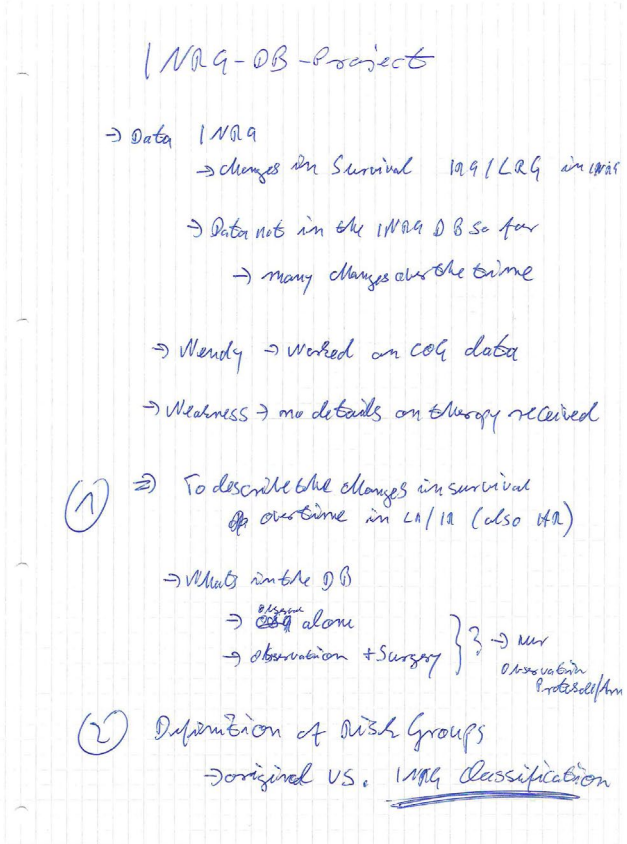
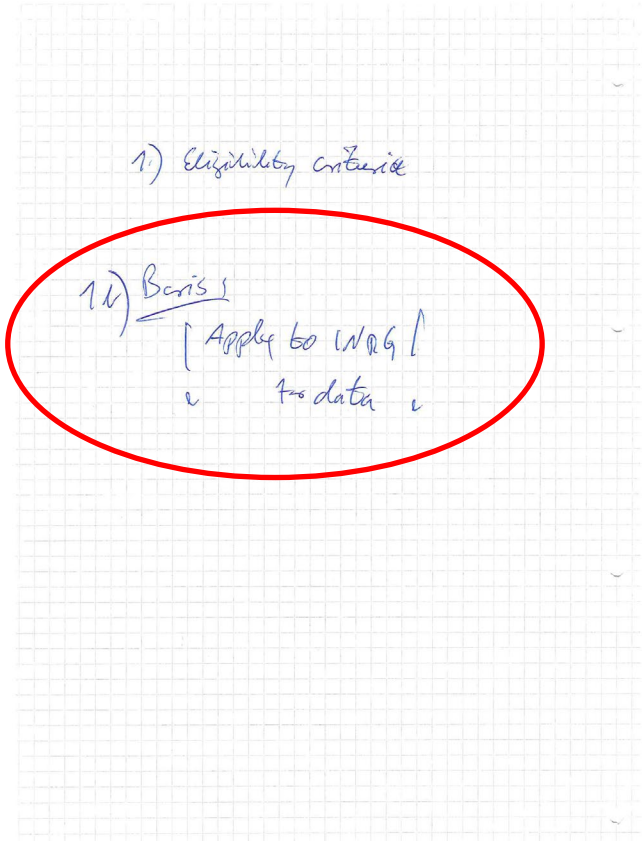




The application process and perspectives from a “YI”

- February 25th 2022 - Kick-Off Meeting (Zoom)

INRG project about improvement in outcome
Boris Decarolis, Andy Pearson, Sue Cohn, and Wendy London
February 25, 2022

Primary objective

1. To describe the changes in outcome over time in patients with neuroblastoma, overall and within patients assigned to low-risk, intermediate-risk and high-risk

Hypothesis: Outcome has improved over time within each risk group.

Secondary objectives

1. To investigate the potential bias introduced by restricting the analytic cohort to patient who have enrolled on a clinical trial
2. To describe the changes in outcome over time in patients with neuroblastoma within risk factor subgroups defined by age and *MYCN*

Primary endpoints
EFS and OS

How to classify pts by risk group? Several approaches:

1. Calculate the risk group for all the pts by retrospectively applying today’s risk stratification
2. Assign pts to a risk group according to the pt’s current era (the stratification in place at the time they were diagnosed)
3. Within pts who were on a clinical trial, Use the risk group assigned according to the clinical trial they enrolled on

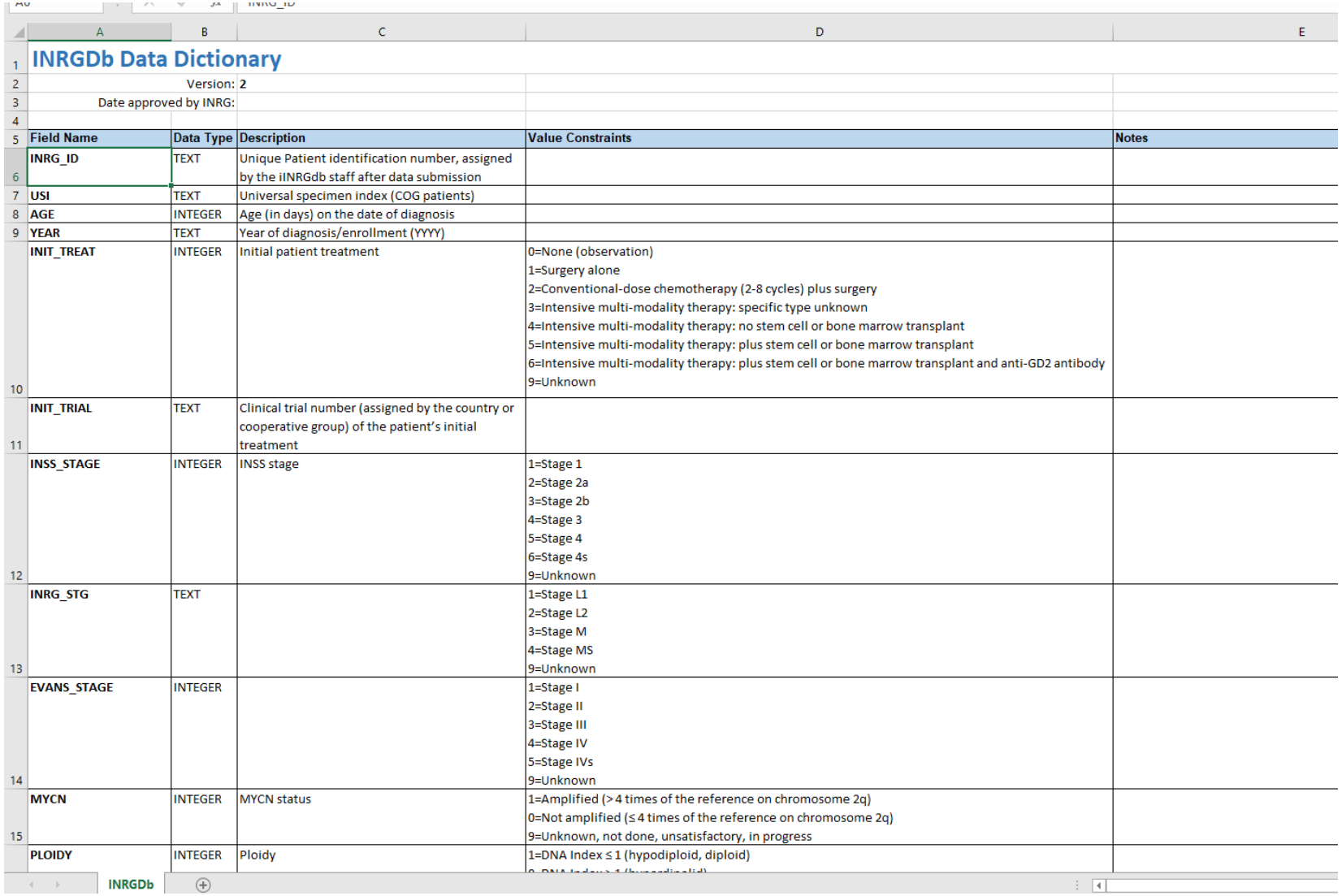
Time periods:

1. Every 2 years
2. By educated guess on treatment era (this will differ for COG, SIOPEN, GPOH)
3. 1990->1996, 1997->2006, 2007->2010, 2010-present (high-risk only)

Only analyze the subgroup of high-risk pts who were enrolled on a clinical trial because we would have greater confidence in how these pts were actually treated. Same for intermediate-risk. This would be excluding about half of the COG pts; all SIOPEN & GPOH pts were on a clinical trial.
Are we introducing a bias by doing this? Yes. Admit this bias in the Discussion [Applebaum et al].

Investigate the distribution by cooperative group, risk group, year of diagnosis for pts on vs not on a clinical trial. Understand the degree of bias that we would introduce by excluding the pts who were not on clinical trials. Make an informed decision at to which pts to include in the analysis. Then determine the eligibility criteria.

The application process and perspectives from a “YI”



INRGDb Data Dictionary

Version: 2

Date approved by INRG:

Field Name	Data Type	Description	Value Constraints	Notes
INRG_ID	TEXT	Unique Patient identification number, assigned by the iINRGdb staff after data submission		
USI	TEXT	Universal specimen index (COG patients)		
AGE	INTEGER	Age (in days) on the date of diagnosis		
YEAR	TEXT	Year of diagnosis/enrollment (YYYY)		
INIT_TREAT	INTEGER	Initial patient treatment	0=None (observation) 1=Surgery alone 2=Conventional-dose chemotherapy (2-8 cycles) plus surgery 3=Intensive multi-modality therapy: specific type unknown 4=Intensive multi-modality therapy: no stem cell or bone marrow transplant 5=Intensive multi-modality therapy: plus stem cell or bone marrow transplant 6=Intensive multi-modality therapy: plus stem cell or bone marrow transplant and anti-GD2 antibody 9=Unknown	
INIT_TRIAL	TEXT	Clinical trial number (assigned by the country or cooperative group) of the patient’s initial treatment		
INSS_STAGE	INTEGER	INSS stage	1=Stage 1 2=Stage 2a 3=Stage 2b 4=Stage 3 5=Stage 4 6=Stage 4s 9=Unknown	
INRG_STG	TEXT		1=Stage L1 2=Stage L2 3=Stage M 4=Stage MS 9=Unknown	
EVANS_STAGE	INTEGER		1=Stage I 2=Stage II 3=Stage III 4=Stage IV 5=Stage IVs 9=Unknown	
MYCN	INTEGER	MYCN status	1=Amplified (>4 times of the reference on chromosome 2q) 0=Not amplified (≤4 times of the reference on chromosome 2q) 9=Unknown, not done, unsatisfactory, in progress	
PLOIDY	INTEGER	Ploidy	1=DNA Index ≤1 (hypodiploid, diploid)	

INRGDb

The application process and perspectives from a “YI”

Thank you for your interest in INRG data.
Please send your completed proposal and any questions to scohn@peds.bsd.uchicago.edu

Proposal Title	
Principal Investigator	
Institution	
E-mail Address	
Co-authors	
Are you including a YI?	❑ Yes ❑ No
If you are not including a YI, please explain	
Statistician name	
Statistician Affiliation	❑ COG ❑ GPOH ❑ JCCG ❑ SIOPEN ❑ Not a member of one of these Cooperative Groups - CV attached ▪ If you would like to perform the analysis locally, in lieu of using a statistician or data manager from COG, GPOH, JCCG, or SIOPEN, please include the CV of your statistician and provide a detailed statistical plan.

NOTE: Please limit your request to 5 pages

Please format your project proposal as follows:

1. Specific Aims
2. Hypothesis
3. Patient Cohort (Eligibility Criteria)
4. Background
5. Significance
6. Proposal description
7. Data Requested

The application process and perspectives from a “YI”

INTERNATIONAL NEUROBLASTOMA RISK GROUP
TASK FORCE
PROJECT PROPOSAL

Thank you for your interest in INRG data.

Please send your completed proposal and any questions to scohn@peds.bsd.uchicago.edu

Proposal Title	Improvement in the outcome of patients with first diagnosis of neuroblastoma over a 30 year period
Principal Investigator	Dr. Boris Decarolis, MD
Institution	Department of Pediatric Oncology and Hematology University Hospital of Cologne Kerpener Str. 62 50937 Cologne (Köln) Germany
E-mail Address	Boris.decarolis@uk-koeln.de
Co-authors	Prof. Wendy London, Prof. Susan Cohn, Prof. Andrew Pearson
Are you including a YI?	X Yes No
If you are not including a YI, please explain	
Statistician name	Prof. Wendy London
Statistician Affiliation	X COG GPOH JCCG SIOPEN Not a member of one of these Cooperative Groups --- CV attached • If you would like to perform the analysis locally, in lieu of using a statistician or data manager from COG, GPOH, JCCG, or SIOPEN, please include the CV of your statistician and provide a detailed statistical plan.

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4. Background
5. Significance
6. Proposal description
7. Data Requested

The application process and perspectives from a “YI”

1. Specific Aims

The primary aim of this project is to describe the changes in outcome over time in patients with diagnosed neuroblastoma, overall and within patients assigned to low risk, intermediate risk and distinct prognostic factors, the changes in outcome in the subgroups defined by age and *MYCN* v analyzed separately. A secondary aim is to investigate the potential bias introduced by restrictin cohort to patient who have enrolled on a clinical trial. Primary endpoints will be event-free survi overall survival (OS). Secondary endpoint will be changes in the pattern of relapse (local vs. meta metastatic sites: (bone marrow, lymph nodes and CNS) and in the occurrence of second maligna course of time.

2. Hypothesis

We hypothesize that with the advances of the multimodal neuroblastoma therapy the outcome has improved continuously over time for the group of all patients as well within the high risk and risk cohort. We further hypothesize that the outcome (EFS and OS) for low risk patients has rema despite lower treatment intensity. This will also hold true for the analyzed risk factors. The patte might also have changed over the time with changes in therapy. The occurrence of second malig shift from radiation related malignancies to hematologic malignancies, but altogether, as this is dependent process, follow-up could be too short for the more recent time periods.

1. Specific Aims

Primary objective:

To describe the changes in outcome over time in patients with newly diagnosed neuroblastoma, overall and within patients assigned to low-risk, intermediate-risk and high-risk.

Secondary objectives:

a) To determine if EFS and OS have improved over time, in patients with newly diagnosed high-risk neuroblastoma.

b) To determine if EFS and OS have not decreased over time, in patients with newly diagnosed low-, and intermediate-risk neuroblastoma.

c) To describe the changes in outcome over time in patients with neuroblastoma within risk factor subgroups defined by age at diagnosis and MYCN.

d) To investigate the potential bias introduced by restricting the analytic cohort to patients who have enrolled on a clinical trial.

Primary endpoints

Event-free survival (EFS) and overall survival (OS)

Secondary endpoints

Enrollment on the biology study ANBL00B1 but no up-front clinical trial.

2. Hypothesis

We hypothesize that the survival of high-risk patients has continuously improved over time with intensification of treatment combined with the addition of immunotherapy.
We hypothesize that excellent survival for low- and intermediate-risk patients has been maintained with reduction in therapy.

The application process and perspectives from a “YI”

6.→ Proposal·description¶

Data·from·all·patients·fulfilling·the·eligibility·criteria·1-3·
including·risk·group,·age·at·diagnosis,·MYCN·status,·tum
trial,·initial·treatment,·event-free·and·overall·survival,·re
will·be·described·for·the·whole·cohort·as·well·as·for·the·
periods.¶

¶

As·the·definition·of·the·risk·groups·used·for·treatment·st
over·time·even·within·the·groups,·we·will·take·two·appr

¶

1.→ By·use·of·the·risk·group·assigned·according·to·th
   a.→ Patients·that·were·enrolled·on·a·clinical·
   clinical·trial·the·patient·has·been·enrolle
   b.→ Patients·that·were·not·enrolled·in·a·clini
   stratification·that·was·used·by·the·respe
   diagnosed.¶
2.→ By·calculating·the·risk·group·for·all·patients·by·r
   to·the·INRG·Classification·System.¶

¶

To·describe·the·changes·in·outcome·over·the·past·decad
periods:¶

··¶

1.→ In·a·very·detailed·approach,·we·define·the·cohor
2.→ In·a·pragmatic·approach,·we·define·the·cohorts·
   cooperative·groups·(COG,·SIOPEN,·GPOH,·and·JC
3.→ With·respect·to·a·previous·COG·analysis·we·will·
   >1994,·1995->1999,·2000->2004,·2005->2010,·2

¶

Ad·2)·As·the·clinical·trials·by·the·large·cooperative·group
defined·by·introduction·of·treatment·modalities·such·as
chemotherapy·with·autologous·stem·cell·transplantatio
restriction·of·use·of·chemotherapy·for·the·low·risk·grou

¶

Details·on·treatment·data·are·only·available·for·patients
data·quality·about·the·treatment,·we·will·only·analyze·th
who·were·enrolled·on·a·clinical·trial.·This·will·exclude·ab
GPOH·and·JCCG·patients·were·on·a·clinical·trial.·We·are·

this,·as·differences·between·patients·in·and·outside·clini
characteristics·and·outcome[14].·To·understand·the·degre
cooperative·group,·risk·group,·year·of·diagnosis·for·patie

¶

6.·Proposal·description¶

Data·from·all·patients·fulfilling·the·eligibility·criteria·will·be·included·in·the·project.·Patient·characteristics,·including·age·at·diagnosis,·MYCN·status,·tumor·stage,·risk·group,·year·of·diagnosis,·trial·enrollment,·and·initial·treatment·(as·defined·in·INRG·Data·Commons)·will·be·described.··Event-free·and·overall·survival·will·be·analyzed·according·to·risk·group·assignment·and·for·subgroups·defined·by·risk·factors·and·time·periods.¶

¶

To·maintain·high·data·quality·for·primary·analysis,·we·will·restrict·the·study·cohort·to·patients·enrolled·in·a·therapeutic·clinical·trial·because·treatment·assigned·is·known·for·this·cohort.·This·will·exclude·about·half·of·the·COG·patients·who·were·only·enrolled·on·the·ANBL00B1·biology·study.·All·other·COG·patients·and·all·the·SIOPEN,·GPOH·and·JCCG·patients·were·enrolled·on·a·therapeutic·clinical·trial.·We·are·aware·that·we·might·be·introducing·a·bias·by·doing·this,·as·differences·have·been·described·among·patients·who·were·enrolled·on·a·clinical·trial·versus·those·who·were·not·with·respect·to·patient·characteristics·and·outcome[14].·To·understand·the·degree·of·this·bias·we·will·investigate·the·distribution·by·risk·group·and·year·of·diagnosis·among·COG·patients·enrolled·only·on·the·ANBL00B1·biology·study·versus·those·enrolled·on·clinical·trials.¶

¶

6.1→Methods¶

As·the·definition·of·the·risk·groups·used·for·treatment·stratification·vary·between·the·cooperative·groups·and·over·time·even·within·the·groups,·we·will·take·three·approaches·to·define·the·risk·group·used·for·this·analysis:¶

¶

1.→ By·use·of·the·risk·group·assigned·according·to·the·time·when·the·patient·was·diagnosed·(“trial-risk-group”):¶
   a.→ Patients·that·were·enrolled·on·a·clinical·trial·will·be·assigned·to·the·risk·group·according·to·the·clinical·trial·the·patient·has·been·enrolled·on.¶
   b.→ Patients·that·were·not·enrolled·in·a·clinical·trial·will·be·assigned·to·a·risk·group·according·to·the·stratification·that·was·used·by·the·respective·cooperative·group·at·the·time·the·patient·was·diagnosed.¶
2.→ By·calculating·the·risk·group·for·all·patients·by·retrospectively·applying·the·risk·stratification·according·to·the·INRG·Classification·System·V1·(2009)·(“INRG-risk·group”).¶
3.→ To·be·used·for·Secondary·Objective·c):·Risk·subgroups·will·be·defined·using·age·and·*MYCN*·status,·as·follows:·(“age-MYCN-risk-group”)¶
   a.→ Age·<547·days,·MYCN·not·amplified¶
   b.→ Age·≥547·days,·MYCN·not·amplified¶
   c.→ Age·<547·days,·MYCN·amplified¶
   d.→ Age·≥547·days,·MYCN·amplified¶

¶

To·describe·the·changes·in·outcome·over·the·past·decades·we·will·use·three·approaches·to·define·time·periods:¶

··¶

1.→ In·a·very·detailed·approach,·we·will·define·the·cohorts·by·year·of·diagnosis·in·2·year-steps.¶
2.→ In·a·pragmatic·approach,·we·will·define·the·cohorts·by·treatment·eras·based·on·the·clinical·trials·by·the·cooperative·groups·(COG,·SIOPEN,·GPOH,·and·JCCG).*¶
3.→ Similar·to·a·previous·COG·analysis[6]·we·will·use·the·following·seven·time·periods:·before·1989·(T_1),·1990->1994·(T_2),·1995->1999·(T_3),·2000->2004·(T_4),·2005->2010·(T_5),·2011->2015·(T_6),·2015-present·(T_7).··With·overall·n=24,000,·it·is·anticipated·there·will·be·about·n=3,428·patients·per·time·period·(n=1371·low-risk,·n=686·intermediate-risk,·n=1371·high-risk).¶

*·As·the·clinical·trials·by·the·large·cooperative·groups·started·in·different·years,·the·cohorts·will·be·defined·by·dates·treatment·modalities·were·introduced,·including·intensification·of·the·induction,·high-dose·chemotherapy·with·autologous·stem·cell·transplantation,·and·immunotherapy·for·high-risk·patients·and·reduction·of·chemotherapy·for·the·low-·and·intermediate-risk·group.¶

¶

Primary·Objective·and·Secondary·Objective·c)¶

To·address·the·Primary·Objective·and·Secondary·Objective·c),·Kaplan-Meier·curves·of·EFS·and·OS·will·be·generated,·once·for·each·of·the·three·different·approaches·that·will·be·taken·to·defining·the·time·periods.··To·summarize·these·numerous·plots,·a·histogram·of·the·5-year·EFS/OS·will·generated,·one·histogram·for·each·of·the·three·different·approaches·that·will·be·taken·to·defining·the·time·periods.··These·analyses·will·be·performed·overall,·by·trial-risk-group,·by·INRG-risk-group,·and·by·age-MYCN-risk-group.¶

¶

Secondary·Objective·a)¶

To·address·Secondary·Objective·a),·high-risk·will·be·defined·according·to·the·‘trial-risk-group’·definition.··Within·the·high-risk·group,·we·will·perform·all·pairwise·comparisons·of·OS·curves·of·the·seven·time·periods·using·a·two-sided·log-rank·test.··P-values·will·be·adjusted·for·multiple·comparisons·using·a·Holm-Bonferroni·correction.··Using·a·significance·level·of·0.05,·this·method·ensures·that·the·family-wise·error·rate·is·no·larger·than·0.05.··This·analysis·will·be·repeated·for·EFS.··¶

¶

A·high-risk·sample·size·of·n=2742·will·provide·82%·power·(alpha=0.05)·in·a·two-sided·log-rank·test·to·detect·a·5%·difference·in·OS·(or·EFS)·(48%·vs·53%)·between·the·two·time·periods·(n=1371·per·time·period).··There·will·be·even·more·power·to·detect·a·5%·difference·at·higher·levels·of·OS/EFS,·e.g.,·70%·vs·75%.¶

¶

¶

Secondary·Objective·b)¶

To·address·Secondary·Objective·b),·low-·and·intermediate-risk·will·be·defined·according·to·their·respective·‘trial-risk-group’·definitions.··Within·low-risk,·for·proving·non-inferiority·of·EFS·over·increasing·time·period,·we·will·set·the·null·and·alternative·hypotheses·as:·¶

H0:·(T_{i-1}—T_i)·≥·M·(T_{i-1}·is·superior·to·T_i)·¶

H1:·(T_{i-1}—T_i)·<·M·(T_i·is·not·inferior·to·T_{i-1})¶

Where·M·is·the·non-inferiority·margin,·and·T_{i-1}·is·the·EFS·for·the·time·period·prior·to·T_i;·i=2·to·7.··This·tests·each·adjacent·time·period,·but·does·not·account·for·the·possibility·of·“creep”,·where·survival·decreases·very·gradually·with·each·successive·time·period,·ultimately·leading·to·a·clinically·significant·decrease·from·the·original·survival·rate.··The·EFS/OS·for·the·time·period·of·1995-1999·(T_3)·will·be·considered·the·benchmark·of·EFS/OS·achieved·prior·to·conducting·reduction·of·therapy·in·low-·and·intermediate-risk·patients.·To·test·for·non-inferiority·of·EFS·or·OS·compared·to·the·EFS/OS·from·1995-1999·(T_3),·the·null·and·alternative·hypotheses·are:¶

H0:·(T_3—T_i)·≥·M···(T_3·is·superior·to·T_i)·¶

H1:·(T_3—T_i)·<·M···(T_i·is·not·inferior·to·T_3)¶

where·T_i·is·the·EFS·for·the·time·periods·after·T_3;·i=4·to·7.··¶

¶

Within·the·low-risk·group,·we·will·set·the·non-inferiority·margin·at·an·EFS/OS·difference·of·M=2%.··To·assess·if·non-inferiority·is·met·(that·is,·whether·the·null·hypothesis·is·rejected)·we·can·perform·a·one-sided·hypothesis·test·at·α·level·of·significance.·A·low-risk·sample·size·of·n=1720·will·provide·80%·power·(alpha=0.05)·in·a·one-sided·log-rank·test·to·detect·a·2%·difference·in·OS·(95%·vs·97%)·between·the·two·time·periods·(n=860·per·time·period).··The·test·will·be·well-powered,·as·we·anticipate·a·larger·low-risk·sample·size·per·time·period·than·n=860.¶

¶

Equivalently,·we·can·compute·a·100(1−2α)·percent·two-sided·confidence·interval·for·the·difference·(T_{i-1}—T_i)·or·(T_3—T_i).·If·the·confidence·interval’s·upper·bound·is·less·than·M,·then·with·100(1−·2α)·percent·confidence,·we·say·the·older·time·period·has·higher·OS·than·the·more·recent·time·period·by·no·more·than·M,·hence·allowing·us·to·claim·non-inferiority·of·the·more·recent·time·period·as·compared·to·the·older·time·period·at·an·α·level·of·significance·[15].·The·latter·approach·will·be·taken·in·this·study,·using·α=0.05.¶

¶

This·analysis·will·be·repeated·within·intermediate-risk·using·the·methods·above,·except·using·a·non-inferiority·margin·of·M=2.6%·for·the·EFS/OS·difference.··An·intermediate-risk·sample·size·of·n=1336·will·provide·80%·power·(alpha=0.05)·in·a·one-sided·log-rank·test·to·detect·a·2.6%·difference·in·OS·(96%·vs·93.4%)·between·the·two·time·periods·(n=668·per·time·period).··¶

¶

Secondary·Objective·d)¶

To·address·Secondary·Objective·d),·histograms·will·be·generated·of·the·proportion·of·patients·by·trial-risk-group,·INRG-risk-group,·age-MYCN-risk-group,·year·of·diagnosis,·age·at·diagnosis,·and·MYCN·status·for·i)·the·overall·cohort;·ii)·patients·on·a·COG·therapeutic·clinical·trial;·and,·iii)·COG·patients·enrolled·on·the·biology·study·ANBL00B1·but·no·up-front·therapeutic·clinical·trial.·¶

The application process and perspectives from a “YI”

7.→ Data·Requested¶

The·following·data·will·be·needed·to·perform·the·analyses·described·above·including·the·assignment·to·the·risk·group·used·by·the·respective·cooperative·group·at·the·time·the·patient·was·diagnosed·and·the·INRG·Classification·System·respectively·(Data·field·name·as·in·the·INRGDb·Data·Dictionary):¶

¶

1.)→INRG_ID¶
2.)→AGE¶
3.)→YEAR¶
4.)→INIT_TREAT¶
5.)→INIT_TRIAL¶
6.)→INSS_STAGE¶

¶

7.→ Data·Requested¶

In·order·to·perform·the·analyses·described·above·including·the·assignment·to·the·risk·group·used·by·the·respective·cooperative·group·at·the·time·the·patient·was·diagnosed·and·the·INRG·Classification·System·respectively·we·request·the·entire·INRG·data·set·for·the·patients·meeting·the·eligibility·criteria.¶

21.)EFSCENS¶
22.)EFSTIME¶
23.)SCENS¶
24.)STIME¶
25.)CAUSE_OF_DEATH¶
26.)SEX¶
27.)REL_SITE_GEN¶
28.)RELAPSE_SITE_SPECIFIC¶
29.)SECOND_MALIG_CENS¶
30.)SECOND_MALIG_TIME¶
31.)SMN_MORPH_SNO¶
32.)SMN_MORPH_ICD0¶
33.)SMN_MORPH_TXT¶

The application process and perspectives from a “YI”

Applying for an INRG data commons project:

- Very well structured application process
- INRG offers great mentorship to young or unexperienced investigators

The application process and perspectives from a “YI”

Working on an INRG data commons project:

- Great opportunity for high quality research
- Be part of the evolution of the INRG data commons

The application process and perspectives from a “YI”

Survival of patients with low-, intermediate-, or high-risk neuroblastoma over a 36 year period (1985-2020)

- Changes in outcome over time overall and within patients assigned to low-risk, intermediate-risk and high-risk
  - Analysis by time periods and “treatment eras”
    - Improvement in HR
    - Maintenance of excellent survival in IR and LR

The application process and perspectives from a “YI”

Thank you

Use of INRG Data Commons to Analyze Rare (and Not So Rare) Patient Cohorts

Steven DuBois, MD MS

Dana-Farber Cancer Institute | Boston Children's

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

There is a new international database…

…we should propose a project.

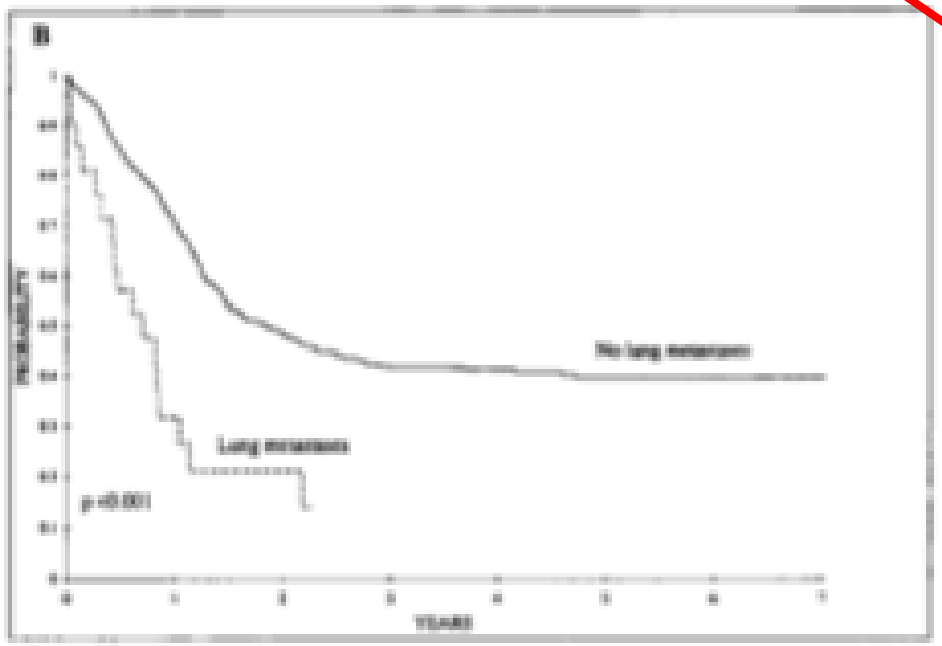
Journal of Pediatric Hematology/Oncology 21(3): 181–189, May/June 1999

Metastatic Sites in Stage IV and IVS Neuroblastoma Correlate With Age, Tumor Biology, and Survival

Steven G. DuBois, M.D., Yan Kalika, D.D.S., John N. Lukens, M.D.,
Garrett M. Brodeur, M.D., Robert C. Seeger, M.D.,
James B. Atkinson, M.D., Gerald M. Haase, M.D., C. Thomas Black, M.D.,
Carlos Perez, M.D., Hiroyuki Shimada, M.D., Robert Gerbing, M.A.,
Daniel O. Stram, Ph.D., and Katherine K. Matthay, M.D.

TABLE 1. *Sites of metastasis at diagnosis for 81 patients with stage IVS, 133 patients with stage IV <1 year, and 434 patients with stage IV ≥1 year*

	Stage IVS n (%)	Stage IV <1 year, n (%)	Stage IV ≥1 year, n (%)	Total %
Bone marrow*†	28 (34.6)	76 (57.1)	353 (81.3)	70.5
Bone†	0 (0.0)	65 (48.9)	296 (68.2)	55.7
Lymph node	7 (8.6)	38 (28.6)	155 (35.7)	30.9
Liver*†	65 (80.2)	71 (53.4)	56 (12.9)	29.6
Intracranial/Orbit	0 (0.0)	34 (25.6)	84 (19.6)	18.2
Adrenal†	5 (6.2)	18 (13.5)	26 (6.0)	7.6
Skin†	11 (13.6)	11 (8.3)	4 (0.9)	4.0
Pleura	0 (0.0)	6 (4.5)	16 (3.7)	3.4
Lung	0 (0.0)	3 (2.3)	18 (4.1)	3.2
Peritoneum	0 (0.0)	5 (3.8)	9 (2.1)	2.2
Other	0 (0.0)	5 (3.8)	7 (1.6)	1.9
Central nervous system	0 (0.0)	0 (0.0)	4 (0.9)	0.6



n=21 patients across two cooperative group studies

Objectives of INRG Proposal

- Describe incidence of lung metastasis in INSS stage IV disease
- Describe predictors of lung metastasis
- Describe prognostic impact of lung metastasis

Proposal Process

- Not sure I can really remember!
- ~2-page proposal with background, aims, proposed statistical plan, and mock tables/figures
- Submitted for review and approved
- Statistical report followed shortly thereafter

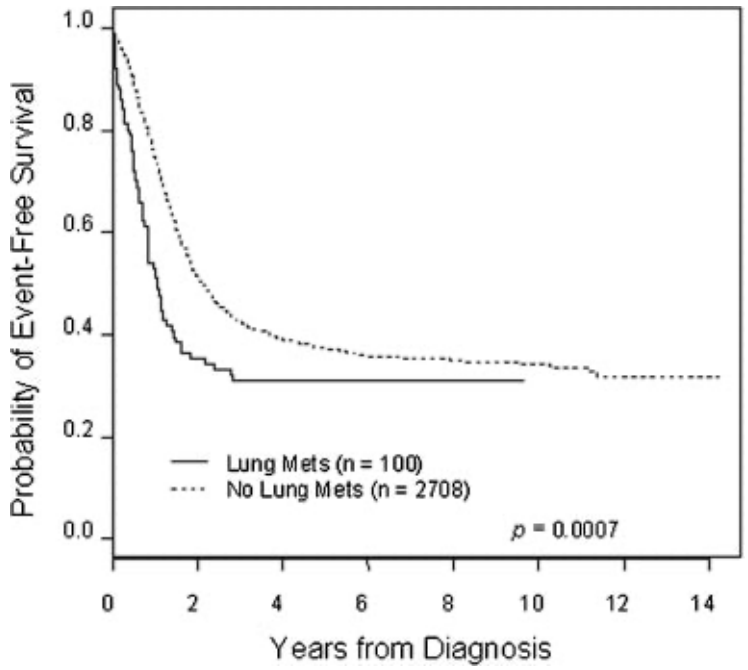
Pediatr Blood Cancer 2008;51:589–592

Lung Metastases in Neuroblastoma at Initial Diagnosis: A Report From the International Neuroblastoma Risk Group (INRG) Project

Steven G. DuBois, MD,[1]* Wendy B. London, PhD,[2] Yang Zhang, MS,[2] Katherine K. Matthay, MD,[1] Tom Monclair, MD,[3] Peter F. Ambros, PhD,[4] Susan L. Cohn, MD,[5] Andrew Pearson, MD,[6] and Lisa Diller, MD[7]

Key Findings of Analysis

- Lung mets in 100 / 2,808 (3.6%) patients with INSS stage IV disease
- Higher rates in patients with other visceral metastasis
- Enriched for patients with *MYCN* amplification
- Confirmed inferior outcomes



Lessons Learned

Pros

- Largest available dataset
- Includes biomarkers of interest
- Quick review process
- Quick statistical analysis
- Face validity in the field

Cons

- Usual limitations of a registry
  - Limited to data originally entered
  - Extent of staging not clear
    - Who had chest imaging??
  - Scans not available for review
  - Tissue not readily available to dive deeper into the biology

Subsequent Projects

Identification of Patient Subgroups With Markedly Disparate Rates of *MYCN* Amplification in Neuroblastoma: A Report From the International Neuroblastoma Risk Group Project

Daria Thompson MD, MPH[1]; Kieuhoa T. Vo MD[1]; Wendy B. London PhD[2]; Matthias Fischer MD[3]; Peter F. Ambros PhD[4]; Akira Nakagawara MD[5]; Garrett M. Brodeur MD[6]; Katherine K. Matthay MD[1]; and Steven G. DuBois MD, MS[1]

Clinical, Biologic, and Prognostic Differences on the Basis of Primary Tumor Site in Neuroblastoma: A Report From the International Neuroblastoma Risk Group Project

Kieuhoa T. Vo, Katherine K. Matthay, John Neuhaus, Wendy B. London, Barbara Hero, Peter F. Ambros, Akira Nakagawara, Doug Miniati, Kate Wheeler, Andrew D.J. Pearson, Susan L. Cohn, and Steven G. DuBois

Received: 5 November 2021 | Revised: 31 January 2022 | Accepted: 1 February 2022

DOI: 10.1002/pbc.29616

Pediatric Blood & Cancer | aspho | WILEY

ONCOLOGY: RESEARCH ARTICLE

Pattern and predictors of sites of relapse in neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project

Kieuhoa T. Vo[1] | Steven G. DuBois[4] | John Neuhaus[2] | Steve E. Braunstein[3] | Brent R. Weil[5] | Arlene Naranjo[6] | Sabine Irtan[7] | Julia Balaguer[8] | Katherine K. Matthay[1]

Received: 7 July 2022 | Revised: 6 September 2022 | Accepted: 21 September 2022

DOI: 10.1002/pbc.30054

Pediatric Blood & Cancer | aspho | WILEY

RESEARCH ARTICLE

Clinical and biological features prognostic of survival after relapse or progression of INRGSS stage M S pattern neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project

Kevin Campbell[1] | Pei-Chi Kao[1] | Arlene Naranjo[2] | Takehiko Kamijo[3] | Ramya Ramanujachar[4] | Wendy B. London[1] | Steven G. DuBois[1]

Additional Lessons Learned

Pros

- Great source of YI projects
  - Learn about the disease and also biostatistics
- Cohort discovery tool to demonstrate feasibility
- Projects build on each other
- Higher impact publications
- Greater international connections

Cons

- Treatment data more limited
- Missing data for biomarkers
- Heterogeneous testing strategies for biomarkers
- Limited data on sites of relapse
- Limited data on events after first relapse

Acknowledgements

Mentors on INRG Projects

- Lisa Diller
- Kate Matthay
- Wendy London

Mentees on INRG Projects

- Daria Thompson
- Kieuhoa Vo
- Kevin Campbell

INRG Leadership

- Sue Cohn
- Andy Pearson

Solving Kids' Cancer

BORNEO project:
BiOmarkers in high-Risk NEurOblastoma

Wendy London, Lucas Moreno

Background and objectives

PROBLEM: **is there an "ultra-high-risk" group?**

- No prognostic biomarker at diagnosis has been implemented into the clinic
- In high risk patients biomarkers could provide **earlier access to innovative therapies & potential changes in treatment strategy**

CHALLENGE → Analyse all biomarkers together

Background and objectives

PROBLEM: **is there an "ultra-high-risk" group?**

- No prognostic biomarker at diagnosis has been implemented into the clinic
- In high risk patients biomarkers could provide **earlier access to innovative therapies & potential changes in treatment strategy**

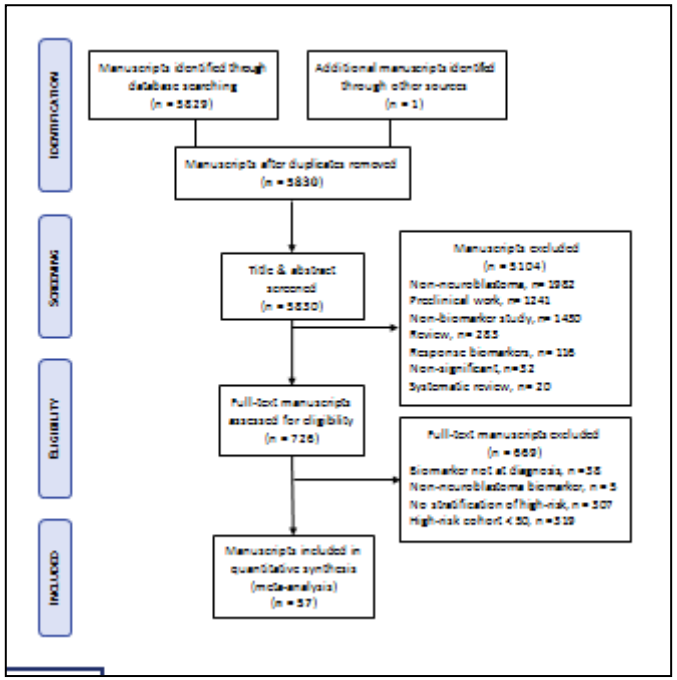
CHALLENGE → Analyse all biomarkers together

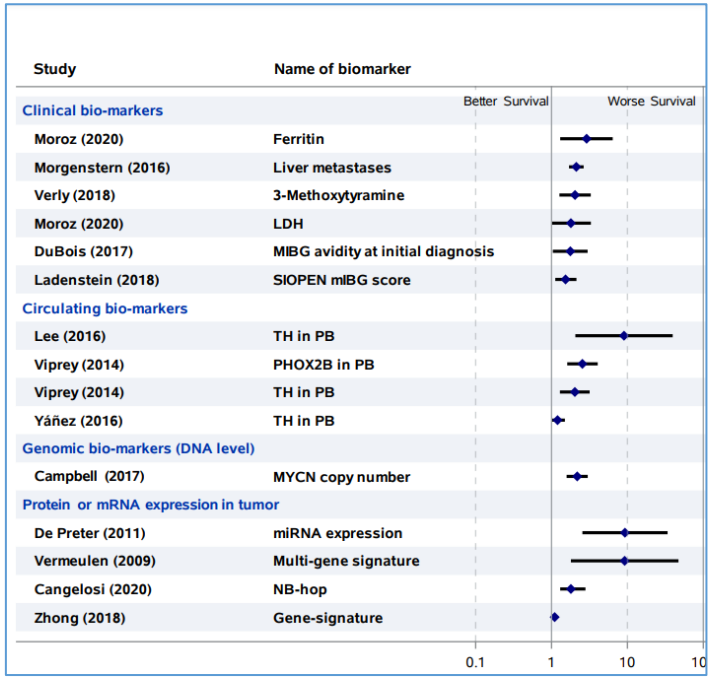
BORNEO: To identify biomarkers of poor outcome in high risk neuroblastoma:

- **Phase 1: Systematic review**
- **Phase 2: Integrate all biomarker data within INRG Data Commons**
- Phase 3: Biomarkers validated in a homogeneous trial cohort

BORNEO Phase 1: Systematic review

- Papers reporting prognostic biomarkers in HR NBL 1995-2020
- Completed! Results presented on Monday at 3pm (Andrea Vilaplana)
- 5830 manuscripts identified →
- 57 manuscripts reporting on 68 biomarkers selected





BORNEO Phase 2: Request to all investigators & cooperative groups

CHILDREN'S ONCOLOGY GROUP

SIOPEN R-NET

INRG
International Neuroblastoma Risk Group
TASK FORCE

1) Investigators fill in Word worksheet with info about the data set

2) Investigators will provide access to the dataset

3) Cooperative group statisticians will be honest brokers

4) Data deposited in INRG for integrated analyses

Next steps

- Data already included: INRG variables, MIBG scores
- Data soon to be included: ALK, response to induction, SCA
- Improve access/data from linked databases: TARGET, GMKF, R2, other repositories
- BORNEO Project Meeting on Wednesday 17th May at 8 am and follow-up Zoom calls with investigators

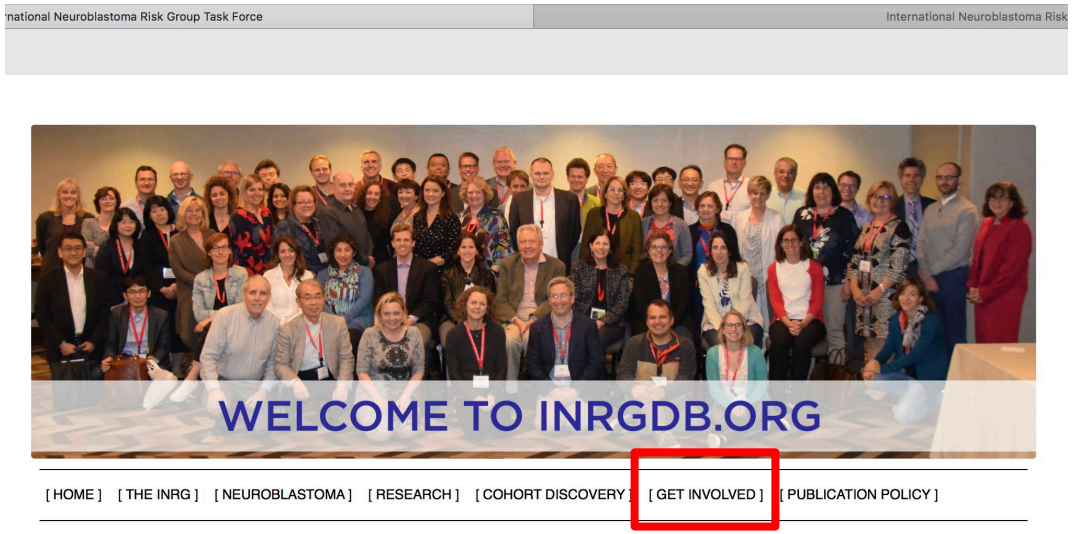
Thanks!

Strategy Committee Update: Opportunities for YIs

Meredith Irwin, Lucas Moreno

Strategy Development Committee

Expand INRG community of investigators



https://inrgdb.org/get-involved/

(1) Increase the number of new/YI investigator initiated projects and involvement in projects with senior investigators

(2) Mentor YIs globally to assist in the development and completion of projects

(3) Generate and facilitate new ideas and innovative projects that utilize the INRG database

INRG Strategy Development Committee

International membership

- Meredith Irwin (Canada)
  - Meredith.irwin@sickkids.ca
- Mark Applebaum (US)
  - mapplebaum@bsd.uchicago.edu
- Emily Greengard (US)
  - emilyg@umn.edu
- Daniel Morgenstern (Canada)
  - Daniel.Morgenstern@sickkids.ca
- Matthias Fischer (Germany)
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  - Patrick.hundsdoerfer@charite.de
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  - scohn@peds.bsd.uchicago.edu
- Andy Pearson (UK, advisory)
  - andy1pearson@btinternet.com
- Sara Federico (US, St Jude)
  - Sara.federico@stjude.org
- Gudrun Schleiermacher (France)
  - Gudrun.scheiermacher@curie.fr

Strategy Development Committee

(1) Expand INRG community of investigators

(1) Increase the number of new/YI investigator initiated projects and involvement in projects with senior investigators

- Engagement at international meetings
- Creation and updates of email address for queries
- Curated and maintain YI list : suzi.birz@uchicagomedicine.org

(2) Mentor YIs globally to assist in the development and completion of projects

- Include YIs in all new INRG projects reviewed by Executive- authorship policy
- Bootcamps
- Identification of mentors (international)

(3) Generate and facilitate new ideas and innovative projects that utilize the INRG database

- List of potential projects: new and re-analyses
- Monitor progress of large data uploads (recent examples, ANBL0032 expansion, HRNBL1 R3)
- Support incorporation of new data (biomarkers, genomic, new centres/consortia) - eg ALK

Increase Engagement from YIs/ New Investigators

- Presentations and small group meetings at large oncology meetings:
  - SIOP events: - YI networking event (Lyon, 2019), YI lunch/pres (*Database Research: INRG and Beyond* virtual/recording, 2020)
  - COG and SIOP-E :meetings and YI groups
  - **ANR 2023: connect with us at YI reception, posters…..**

- Collected Lists (and contact/meet with) new investigators to identify interests, mentors ; Matching for new/ongoing projects with sr investigators

- INRG db applications for new projects- involvement of YI as collaborator

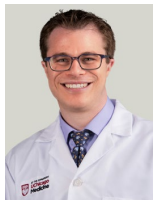
- Identify /develop list of projects for new investigators

(2) YI mentorship program /who's who?

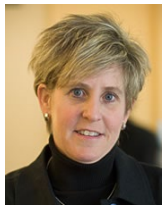
Lucas Moreno

Meredith Irwin

- **Team up new investigator/YI** with mentors for new projects (and as collaborators)
- **Assistance w/ INRG discovery tool** (to determine feasibility)
  - Mark Applebaum, U Chicago, mapplebaum@bsd.uchicago.edu



- **Statistical expertise** for YIs under development
  - Wendy London, Dana-Farber (Stats Chair, INRG)



- Bootcamps
- Email : mentorship@inrgdb.org to be on YI list, and/or to get mentorship

Lieve Tytgat

Suzi Birz

Zoom meetings for YIs- information to action

- 2020-2022: virtual meetings: information, bootcamps
  - Review of data dictionary and past projects
  - Practical discussions about formulating ideas and practical use of database to identify cohorts, test questions/feasibility

- Feedback provided by participants used to shape sessions and strategies

(3) Generate and facilitate new ideas and projects that utilize INRG data commons

Non data projects

-white paper (Schleiermacher, Fischer, Irwin)–biomarker assay standards

-systematic review of HR biomarkers biomarkers (BORNEO, London, Moreno, SKC)

“Repeat Projects”

-list of prior INRG publications to repeat with newer cohort

- includes new risk classifier

New Projects/ Fresh ideas

INRG database and projects – Repeat Analyses

- Repeat analyses that can be done w/ newer cohort data vs. initial N=8800, 1990-2002 cohort (will be facilitated by new data uploads!)
- As of 2023: N>24,000 patients!
- New patients from all cooperative groups including significant numbers treated with immunotherapy
- Always more data possible… but now is time to move forward

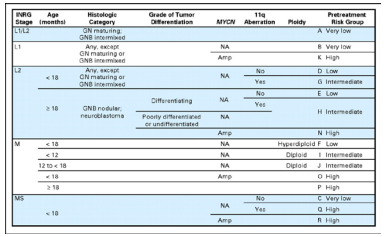
(1) 2020: Histologic Features still prognostic

original reports

Age, Diagnostic Category, Tumor Grade, and Mitosis-Karyorrhexis Index Are Independently Prognostic in Neuroblastoma: An INRG Project

Elizabeth Sokol, MD[1]; Ami V. Desai, MD, MSCE[2]; Mark A. Applebaum, MD[2]; Dominique Valteau-Couanet, MD, PhD[3]; Julie R. Park, MD[4]; Andrew D.J. Pearson, MD[5]; Gudrun Schleiermacher, MD, PhD[6]; Meredith S. Irwin, MD[7]; Michael Hogarty, MD[8]; Arlene Naranjo, PhD[9]; Samuel Volchenboum, MD, PhD[2]; Susan L. Cohn, MD[2]; and Wendy B. London, PhD[10]

(2) Revised INRG pre-treatment classification



INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS					No		C Very low
	< 18			NA	Yes		Q High
				Amp			R High

Cohn et al, JCO 2009

Repeat Analyses

- List of previous publications with INRG data commons N= 8,800

		Mean	Rank
1	**Complete dataset**	**7.0**	**2**
2	**Stage 3**	**6.3**	**4**
3	MYCN amplification in stage 1 or 2	6.1	5
4	Older patients	6.0	6
5	4S pattern vs tumour biology	5.3	7
6	Nodular ganglioneuroblastoma	4.8	9
7	**Survival after relapse**	**8.2**	**1**
8	Primary site	4.4	10
9	4N	5.3	8
10	**Pattern of metastatic sites**	**6.6**	**3**
11	MYCN amplification subgroups	3.3	11

- #4,5,7- approved or under review
- Plan to work with identified mentors and YIs for others

Progress to Date: new /YI projects

- Survival over time analyses (Decarolis, presented today)- in progress
- 2 ANR abstracts (oral presentations)
  - O2.1 -12-18 mo with metastatic MYCN-NA and unfavorable biologic features (Taylor, Cash et al) Monday 10:45, Parallel Session 2
  - O 4.3 - BORNEO biomarker systematic review (Vilaplana, Moreno & London): Monday 15.54, Parallel Session 4
- New investigator (1st application from China) - matched with 2 expert mentors with content and database expertise
- Encouraging inclusion of YIs as collaborators on new applications to gain experience

Next Steps

- List of repeat projects: communicate to YIs and mentors with guidelines
- Establish Timeframes – for submission/revision of proposals
  - oversight from INRG exec and SDC
- Development of new projects
  - not just repeat projects but big new ideas
- Need to further optimize matching with mentors and more stats resources
- Plan for INRG stats committee to discuss (lead : Wendy London)

Updates from the INRG Data Commons

Sam Volchenboum

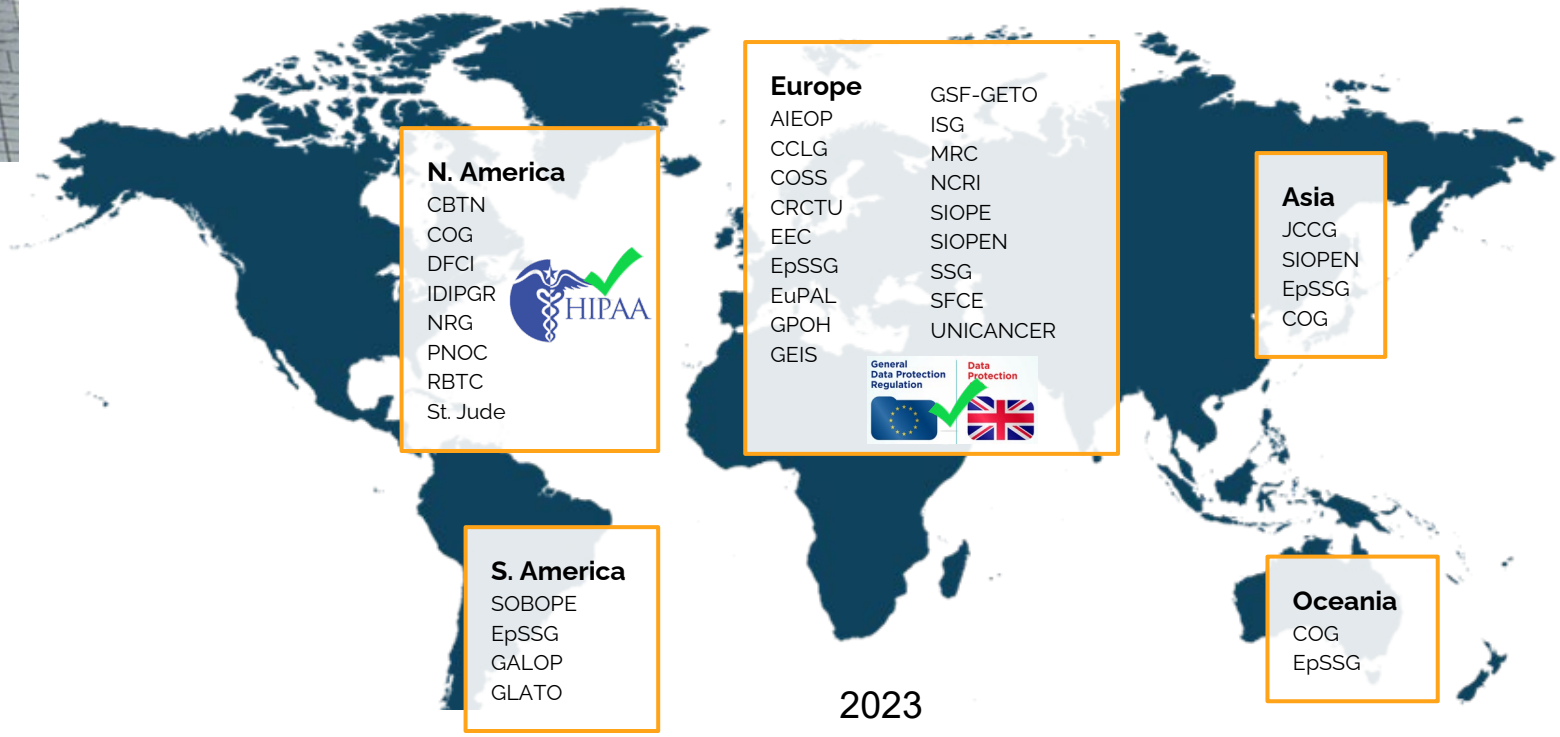
Topics

1. PCDC/D4CG – status update
2. Data Portal updates
3. Preview: new data elements to the INRG data commons
4. GEARBOx

PCDC/D4CG – status update

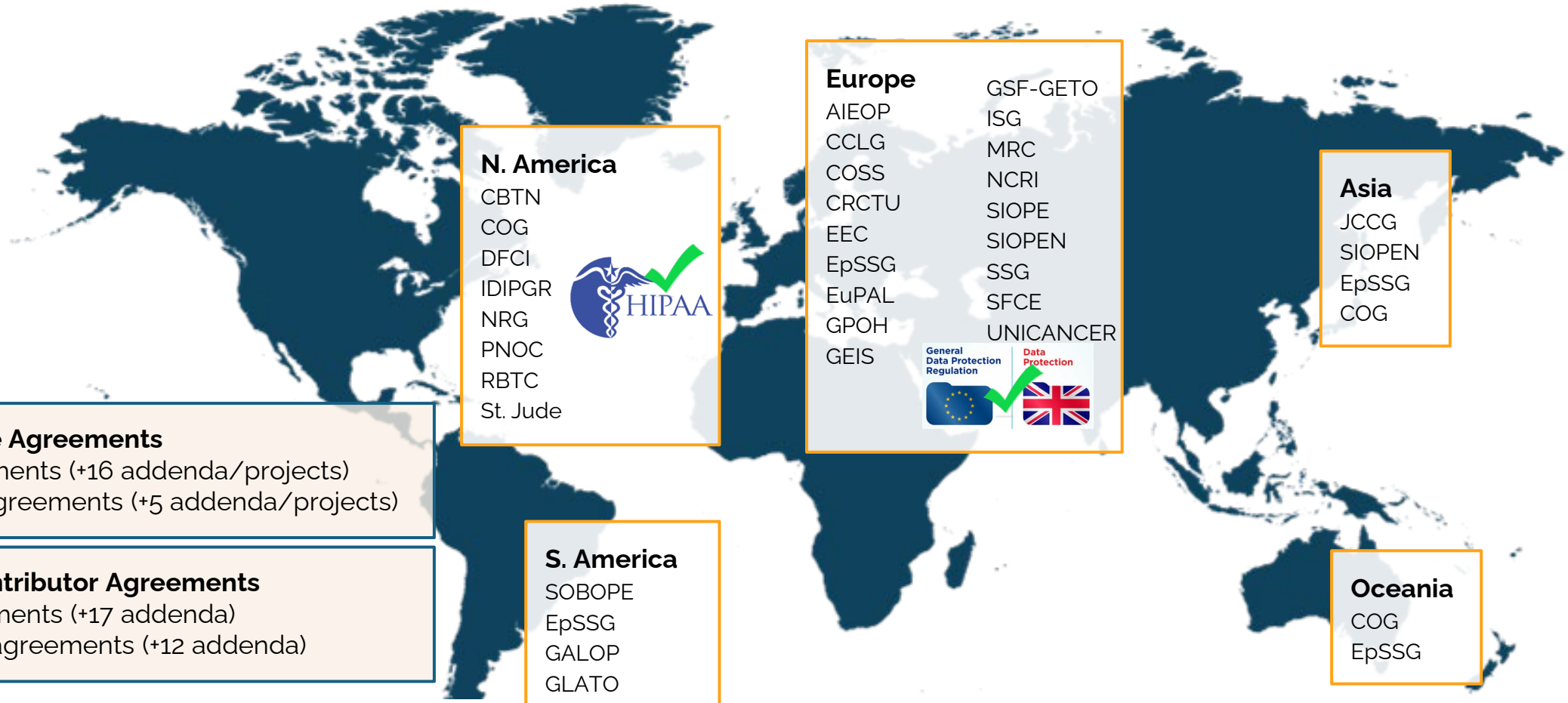
From then to now

2004



2023

PCDC worldwide participation



N. America
CBTN
COG
DFCI
IDIPGR
NRG
PNOC
RBTC
St. Jude

HIPAA

Europe
AIEOP
CCLG
COSS
CRCTU
EEC
EpSSG
EuPAL
GPOH
GEIS
GSF-GETO
ISG
MRC
NCRI
SIOPE
SIOPEN
SSG
SFCE
UNICANCER

General Data Protection Regulation
Data Protection

Asia
JCCG
SIOPEN
EpSSG
COG

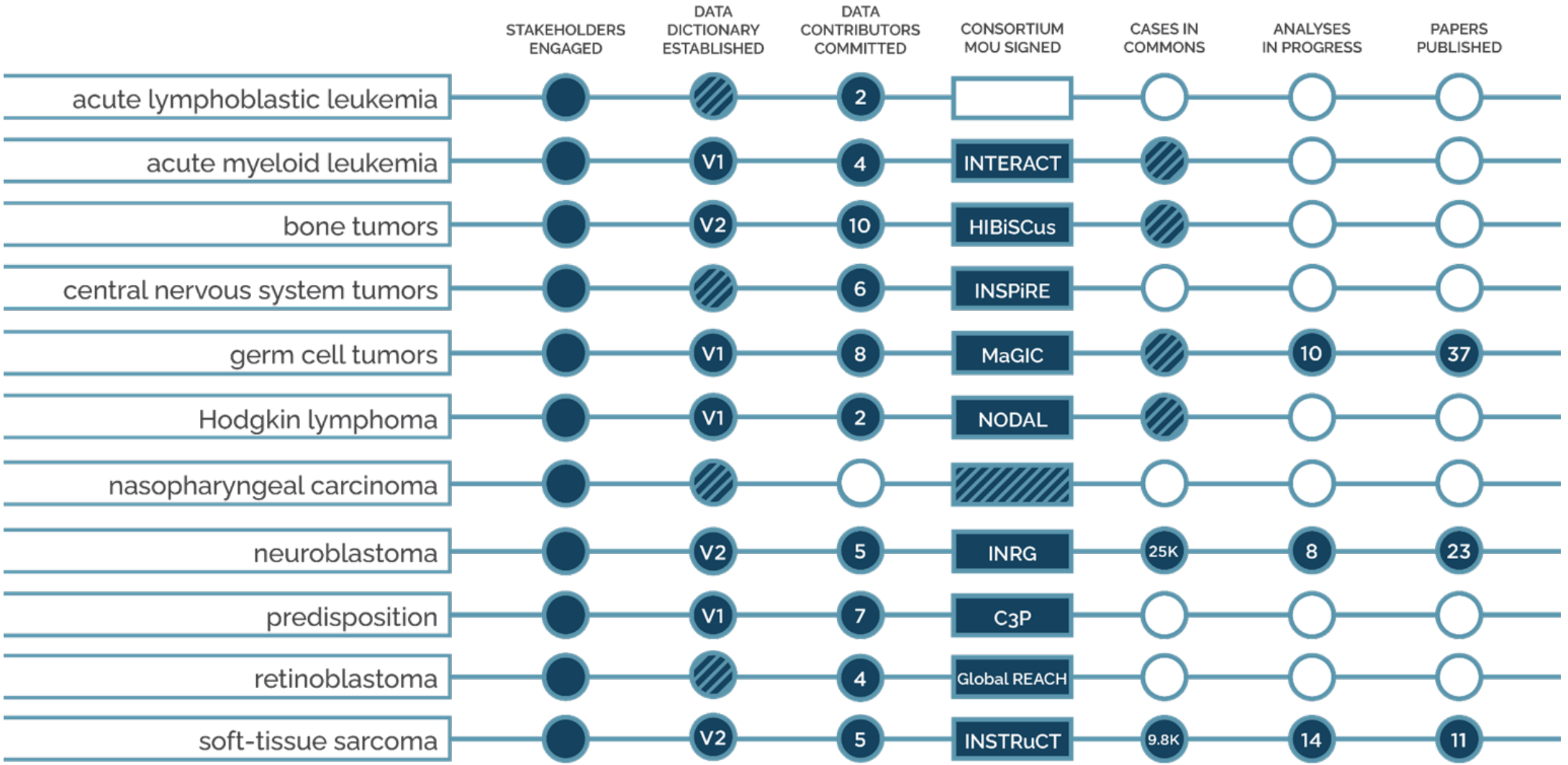
S. America
SOBOPE
EpSSG
GALOP
GLATO

Oceania
COG
EpSSG

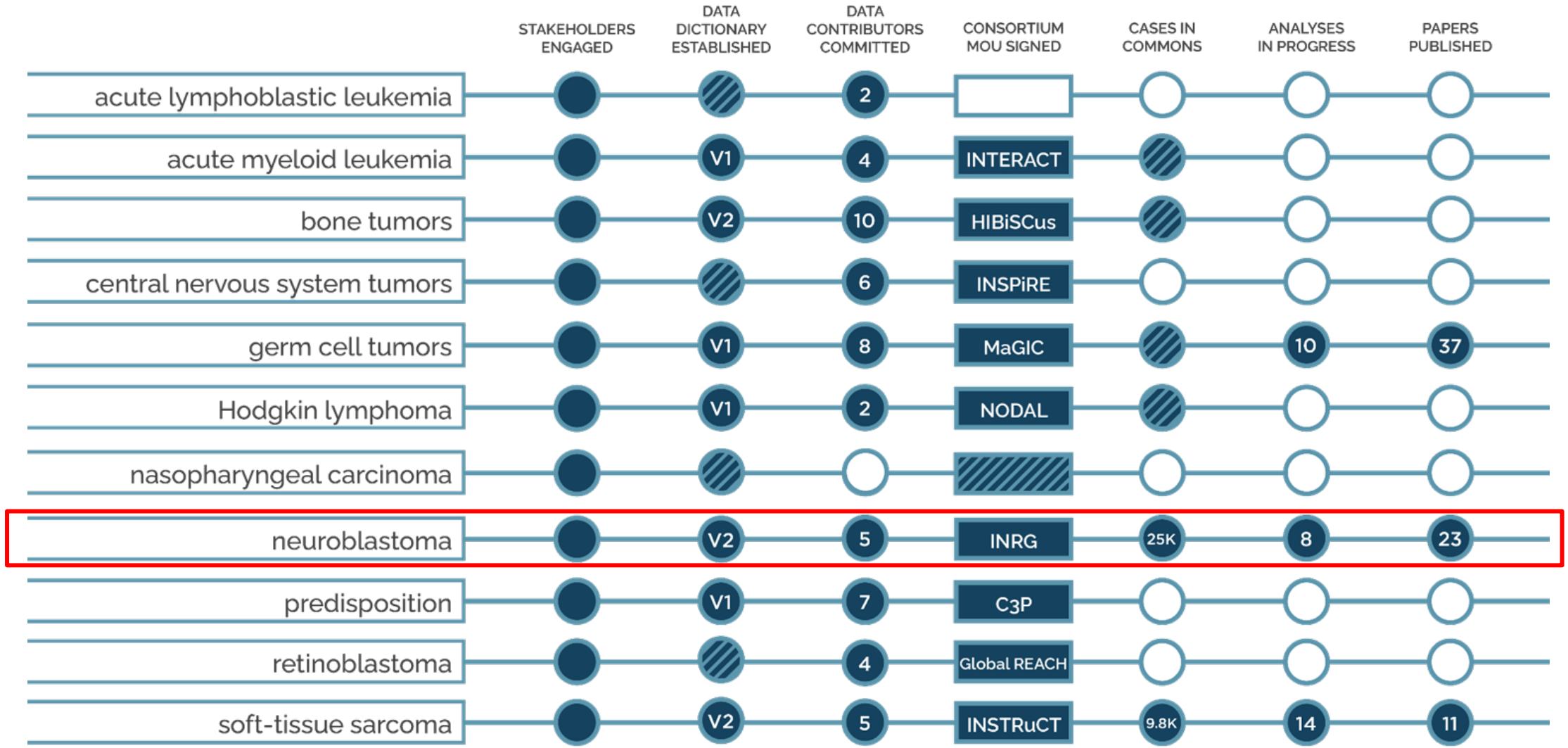
Worldwide Data Use Agreements
US - 4 master agreements (+16 addenda/projects)
Non-US - 3 master agreements (+5 addenda/projects)

Worldwide Data Contributor Agreements
US - 6 master agreements (+17 addenda)
Non-US - 13 master agreements (+12 addenda)

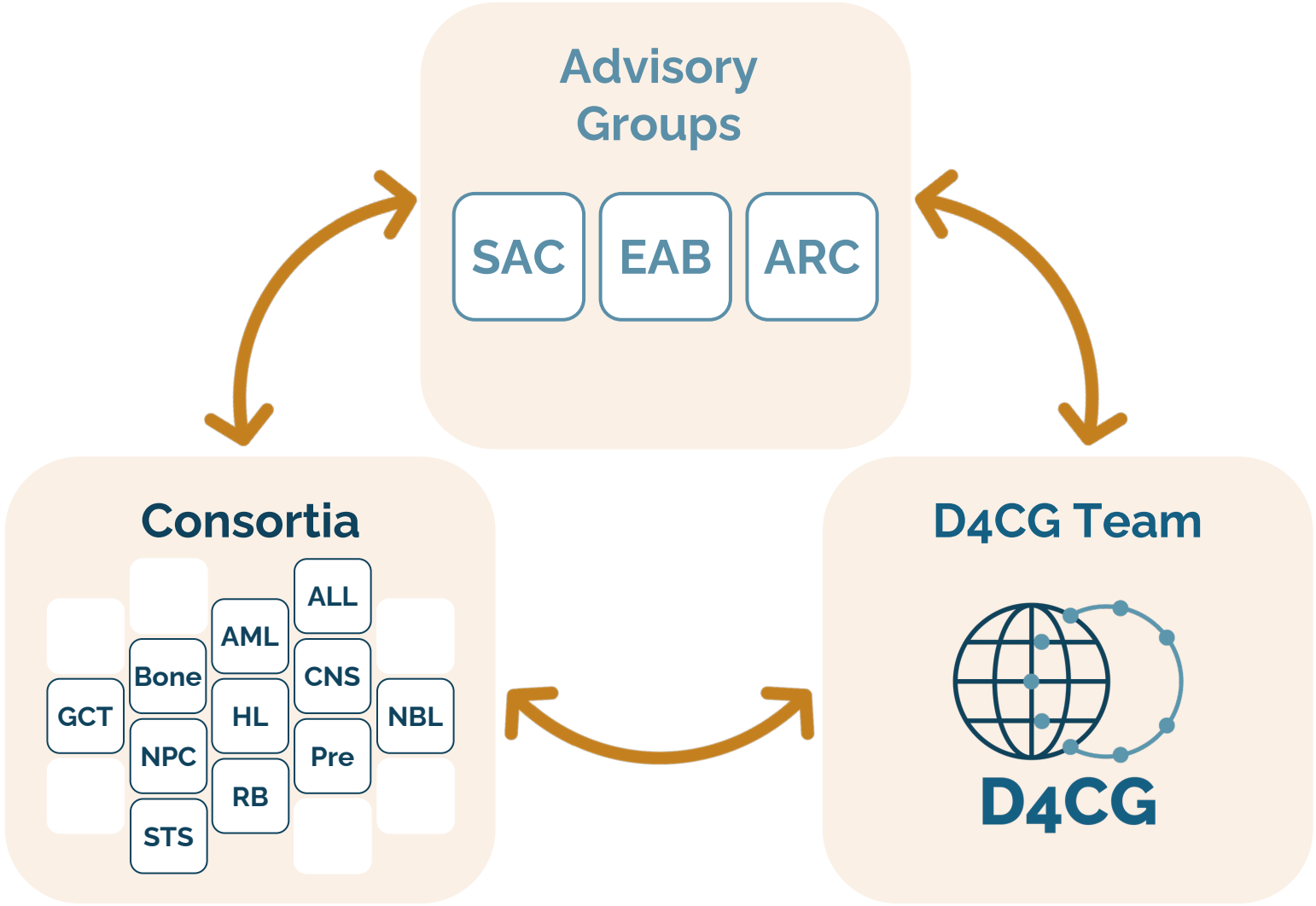
PCDC Progress



PCDC Progress



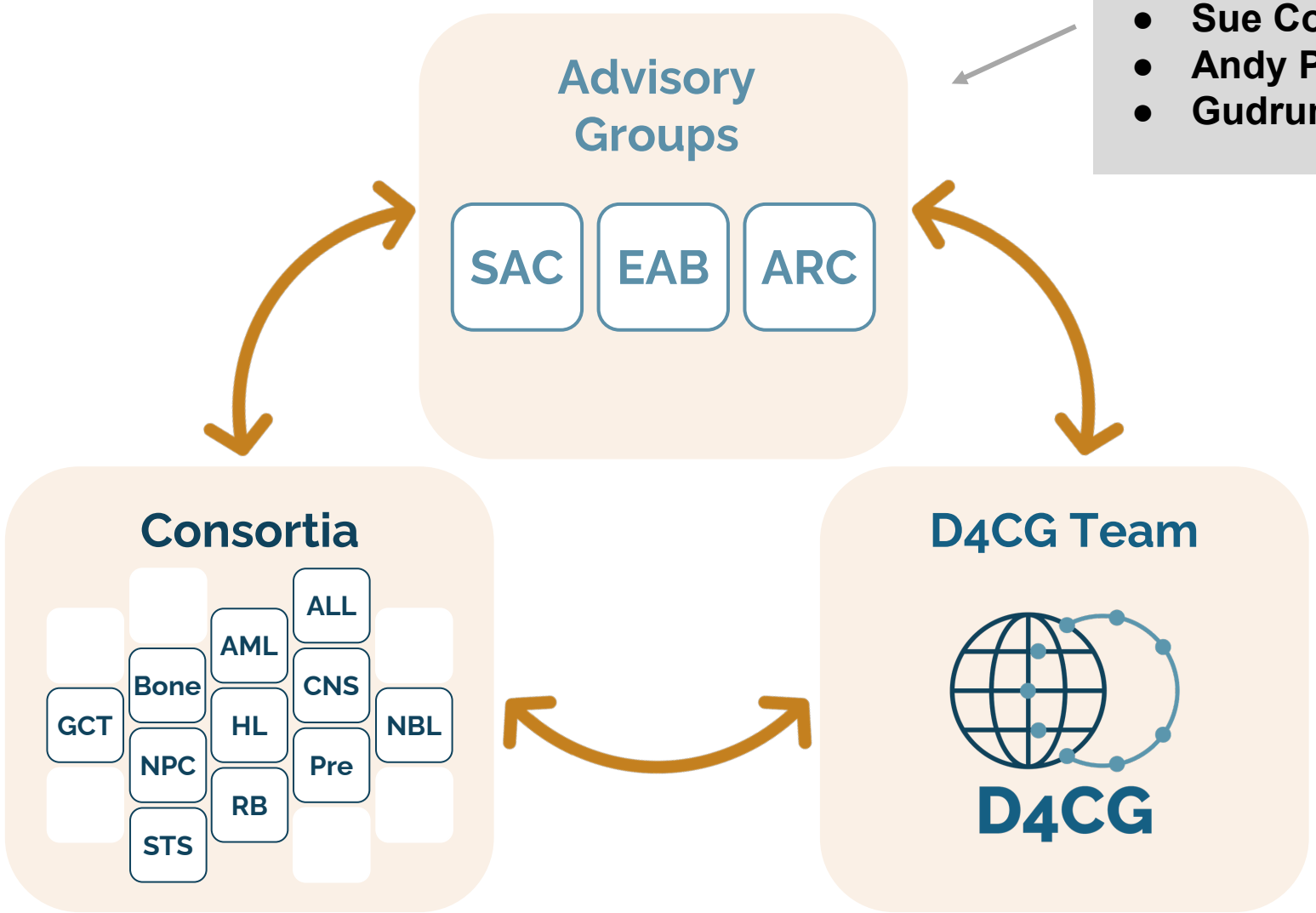
PCDC structure



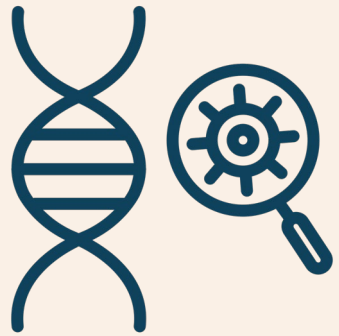
PCDC structure

SAC Members include INRG

- **Sue Cohn**
- **Andy Pearson**
- **Gudrun Schleiermacher**



Applying our approach beyond pediatric cancer



Other diseases

- **Rare diseases** - benefit from larger study cohorts
- **Rarer subtypes** of common diseases
- Diseases associated with **specific genetic markers**

The sociome

- Studying the **social determinants of health**
- Combining medical data with other types of information to make new connections

Current D4CG initiatives

Cancer

Food allergies

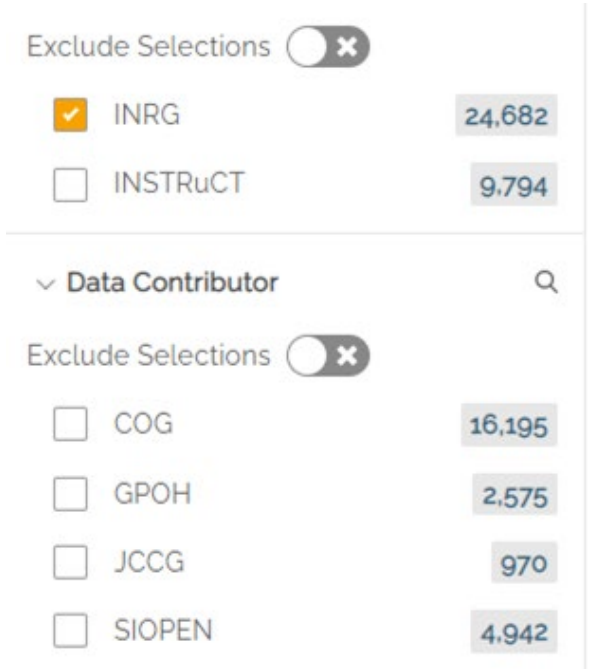
Other rare diseases

Crohn's disease

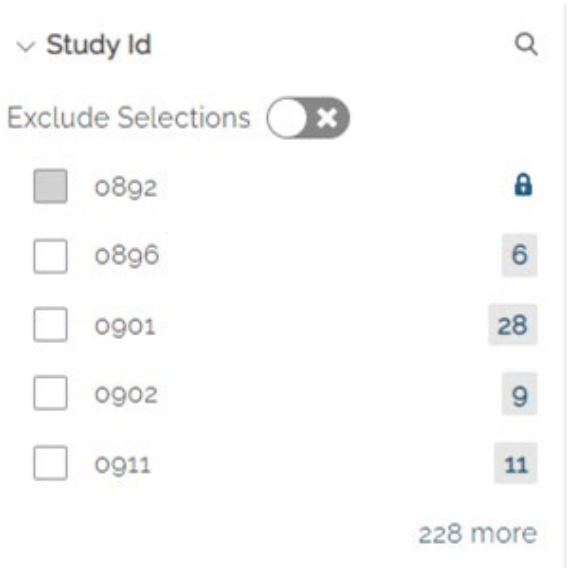
Sociome

Data portal updates

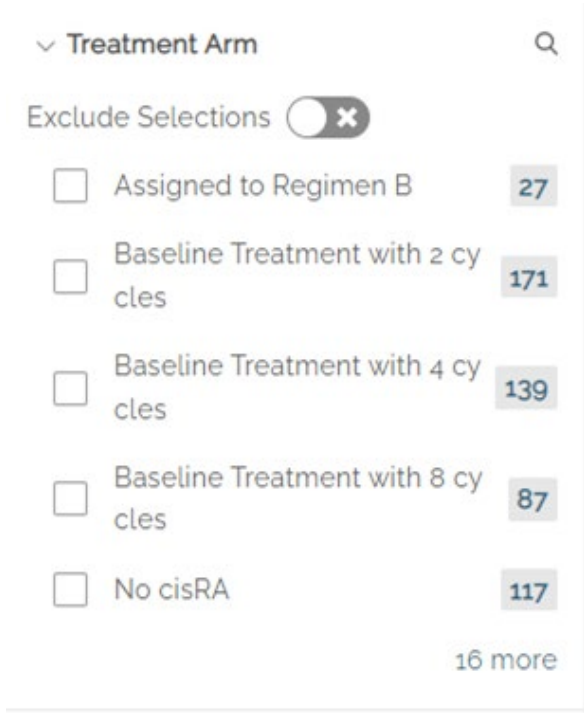
New filters added for cohort discovery



Data Contributor

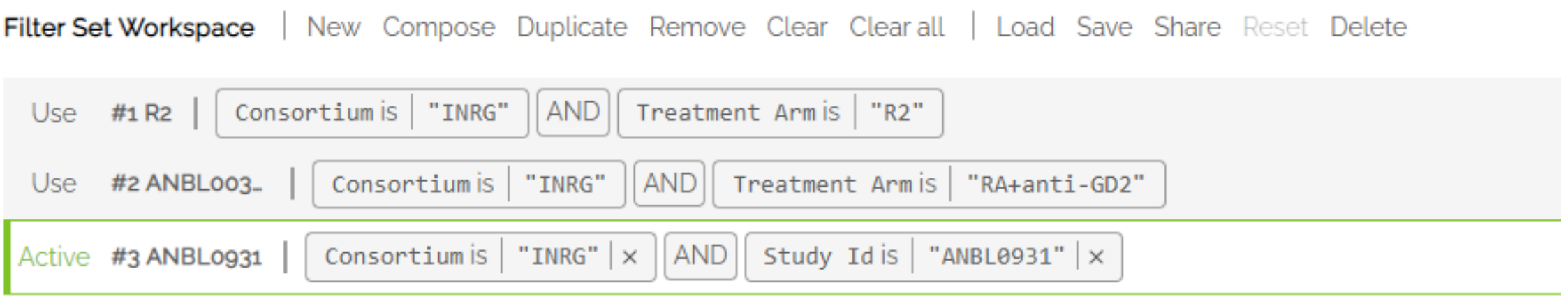


Study Id



Treatment Arm

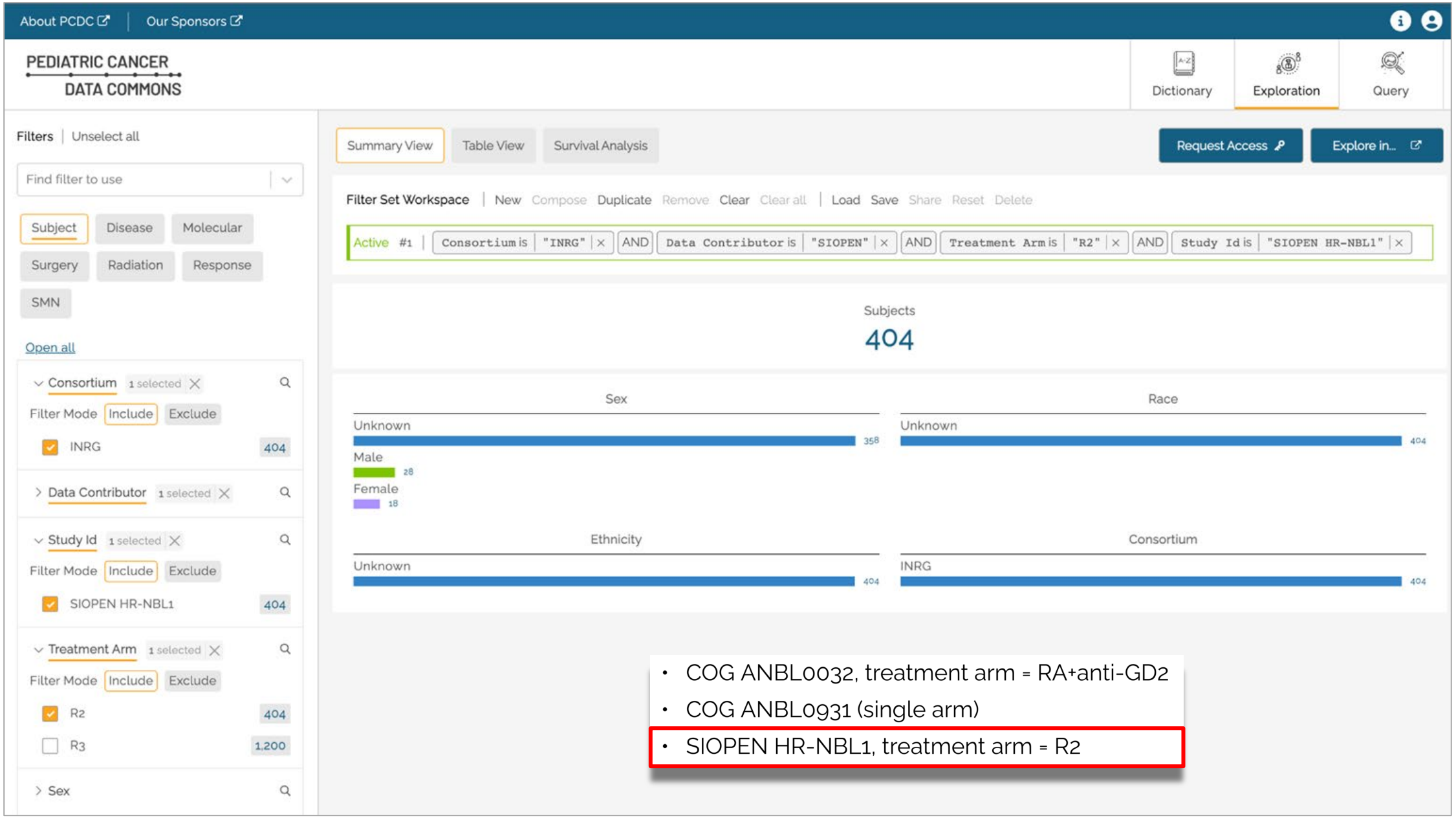
New features in the Filter Work Space



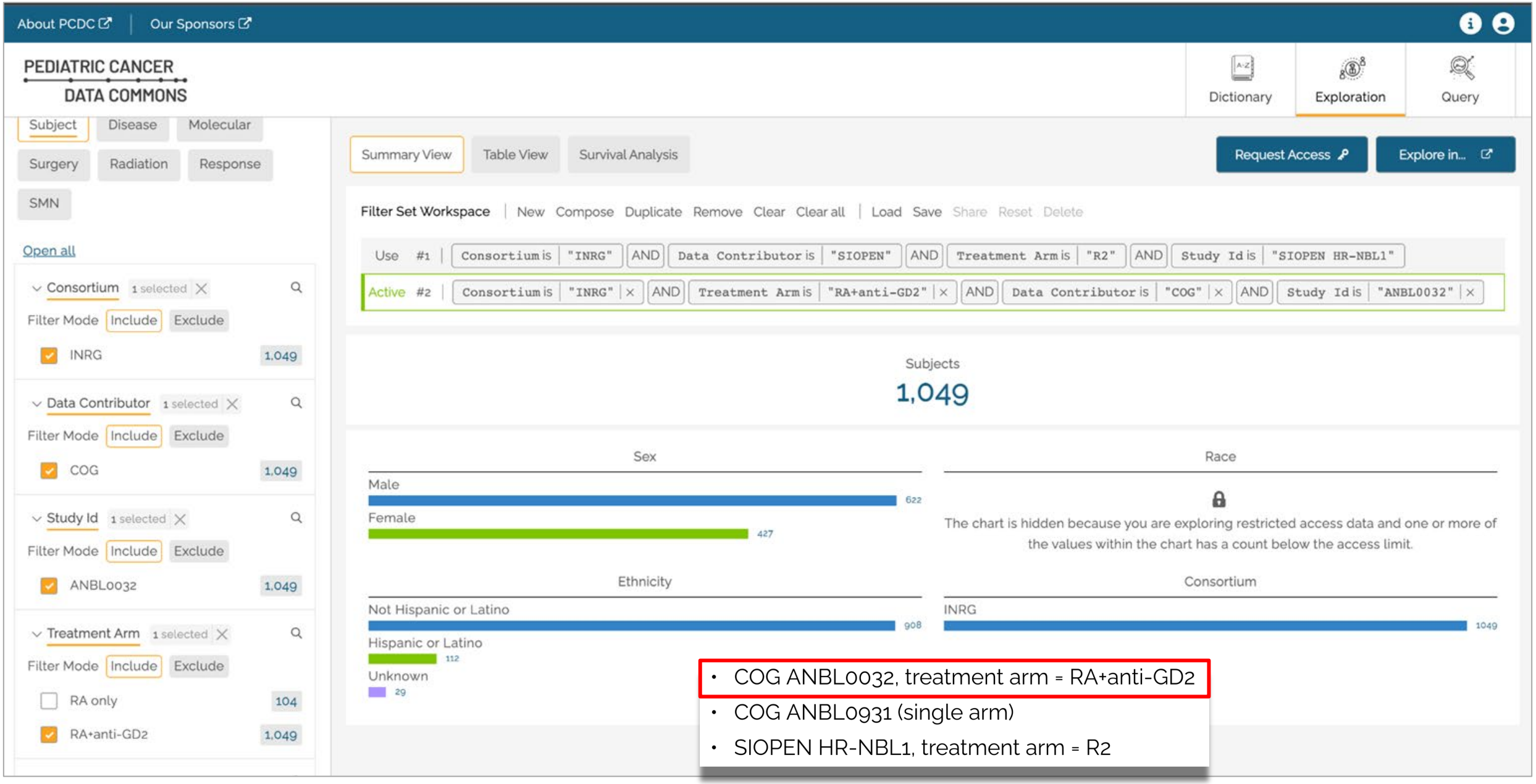
- Duplicate
- Compose
- Share

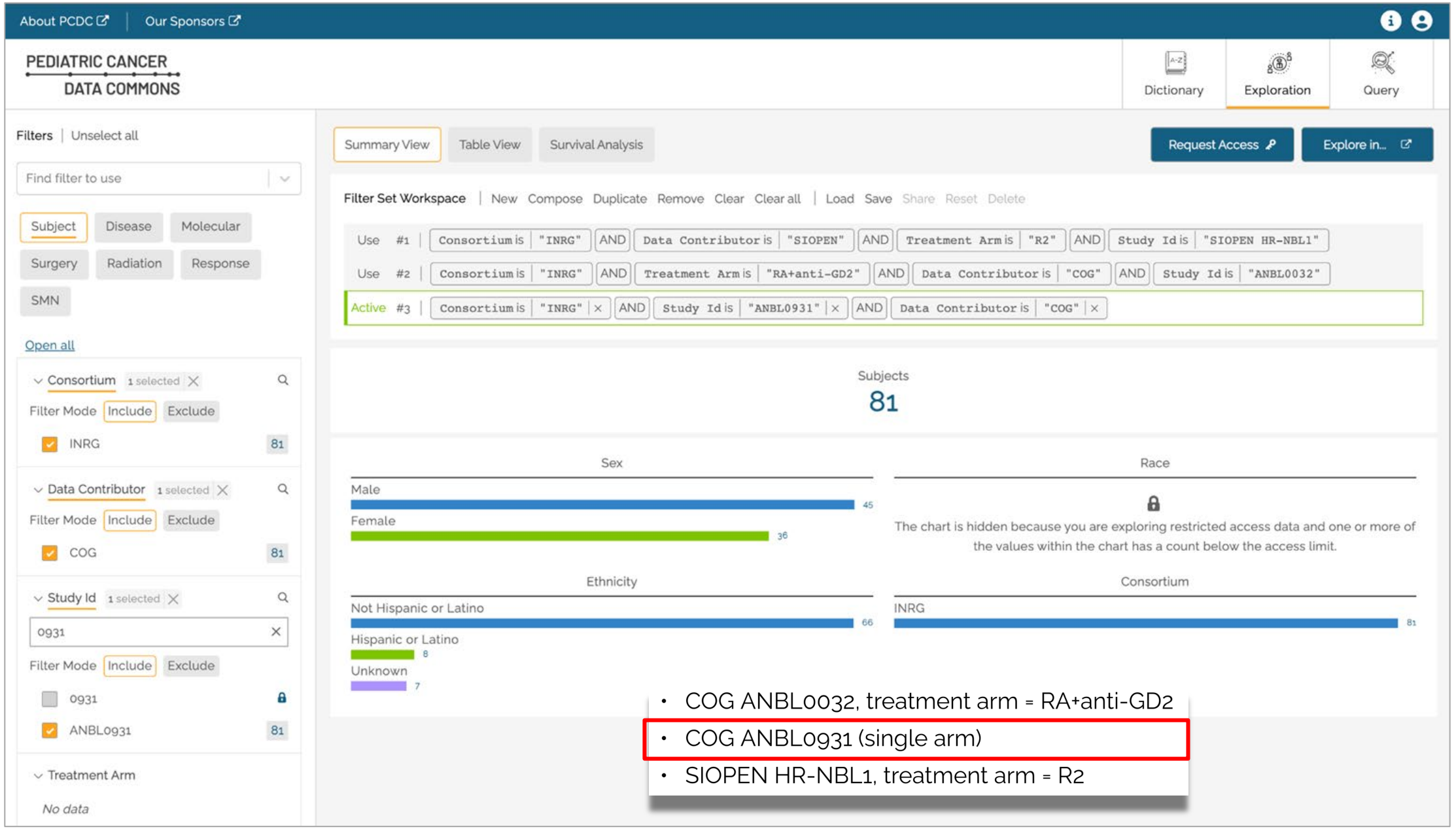
Example: *Search for patients enrolled on clinical trials on arms that received antibody treatment*

- COG ANBL0032, treatment arm = RA+anti-GD2
- COG ANBL0931 (single arm)
- SIOPEN HR-NBL1, treatment arm = R2



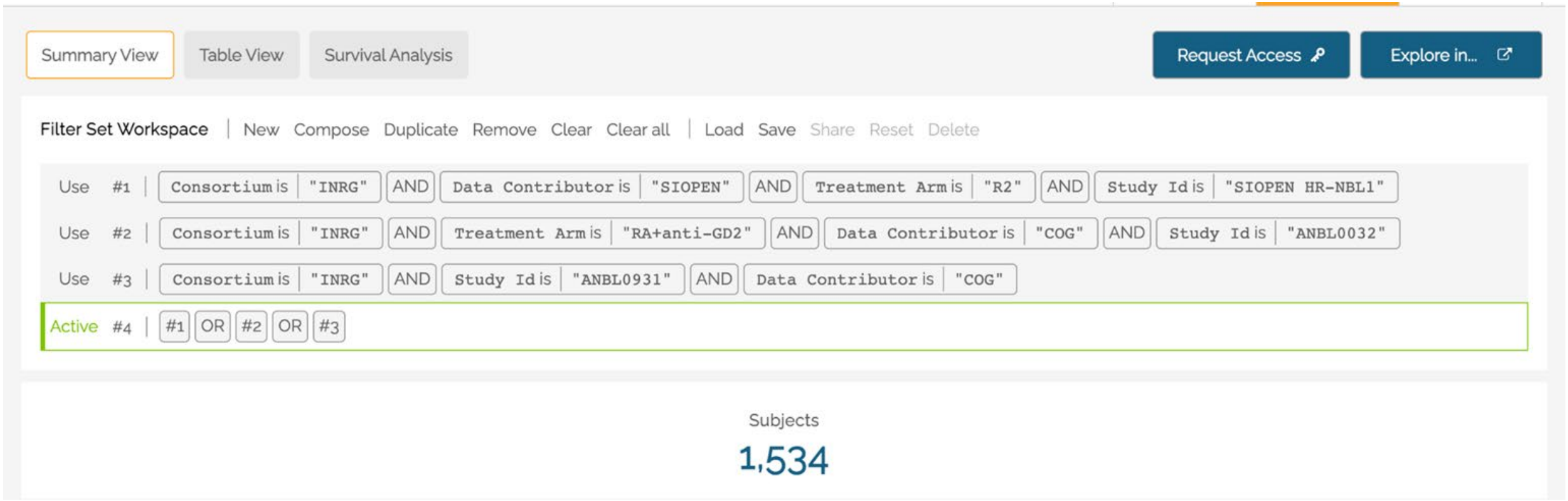
- COG ANBL0032, treatment arm = RA+anti-GD2
- COG ANBL0931 (single arm)
- SIOPEN HR-NBL1, treatment arm = R2


About PCDC
Our Sponsors
PEDIATRIC CANCER DATA COMMONS
Dictionary
Exploration
Query
Subject
Disease
Molecular
Surgery
Radiation
Response
SMN
Summary View
Table View
Survival Analysis
Request Access
Explore in...
Filter Set Workspace
New
Compose
Duplicate
Remove
Clear
Clear all
Load
Save
Share
Reset
Delete
Use #1 | Consortium is "INRG" AND Data Contributor is "SIOPEN" AND Treatment Arm is "R2" AND Study Id is "SIOPEN HR-NBL1"
Active #2 | Consortium is "INRG" AND Treatment Arm is "RA+anti-GD2" AND Data Contributor is "COG" AND Study Id is "ANBL0032"
Open all
Consortium 1 selected
Filter Mode Include Exclude
INRG 1,049
Data Contributor 1 selected
Filter Mode Include Exclude
COG 1,049
Study Id 1 selected
Filter Mode Include Exclude
ANBL0032 1,049
Treatment Arm 1 selected
Filter Mode Include Exclude
RA only 104
RA+anti-GD2 1,049
Subjects
1,049
Sex
Male 622
Female 427
Race
The chart is hidden because you are exploring restricted access data and one or more of the values within the chart has a count below the access limit.
Ethnicity
Not Hispanic or Latino 908
Hispanic or Latino 112
Unknown 29
Consortium
INRG 1049
• COG ANBL0032, treatment arm = RA+anti-GD2
• COG ANBL0931 (single arm)
• SIOPEN HR-NBL1, treatment arm = R2

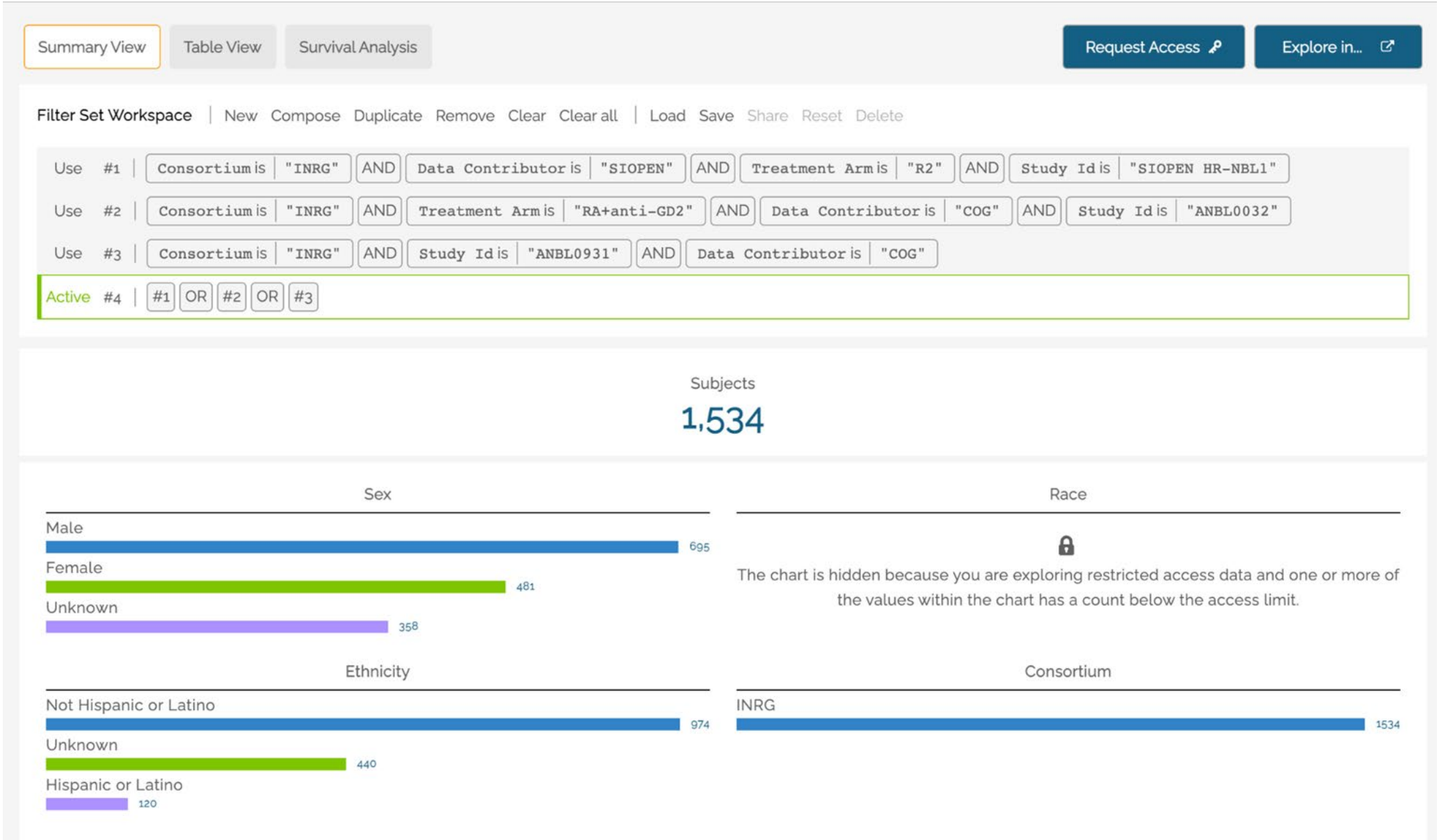


- COG ANBL0032, treatment arm = RA+anti-GD2
- COG ANBL0931 (single arm)
- SIOPEN HR-NBL1, treatment arm = R2

Compose to find all on study to receive antibody treatment



- COG ANBL0032, treatment arm = RA+anti-GD2 1049
- COG ANBL0931 (single arm) 81
- SIOPEN HR-NBL1, treatment arm = R2 404


Summary View
Table View
Survival Analysis
Request Access
Explore in...
Filter Set Workspace | New Compose Duplicate Remove Clear Clear all | Load Save Share Reset Delete
Use #1 | Consortium is "INRG" AND Data Contributor is "SIOPEN" AND Treatment Arm is "R2" AND Study Id is "SIOPEN HR-NBL1"
Use #2 | Consortium is "INRG" AND Treatment Arm is "RA+anti-GD2" AND Data Contributor is "COG" AND Study Id is "ANBL0032"
Use #3 | Consortium is "INRG" AND Study Id is "ANBL0931" AND Data Contributor is "COG"
Active #4 | #1 OR #2 OR #3
Subjects
1,534
Sex
Male 695
Female 481
Unknown 358
Race
The chart is hidden because you are exploring restricted access data and one or more of the values within the chart has a count below the access limit.
Ethnicity
Not Hispanic or Latino 974
Unknown 440
Hispanic or Latino 120
Consortium
INRG 1534

Preview: new data elements coming to INRG

Elements in development

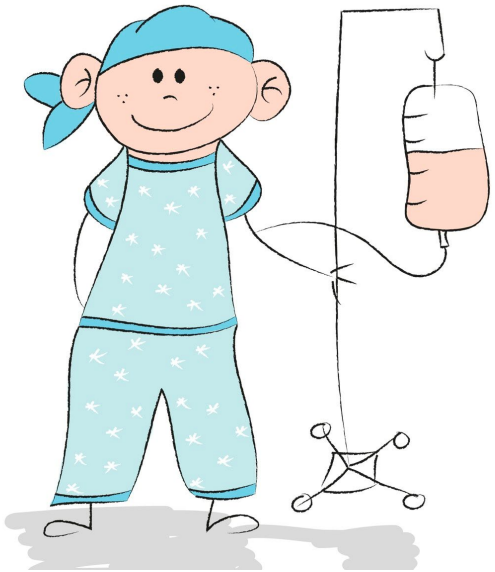
- INRG Genomics Committee
  - ALK
  - Groundwork for more genomics data
- INRG Response Data Committee
  - Response
  - Relapse

17q Gain
Loss of Chromosome 11q (Deletion)
Loss of Chromosome 1p (Deletion)
MYCN Amplification
ALK Amplification
p.G1128A
p.M1166R
p.I1170N
p.I1170S
p.I1171N
p.F1174*
p.R1192P
p.L1196M
p.F1245*
p.R1275*
p.Y1278S
ALK Missense Mutation, NOS
ALK Translocation, NOS

INRC Park 2017, PD
INRC Park 2017, CR
INRC Park 2017, PR
INRC Park 2017, SD
INRC Park 2017, MR
INRC Park 2017, MD
INRC Park 2017, UE
INRC Brodeur 1993, PD
INRC Brodeur 1993, CR
INRC Brodeur 1993, VGPR
INRC Brodeur 1993, PR
INRC Brodeur 1993, MR
INRC Brodeur 1993, NR
INRC Brodeur 1993, UE
Not Involved
Not Done

GEARBOx

Relapsed patients struggle to find therapies



Child with relapsed NBL

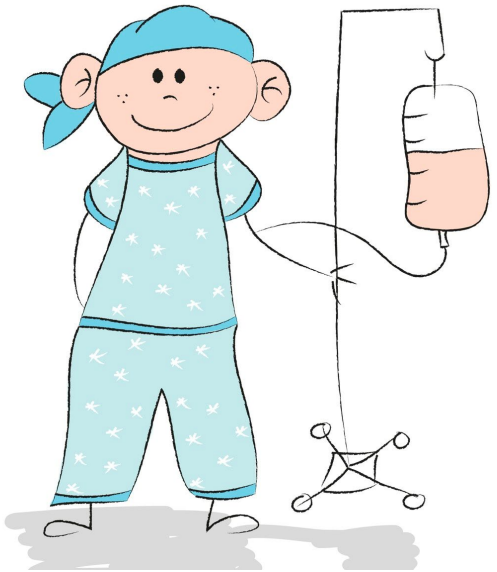
Traditional therapy

Additional testing

weeks/months

Phase I/II/III clinical trial

Relapsed patients struggle to find therapies



Child with relapsed NBL

Traditional therapy

Additional testing

weeks/months

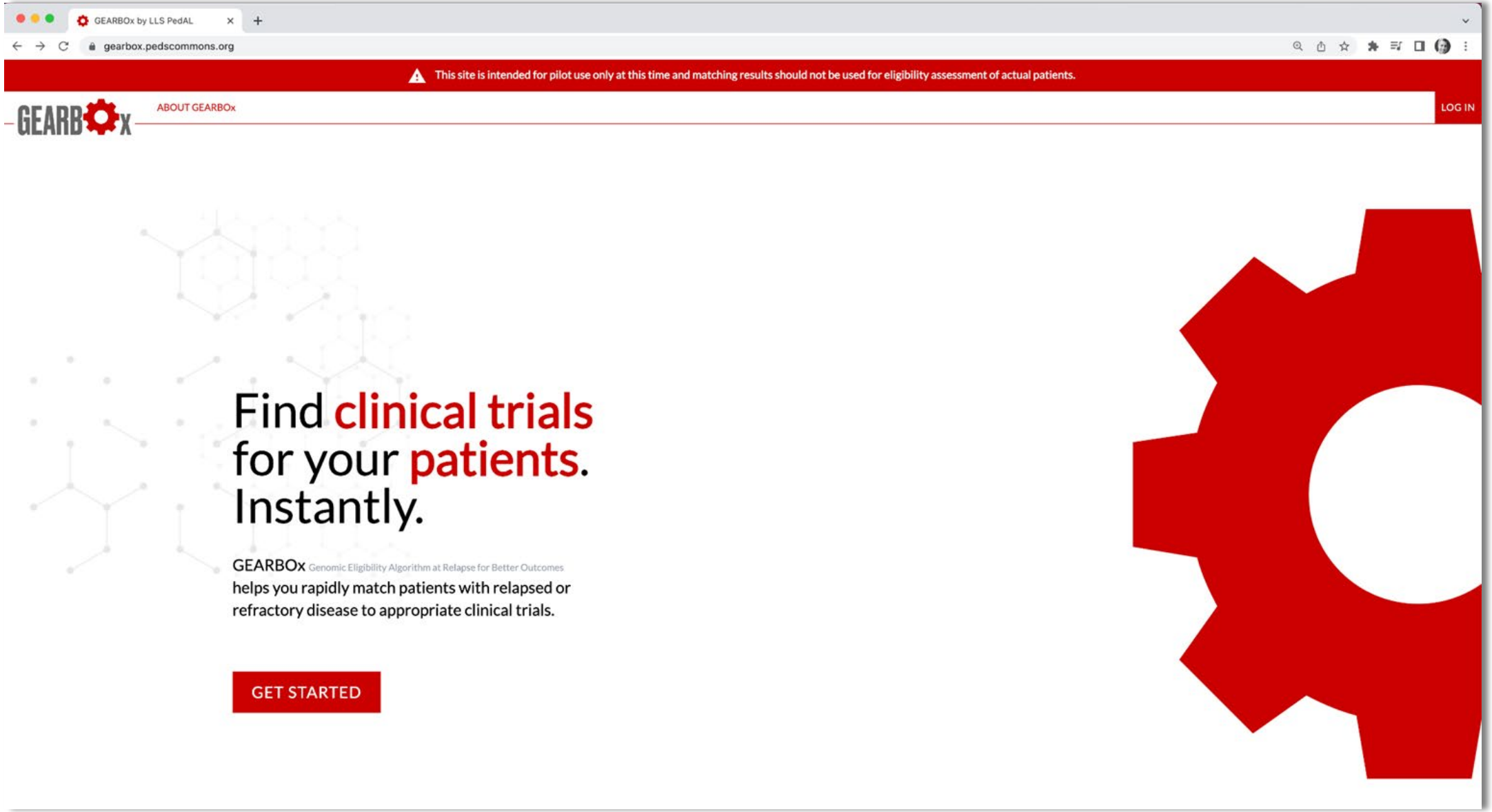
GEARBOx

48-72 hours

Genomic Eligibility Algorithm at Relapse for Better Outcomes

Phase I/II/III clinical trial

LEUKEMIA & LYMPHOMA SOCIETY®


GEARBOx by LLS PedAL
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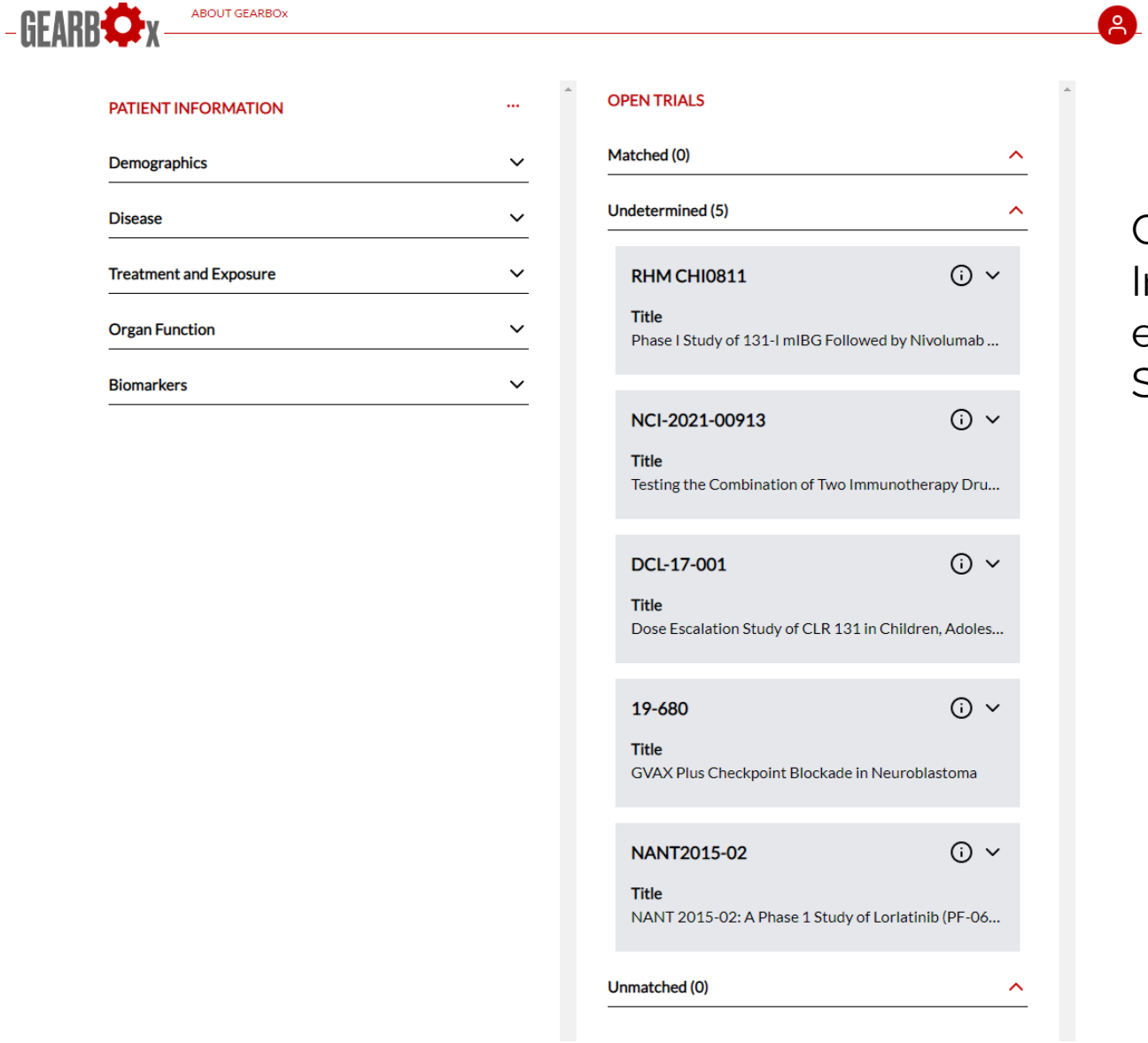
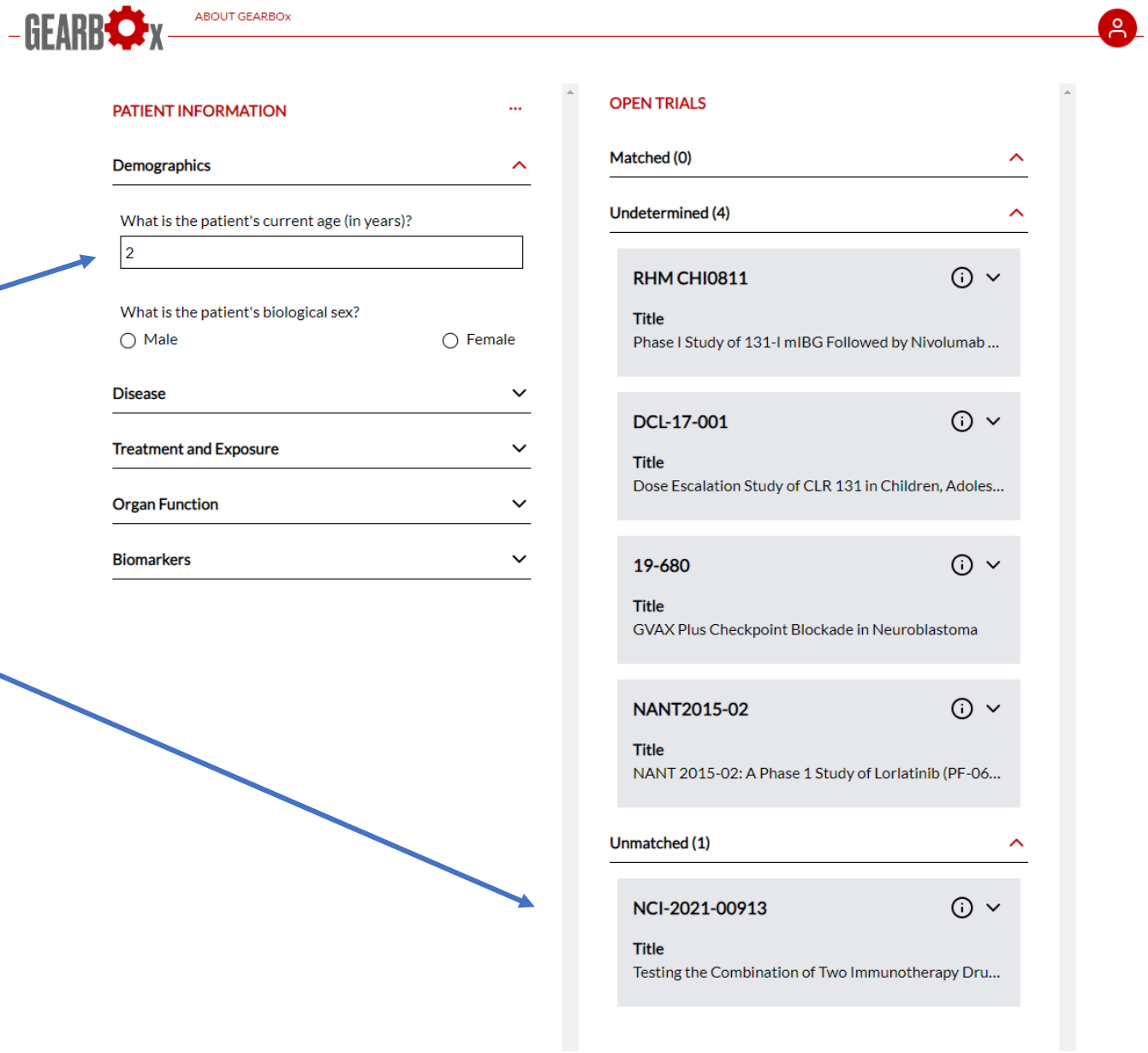
GEARBOx
ABOUT GEARBOx
LOG IN
Find clinical trials for your patients. Instantly.
GEARBOx Genomic Eligibility Algorithm at Relapse for Better Outcomes helps you rapidly match patients with relapsed or refractory disease to appropriate clinical trials.
GET STARTED

- Patient characteristics
- Disease characteristics
- Lab tests
- Genomic testing



- Clinical trials
- Information about enrollment
- Study locations



Age = 2

Eliminates 1 trial

PATIENT INFORMATION

Demographics

What is the patient's current age (in years)?

3

What is the patient's biological sex?

- ○ Male
- ○ Female

Disease

What is the patient's current diagnosis?

High-risk Neuroblastoma (NBL)

Does the patient currently have, or have they in the past had, refractory disease?

- ○ Yes
- ○ No
- ○ Not sure

Does the patient currently have, or have they in the past had, confirmed or suspected relapse disease?

- ○ Yes
- ○ No
- ○ Not sure

What is the patient's ECOG score?

ECOG 1 (Lansky/Karnofsky 70-80)

Does the patient have documented active, uncontrolled infection?

- ○ Yes
- ◉ No
- ○ Not sure

Has the patient been diagnosed with: clinically significant uncontrolled central nervous system (CNS) pathology (e.g. epilepsy, childhood seizure, paresis, aphasia, stroke, severe brain injuries, organic brain syndrome, or psychosis)

- ○ Yes
- ○ No
- ○ Not sure

OPEN TRIALS

Matched (0)

Undetermined (4)

RHM CHI0811

Title
Phase I Study of 131-I mIBG Followed by Nivolumab & ...

DCL-17-001

Title
Dose Escalation Study of CLR 131 in Children, Adolesce...

19-680

Title
GVAX Plus Checkpoint Blockade in Neuroblastoma

NANT2015-02

Title
NANT 2015-02: A Phase 1 Study of Lorlatinib (PF-0646...

Unmatched (1)

NCI-2021-00913

Title
Testing the Combination of Two Immunotherapy Drugs ...

PATIENT INFORMATION ...

Treatment and Exposure

Does the patient have any prior exposure to: Other substantial BM radiation
○ Yes ○ No ○ Not sure

Does the patient have any prior exposure to: Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG)?
○ Yes ○ No ○ Not sure

Does the patient have any prior exposure to: DLI (donor lymphocyte infusion) or any type of cellular therapy (eg, modified T cells, NK cells, dendritic cells, etc.)
○ Yes ● No ○ Not sure

Does the patient have any prior exposure to: monoclonal antibodies
○ Yes ● No ○ Not sure

Does the patient have any prior exposure to: Radiotherapy (RT)
○ Yes ● No ○ Not sure

Does the patient have any prior exposure to: Abdominal radiotherapy (RT)
○ Yes ○ No ○ Not sure

Does the patient have any prior exposure to: live cellular therapy (natural killer [NK] cell, chimeric antigen receptor T-cell [CAR-T cell])
○ Yes ○ No ○ Not sure

Has the patient had previous toxicity or hypersensitivity directly attributed to GM-CSF or dimethyl sulfoxide (DMSO)
○ Yes ○ No ○ Not sure

OPEN TRIALS

Matched (1)

NANT2015-02
Title
NANT 2015-02: A Phase 1 Study of Lorlatinib (PF-06...

Undetermined (1)

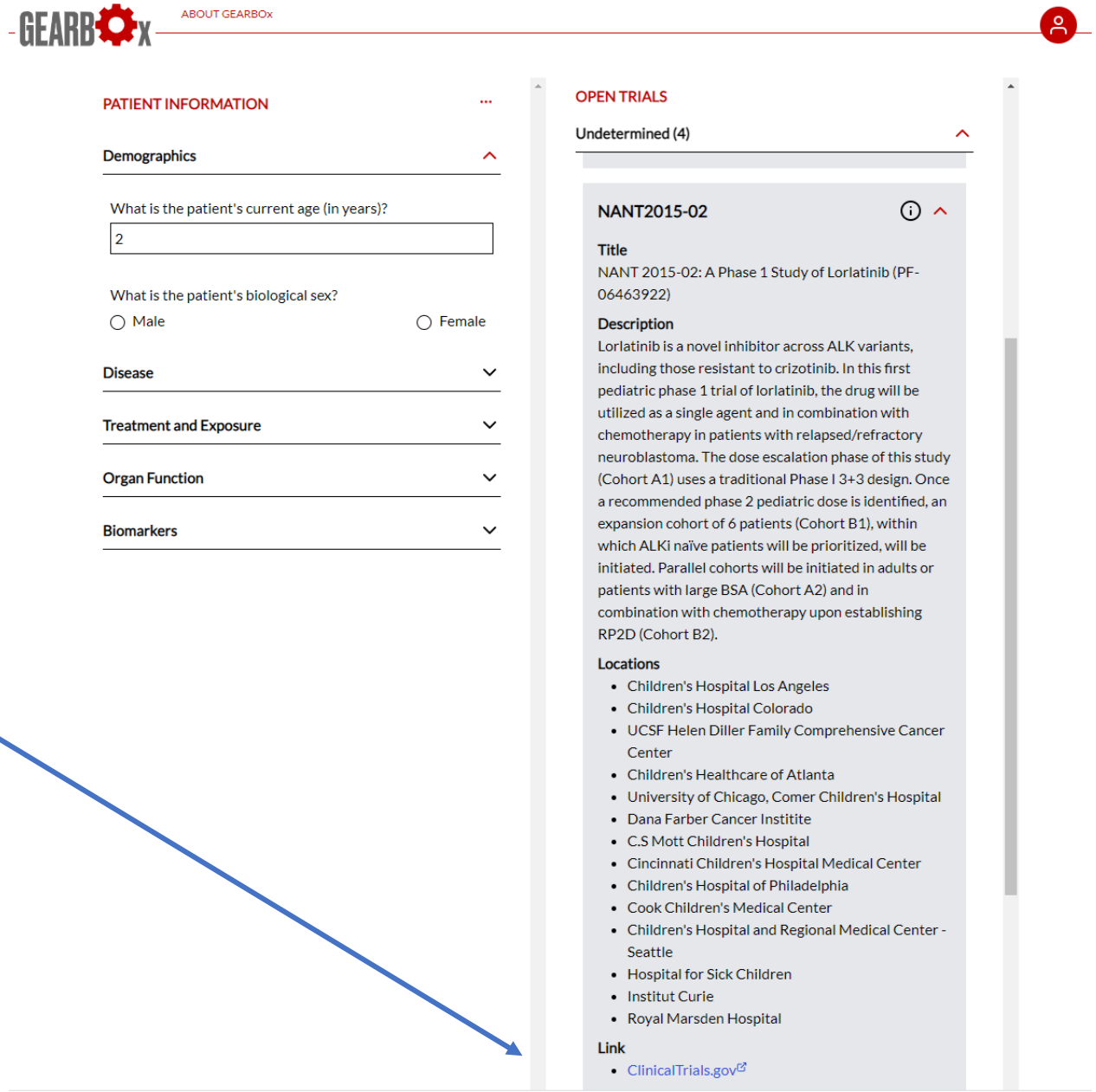
19-680
Title
GVAX Plus Checkpoint Blockade in Neuroblastoma

Unmatched (3)

RHM CHI0811
Title
Phase I Study of 131-I mIBG Followed by Nivolumab ...

NCI-2021-00913
Title
Testing the Combination of Two Immunotherapy Dru...

DCL-17-001
Title
Dose Escalation Study of CLR 131 in Children, Adoles...



Link to the trial on ClinicalTrials.gov

PCDC Consortium Research Projects

File Edit View Insert Format Data Tools Extensions Help

100% View only

A1:G1 INRG Research

INRG Research

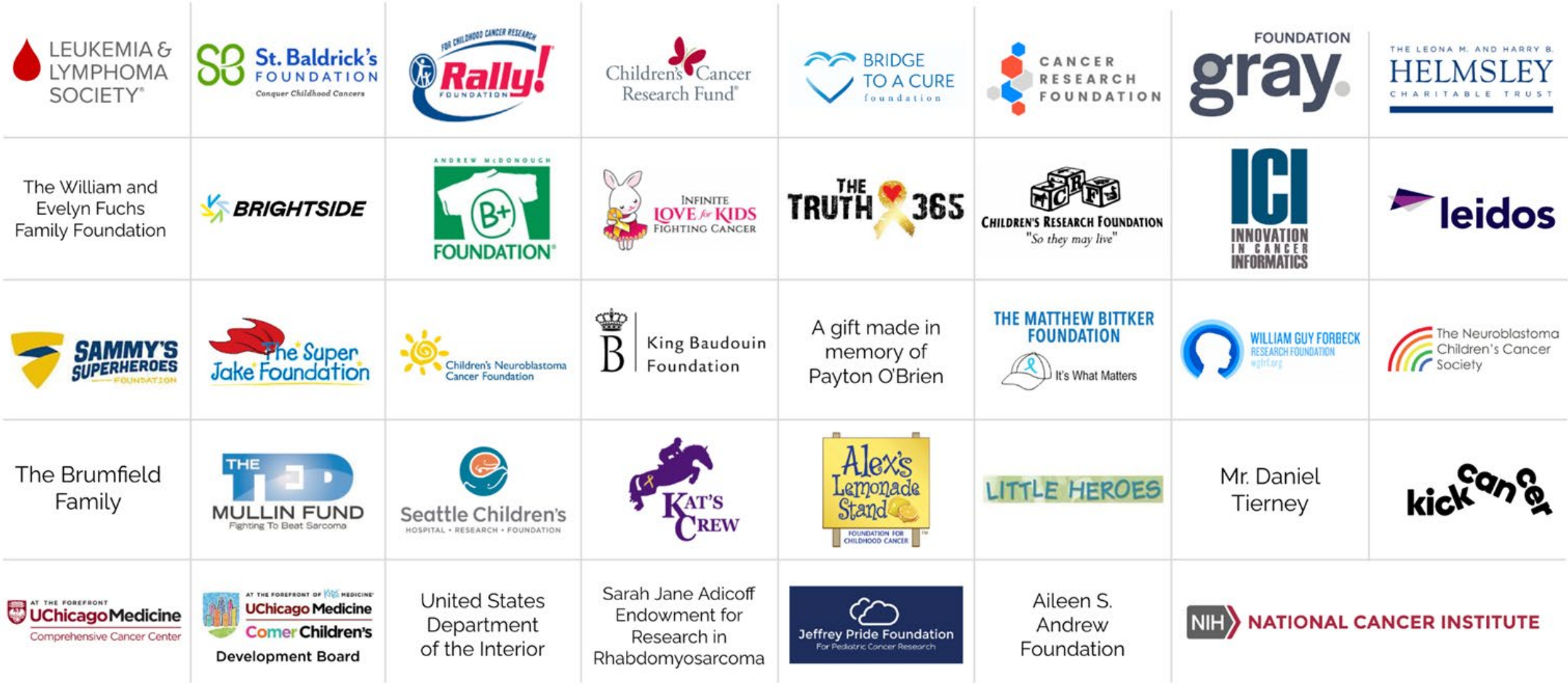
Click on a description to view the original project proposal.

INRG #	Investigator(s)	Project Type	Description	Status	Publication	Presentation
2022-04	Mallory Taylor Thomas Cash Wendy London Julie Park Meredith Irwin	Investigator	Outcomes for patients aged 12-18 months with Stage M MYCN non-amplified neuroblastoma and unfavorable biologic features ('Mixed Phenotype Toddlers')	In Progress		
2022-03	Hanxaio Yu Xingda Zhan Mark Appelbaum Gudrun Schleiermacher	Investigator	Prognostic impact of segmental chromosome alterations in high-risk neuroblastoma patients on immunotherapy: A report from the International Neuroblastoma Risk Group (INRG) project	Approved		
2022-02	Boris Decarolis Wendy London Susan Cohn Andrew Pearson	Investigator	Survival of patients with low-, intermediate-, or high-risk neuroblastoma over a 35 year period	In Progress		
2022-01	Wendy London Ramya Ramanujachar Kavitha Srivatsa Paola Angelini	Investigator	Neuroblastoma in adolescents and adults- a study of clinical and biological features and outcomes	Approved		
2021-01	Kevin Campbell Pei-Chi Kao Arlene Naranjo Takehiko Kamijo Ramya Ramanujachar Wendy London Steven DuBois	Investigator	Clinical and Biological Features Predictive of Survival After Relapse of Stage MS Neuroblastoma: A Report From the International Neuroblastoma Risk Group Project	Published	Clinical and biological features prognostic of survival after relapse or progression of INRGSS stage MS pattern neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project. *Pediatr Blood Cancer.* 2023 Feb;70(2):e30054. Epub 2022 Oct 31. doi: 10.1002/pbc.30054.	
2020-03	Riyue Bao Stefani Spranger Kyle Hernandez Yuanyuan Zha Peter Pytel Jason Luke Thomas Gajewski Samuel Volchenboum Susan Cohn Ami Desai	Investigator	Validation of a T-cell inflammatory signature and outcomes in patients with neuroblastoma	Published	Immunogenomic determinants of tumor microenvironment correlate with superior survival in high-risk neuroblastoma. *J Immunother Cancer.* 2021 Jul;9(7):e002417. doi: 10.1136/jitc-2021-002417. PMID: 34272305; PMCID: PMC8287618.	
2020-02	Stephen Skapek Lin Xu Susan Cohn Mark Applebaum	Investigator	Identifying neuroblastoma drivers and bringing them to the clinic	In Progress		
2020-01	Caileigh Pudela Ami Desai Mark Applebaum Tara Henderson Susan Cohn	Investigator	Racial and Ethnic Disparities in Risk and Survival in Children With Neuroblastoma: An Updated Analysis Using the International Neuroblastoma Risk Group Database	Presented		Presented at ASCO 2021

Sam Volchenboum
PCDC Director
slv@uchicago.edu

Sign up for our quarterly newsletter
sam.am/PCDCnews

Our funders


LEUKEMIA & LYMPHOMA SOCIETY
St. Baldrick's FOUNDATION
Conquer Childhood Cancers
Rally! FOUNDATION
Children's Cancer Research Fund
BRIDGE TO A CURE foundation
CANCER RESEARCH FOUNDATION
FOUNDATION gray
THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST
The William and Evelyn Fuchs Family Foundation
BRIGHTSIDE
ANDREW McDONOUGH B+ FOUNDATION
INFINITE LOVE for KIDS FIGHTING CANCER
THE TRUTH 365
CHILDREN'S RESEARCH FOUNDATION "So they may live"
ICI INNOVATION IN CANCER INFORMATICS
leidos
SAMMY'S SUPERHEROES FOUNDATION
The Super Jake Foundation
Children's Neuroblastoma Cancer Foundation
King Baudouin Foundation
A gift made in memory of Payton O'Brien
THE MATTHEW BITTKER FOUNDATION
It's What Matters
WILLIAM GUY FORBECK RESEARCH FOUNDATION
The Neuroblastoma Children's Cancer Society
The Brumfield Family
THE MULLIN FUND Fighting To Beat Sarcoma
Seattle Children's HOSPITAL • RESEARCH • FOUNDATION
KAT'S CREW
Alex's Lemonade Stand FOUNDATION FOR CHILDHOOD CANCER
LITTLE HEROES
Mr. Daniel Tierney
kick cancer
AT THE FOREFRONT UChicagoMedicine Comprehensive Cancer Center
AT THE FOREFRONT OF KIDS MEDICINE UChicago Medicine Comer Children's Development Board
United States Department of the Interior
Sarah Jane Adicoff Endowment for Research in Rhabdomyosarcoma
Jeffrey Pride Foundation For Pediatric Cancer Research
Aileen S. Andrew Foundation
NIH NATIONAL CANCER INSTITUTE

Approach to INRG Governance

Suzi Birz

The changing landscape

- Increasing privacy protection regulations
- Bringing in more data to the INRG data commons
  - New data contributors
  - New data elements from existing contributors
  - New studies from existing contributors housed at different coordinating centers

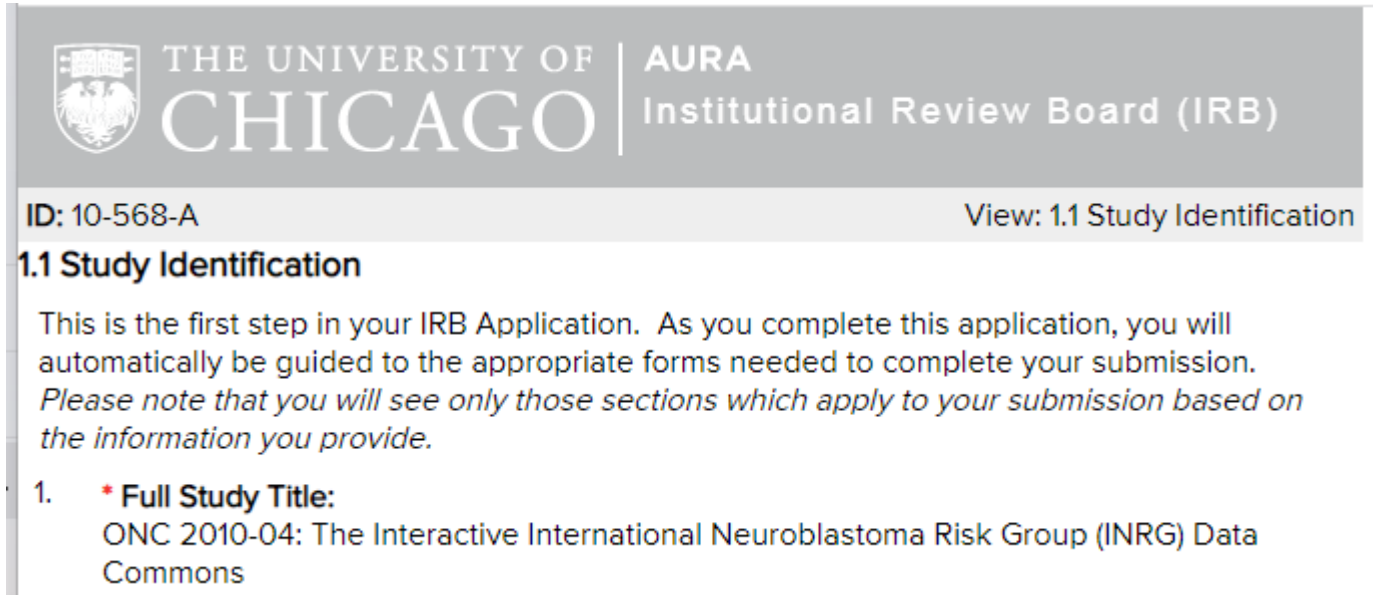
Guiding principles of governance

- The workflow must focus on the goal of lifting barriers to the data; we want to connect the researchers to the data.
- No data from any disease-commons will be released without the approval of consortium. [Each consortium creates its own project review process.]
- Recognize that regional regulations are different.

UChicago's IRB protocol for INRG Data Commons

IRB Approved

- Data commons for data collection and secondary analyses
- Deidentified retrospective data



THE UNIVERSITY OF CHICAGO | AURA Institutional Review Board (IRB)

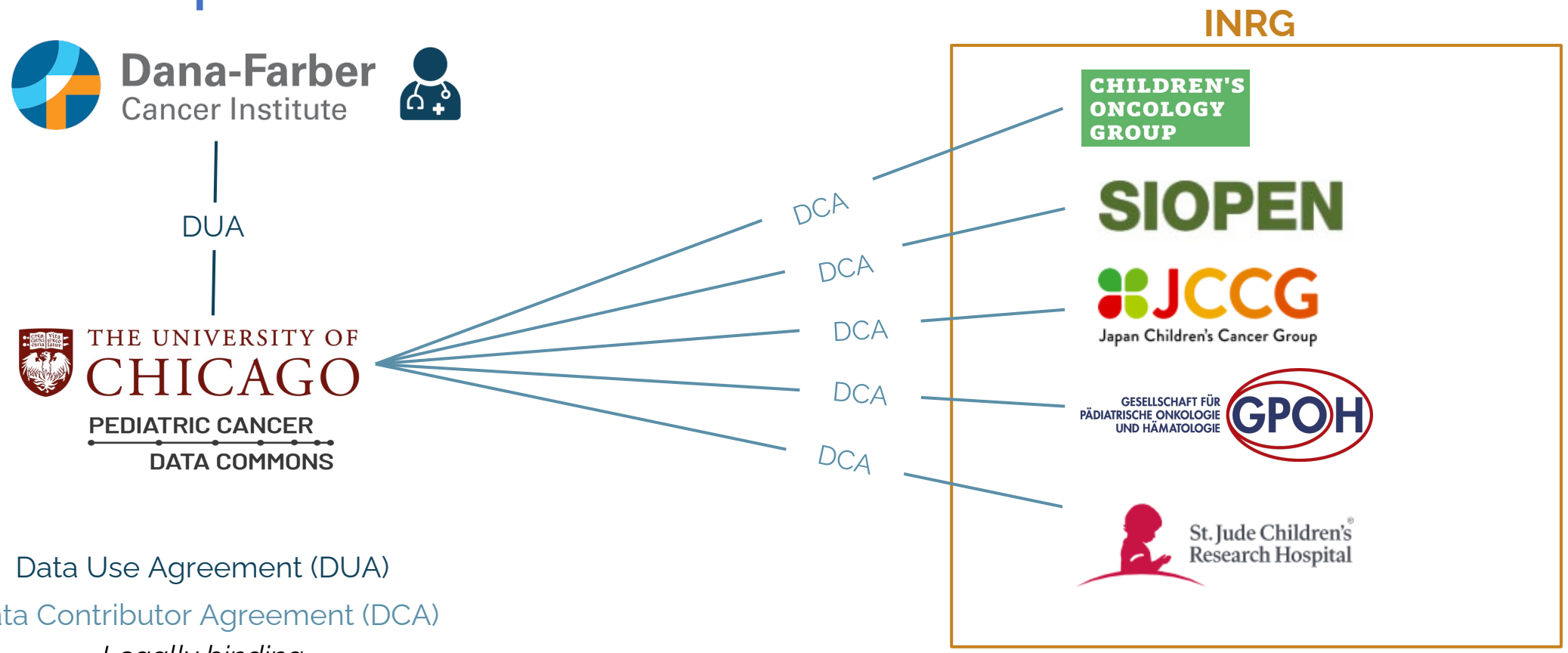
ID: 10-568-A View: 1.1 Study Identification

1.1 Study Identification

This is the first step in your IRB Application. As you complete this application, you will automatically be guided to the appropriate forms needed to complete your submission. *Please note that you will see only those sections which apply to your submission based on the information you provide.*

1. * **Full Study Title:**
ONC 2010-04: The Interactive International Neuroblastoma Risk Group (INRG) Data Commons

Relationships



Data Use Agreement (DUA)

Data Contributor Agreement (DCA)

Legally binding

How data must be stored and protected

How data can be used for research

Memorandum of Understanding (MOU)

Not legally binding

Executive Committee membership

Authorship

Project review

Documents

	MOU	DCA	DUA
Full name	Memorandum of Understanding	Data Contributor Agreement	Data Use Agreement
Purpose	Establishes a consortium and the committee which approves data contributions and data use	Lists studies/registries to be contributed and the terms	Lists the specific approved project, the data to be provided to the researcher, and the terms
Parties to the agreement	Data contributors	UChicago and data contributing group	UChicago and researcher/ researcher's institution
Binding?	Not legally binding	Binding	Binding

Memorandum of Understanding

MEMORANDUM OF UNDERSTANDING

FOR THE

INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG)

This Memorandum of Understanding (this "MOU"), effective as of February 2, 2023 (the "Effective Date") for the International Neuroblastoma Risk Group (INRG) (the "Consortium"), are entered into by and among Children's Oncology Group (COG), Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), Japan Children's Cancer Group (JCCG), Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN), and St. Jude Children's Research Hospital (SJCRH).

RECITALS

A. Each Cooperative Group and/or its members possesses, or has rights to, certain clinical trial and other data and materials relating to neuroblastoma and the diagnosis, treatment, and study thereof.

Children's Oncology Group (COG)

Rochelle Bagatell

Name: Ro Bagatell

Date: Mar 5, 2023

Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)

Name: Angelika Eggert

Date: Mar 17, 2023

Japan Children's Cancer Group (JCCG)

Takehiko Kamijo

Takehiko Kamijo (Mar 6, 2023 07:44 GMT+9)

Name: Takehiko Kamijo

Date: Mar 6, 2023

Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN)

Maja Beck Popovic

Maja Beck Popovic (Mar 7, 2023 12:52 GMT+1)

Name: Maja Beck Popovic

Date: Mar 7, 2023

St. Jude Children's Research Hospital (SJCRH)

Sara Federico

Sara Federico (Mar 3, 2023 19:34 CST)

Name: Sara Federico

Date Mar 3, 2023

Executive Committee Reponsibilities

a. strategic planning
b. appointing and changing the Data Commons Service Provider
c. coordination with the Data Commons Service Provider
d. amending this MOU
e. approving and managing Membership
f. reviewing and approving requests to access the Data Commons
g. reviewing and approving contributions of data to the Data Commons
h. approval of grant or funding applications submitted on behalf of, or which rely upon, the Consortium
i. adopt a publication policy

Master Data Contributor Agreement

DATA FOR THE COMMON GOOD DATA CONTRIBUTOR AGREEMENT

This Data for the Common Good Data Contributor Agreement (this "**Agreement**") is made as of the date of last signature (the "**Effective Date**"), by and between The University of Chicago (the "**University**"), an Illinois non-profit institution of higher education having a place of business at 5801 South Ellis Avenue, Chicago, IL 60638 and [organization] [address] ("**Partner**"); each individually a referred to as a "Party" and together the "**Parties**").

RECITALS

WHEREAS, the University has created a technology platform (the "**Platform**"), including software, hardware, and other technologies, for storing and harmonizing data sets of genomic, electronic medical record, and other information ("**Data for the Common Good**");

WHEREAS, as part of the Platform, the University owns and operates a data service that provides authorized researchers and other users with access to Data provided by various data contributors;

WHEREAS, Partner has assembled large data sets of data associated with de-identified individuals and associated clinical data ("**Clinical Data**");

WHEREAS, Partner desires to: (i) contribute certain of its data (the "**Contributed Data**"), as further described on one or more Contributed Data Addenda (as defined below), to the Platform and (ii) permit the University to provide researchers and others with access to the Contributed Data, subject to the restrictions set forth in this Agreement; and

WHEREAS, the University is willing to accept such Contributed Data.

Appendix III

Joint Controllership according to Art. 26 GDPR

Parties are designated as "joint- controllers" under Art. 26 GDPR.

I. Regulation

The Recipient shall process Contributed Data in accordance with the requirements of Applicable Laws.

Terms and definitions set forth in the Applicable Laws also apply to the interpretation of this Agreement except as otherwise provided

II. Description of joint-processing

Recipient shall process Contributed Data as described in the form in Exhibit A, which will precise:

- Nature and purpose of the processing
- Subject matter and duration of the processing
- Contributed Data processed
- The data subject categories
- Data subjects types

← GDPR Appendix when required

Data contributor agreement

What	Signed by	When
Master Data Contributor Agreement	•Contributing institutions or cooperative group •University of Chicago	Prior to first contribution to the Data Commons (after the consortium has added this group)
Data Contributor Addendum	•Contributing institutions or cooperative group •University of Chicago	Each time a new data set is contributed by the same group, describing •Contributed data •Authorized user terms •Contributed data-specific terms

Data contributor is solely responsible for obtaining all necessary consents and otherwise complying with all Applicable Laws and other restrictions:

- to transmit any Contributed Data to the UChicago
- to permit UChicago to store such Contributed Data as part of the Platform
- to provide Authorized Users access to such Contributed Data
- to permit UChicago to perform its obligations pursuant to this Agreement

Master Data Use Agreement

DATA FOR THE COMMON GOOD
MASTER DATA USE AGREEMENT

This Data for the Common Good Data Use Agreement (this "**Agreement**") is made as of the date of last signature (the "**Effective Date**"), by and between The University of Chicago (the "**University**"), an Illinois non-profit institution of higher education having a place of business at 5801 South Ellis Avenue, Chicago, IL 60638 and _____ **a** _____, _____, _____ ("**Partner**"), each individually a referred to as a "Party" and, together, the "**Parties**").

RECITALS

WHEREAS, the University has created a technology platform (the "**Platform**"), including software, hardware, and other technologies, for storing and harmonizing massive data sets of genomic, electronic medical record, and other information ("**Data for the Common Good**");

WHEREAS, as part of the Platform the University owns and operates a data service that provides authorized researchers and other users with access to such genomic, electronic medical record and other information ("**Contributed Data**") provided by various data contributors (each a "**Data Contributor**");

WHEREAS, Partner desires to permit its researchers to access the Contributed Data, subject to the restrictions set forth in this Agreement; and

WHEREAS, the University is willing to provide such access subject to the terms and conditions set forth in this Agreement.

Appendix 1
Standard Contractual Clauses

Controller to Controller

Parties are designated as "joint- controllers" under Art. 26 GDPR.

The University and the Partner may require the transfer of personal data for which Customer is the data controller for processing outside the European Economic Area ("EEA") or Switzerland. The Standard Contractual Clauses below are an addendum to the Agreement and shall apply to personal data transferred from the EEA or Switzerland to a location outside the EEA or Switzerland that is not in a country recognized by the European Commission as providing an adequate level of protection for personal data or is an organization not covered other appropriate safeguards, such as an approved certification mechanism.

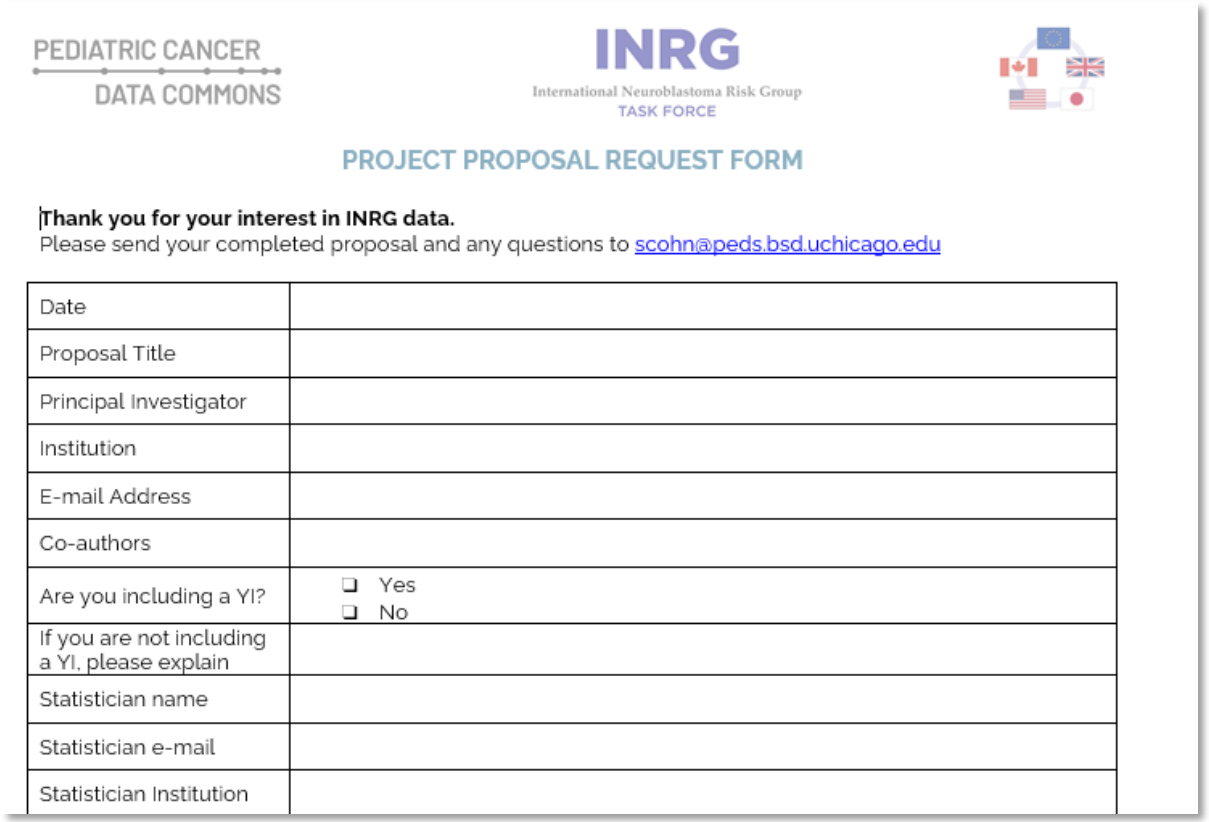
← GDPR Appendix

Governance and you

- Project application review process
- Publication policy
- Acknowledgements paragraph

Project application review process

- Complete the project application form https://inrgdb.org/publication-policy/apply/
- Submit to Sue Cohn
- Application will be reviewed by the INRG Application Review Committee, response will be:
  - Approve
  - Revise and resubmit
  - Decline



PEDIATRIC CANCER DATA COMMONS

INRG
International Neuroblastoma Risk Group
TASK FORCE

PROJECT PROPOSAL REQUEST FORM

Thank you for your interest in INRG data.
Please send your completed proposal and any questions to scohn@peds.bsd.uchicago.edu

Date	
Proposal Title	
Principal Investigator	
Institution	
E-mail Address	
Co-authors	
Are you including a YI?	❑ Yes ❑ No
If you are not including a YI, please explain	
Statistician name	
Statistician e-mail	
Statistician Institution	

Publication policy https://inrgdb.org/publication-policy/

- On behalf of the INRG Executive Committee, the INRG Research Application Review Committee reviews all applications.
- ***Authorship of Abstracts and Manuscripts***: Immediately after an INRG application is approved authorship will be considered by the INRG Executive Committee
- Authorship will be determined by the primary investigators, in alignment with the above rules
- Co-authorship will only be warranted for collaborators who meet the ICJME recommendations for authorship.
- The Co-chairs of INRG are not automatically co-authors, they will be co-authors only if they have been actively and intellectually involved in the project.
- Information: The authors must inform the INRG Executive Committee when an abstract or manuscript arising from the research project is submitted.

Authorship considerations

- Group chairs nominate a **researcher** and a **statistician (prior to data being released)**
- Executive Committee will determine if any **discipline experts** are needed
- Involvement of **young investigators** will be very strongly encouraged
- Nominated individuals MUST be **actively and intellectually** involved in the project to be a co-author.
- For projects with data from only a **single cooperative group**, the **cooperative group chair** will nominate individuals
- For details, please see https://inrgdb.org/publication-policy/

Key messages

- At the direction of the INRG Executive Committee, Data Contributor Agreements are executed prior to bringing data into the INRG Data Commons
- The INRG Application Review Committee on behalf of the INRG Executive Committee determines which projects are approved
- The INRG Executive Committee determines if additional authors will be added to the project team
- A Data Use Agreement is executed prior to providing data to the investigators

Thank you. Have questions? Have data?

Contact

suzi@uchicago.edu

Genomics Committee Update

- ALK data addition to the INRG
- Future genomic data linking beyond ALK
- Links to genomic data – SIOPEN BioPortal

Gudrun Schleiermacher, Matthias Fischer, Meredith Irwin

INRG Genomics Committee

Chair: Gudrun Schleiermacher, Co-Chair: Matthias Fischer, Meredith Irwin

Close collaboration with Sam Volchenboum, chief informatics officer of INRG

COG	Shahab Asgharzadeh, Sharon Diskin, Meredith Irwin, Javed Khan
	advisor : John Maris
GPOH	Matthias Fischer, Angelika Eggert, Johannes Schulte
JNBSG	Takehiko Kamijo, Miki Ohira
SIOPEN	Rosa Noguera, Katleen de Preter,
	Sabine Taschner-Mandl
Dutch group	Jan Molenaar, Jan Koster

Aims of the INRG genomics subcommittee:

- To collaborate for the definition of the format and nomenclature of genomics data to be included in iINRG
- To assist with cataloguing of genomic data for iINRGdb
- To collaborate with the INRG informatics team led by Sam Volchenboum, University of Chicago, to establish links between patient specific phenotype data in iINRGdb, and genomics data stored in other databases
- To contribute to the review of research applications to iINRGdb with genomic specific aims, within the governance rules which are to be defined

Challenges

- **Definition of features** to be directly coded in the INRG data commons, versus information to be given with relevant links to the data
- For data to be included directly in the database, definition of a clear and universally applied **nomenclature**
  - example ALK

- **Quality control** of the data to be transmitted into INRG data commons;
  - Definition of minimal criteria to apply for data to be included in INRG data commons
  - for example : overall genomic profile – requirement of minimal coverage on array CGH analysis to enable a definitive conclusion

- **Definition of the source of the data** (clinical trial database or biology laboratories or public databases), depending on the type of analysis.
  - Who transmits the genomics data to be included directly in INRG data commons?

- For genomics data to be linked to the INRG data commons, definition of a minimal set of criteria to “validate” data prior to linking it up (quality control; check for possible redundancies in patient identification, etc.)

Which genomic data in INRG data commons:

Genetic feature :	Proposition
ALK genomic status	**Data dictionary for INRG data commons validated/ PCDC update**
Other recurrent copy number alterations : Including chr 1p, 1q, 2p, 3p, 4p, 11q and 17q	Data dictionary for INRG data commons to be validated 0=no alteration 1=gain (or loss) depending on the alteration 9=Unknown, pending, cannot be determined
Overall tumor copy number profile Some prospective clinical trials are stratifying treatment according to the overall genomic profile.	Common definition for the nomenclature for the overall genomic profile (INRG biology white paper)
other genetic SVs/SNVs/alterations: TMM/ TERT, ATRX alterations Other genes (e.g. RAS/MAPK, p53)	Currently only studied in a subset of patients in most collaborative groups Data dictionary to be validated

Data dictionary: ALK step 1

ALK genomic copy number status

0= Not amplified

1= Amplified

9= Unknown, not done, no result

ALK rearrangement

0 = no ALK rearrangement

1= ALK rearrangement present

9 = Unknown, not done, no result

ALK mutational status

0 = no ALK mutation present

1= ALK mutation present

9 = Unknown, not done, no result

Type of ALK mutation

p.F1174L. c. ___ > ___

p.R1275L c. ___ > ___

other, specify : c. ___ > ___; p. _____

mutated allele fraction: ___ ___ % (range : 1-100%)

Somatic/germline

somatic mutation (both tumor and germline analyzed, detected in tumor only)

germline mutation

unknown / tumor tissue only analyzed

at diagnosis / at relapse/ other / unknown

% of tumor cells in analyzed sample : _____ % (range : 1 – 100%)

Data dictionary: ALK – step 2

Minor adjustments

Variable Name	Data Type	Variable Description	Permissible Values Term
Molecular Analysis: one row per subject per molecular analysis method per molecular abnormality			
AGE_AT_MOLECULAR_ANALYSIS	Number	Age in Days at Molecular Analysis	
DISEASE_PHASE	Code	Disease Phase	Initial Diagnosis Relapse Progression Refractory
DISEASE_PHASE_NUMBER	Number	Disease Phase Sequence Number	
TUMOR_CLASSIFICATION	Code	Molecular Analysis Classif	Primary Metastatic Unknown Not Reported
MOLECULAR_ANALYSIS_SAMPLE_SOUI	Code	Molecular Analysis Sampl	Blood Bone Marrow Cerebrospinal Fluid (CF Tumor Lymph Node Other Unknown Not Reported
SOURCE_PCT	Code	Percent of Tumor Cells in the Sample (categorical)	<5% 5-20% 21-50% >50%
SOURCE_PCT_NUM	Number	Percent of Tumor Cells in	
BIOLOGICAL_ANALYTE	Code		DNA RNA ctDNA Other
GENE1	String	Gene 1	
MOLECULAR_ABNORMALITY_RESULT	Code	Molecular Abnormality Res	Wild type ~~Mutation~~ Unknown
MUTATION_TYPE	Code	Mutation Type	Somatic Germline Unknown
VARIANT_TYPE	Code	Variant Type	Amplification Rearrangement Unknown
HGVS_DNA	String	HGVS string for mutation description at the DNA level (e.g., c.5096G>A)	
HGVS_PROTEIN	String	HGVS string for mutation description at the protein level (e.g., p.F1174L)	
ALLELIC_RATIO	Number	Allelic Ratio	

alteration

SNV/ mutation

NB and *ALK* data

British Journal of Cancer www.nature.com/bjc

ARTICLE OPEN

Genetics and Genomics

Genomic *ALK* alterations in primary and relapsed neuroblastoma

Carolina Rosswog[1,2,3,4], Jana Fassunke[5], Angela Ernst[4], Birgid Schömig-Markiefka[5], Sabine Merkelbach-Bruse[5], Christoph Bartenhagen[1,2], Maria Cartolano[2], Sandra Ackermann[1,2], Jessica Theissen[1,4], Mirjam Blattner-Johnson[6,7], Barbara Jones[6,7,8], Kathrin Schramm[6,7], Janine Altmüller[9,10,11], Peter Nürnberg[2,9], Monika Ortmann[5], Frank Berthold[4], Martin Peifer[2,12], Reinhard Büttner[5], Frank Westermann[13], Johannes H. Schulte[14], Thorsten Simon[4], Barbara Hero[4] and Matthias Fischer[1,2,4]✉

943 pts, 101 diagnosis-relapse pairs
ALK mutations 10.5% at diagnosis, increased at relapse
ALK amplifications 4.7%

original reports

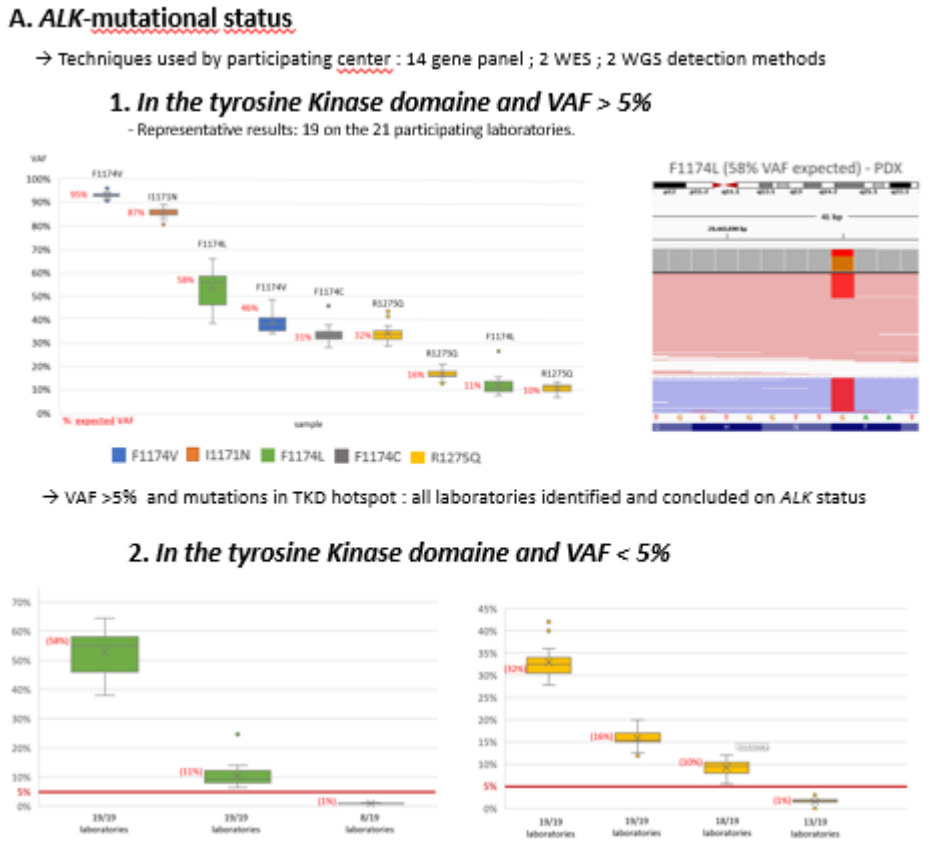
Frequency and Prognostic Impact of *ALK* Amplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1)

Angela Bellini, PhD[1,2,3]; Ulrike Pötschger, PhD[4,5]; Virginie Bernard, PhD[6]; Eve Lapouble, PhD[7]; Sylvain Baulande, PhD[6]; Peter F. Ambros, PhD[8]; Nathalie Auger, PhD[9]; Klaus Beiske, MD, PhD[8]; Marie Bernkopf, PhD[5]; David R. Betts, PhD[10]; Jaydutt Bhalshankar, MSc[1,2,3]; Nick Bown, PhD[11]; Katleen de Preter, PhD[12]; Nathalie Clément, PhD[1,2,3]; Valérie Combaret, PhD[13]; Jaime Font de Mora, PhD[14]; Sally L. George, MD, PhD[15]; Irene Jiménez, MD[1,2,3]; Marta Jeison, PhD[16]; Barbara Marques, PhD[17]; Tommy Martinsson, PhD[18]; Katia Mazzocco, PhD[19]; Martina Morini, PhD[20]; Annick Mühlethaler-Mottet, PhD[21]; Rosa Noguera, MD[22]; Gaelle Pierron, PhD[7]; Maria Rossing, PhD[23]; Sabine Taschner-Mandl, PhD[8]; Nadine Van Roy, PhD[12]; Ales Vicha, PhD[24]; Louis Chesler, MD, PhD[25]; Walentyna Balwierz, MD[26]; Victoria Castel, MD, PhD[27]; Martin Elliott, MD[28]; Per Kogner, MD, PhD[29]; Geneviève Laureys, MD, PhD[30]; Roberto Luksch, MD[31]; Josef Malis, MD[24]; Maja Popovic-Beck, MD[32]; Shifra Ash, MD[33]; Olivier Delattre, MD[2,3,4]; Dominique Valteau-Couanet, MD, PhD[34]; Deborah A. Tweddle, MD, PhD[35]; Ruth Ladenstein, MD, PhD[36,37]; and Gudrun Schleiermacher, MD, PhD[1,2,3]

1092 pts at diagnosis,
ALK mutations 10% clonal, 3,9% subclonal
ALK amplifications 4.5%

Harmonisation : SIOPEN ***ALK*** « Round Robin »

- SOPs in SIOPEN biology reference laboratories
- 21 laboratories
- 14 ALK altered samples
- Harmonised language for reporting



Saint-Charles et al, poster ANR2023

Next step:

Patient Identifier HR NBL1	*MYCN* amplification (yes/no/MD)	technique for *ALK* mutational status (NGS/sanger/ TDS; ND not done)	Presence of an ALK mutation in the tyrosine kinase domain (yes/no; MD)	If *ALK* mutation present: type of mutation	If *ALK* mutation present: MAF	If *ALK* mutation present: MAF in categories (0-5=1; 5-10=2; 10-20=3; >20=4; MD; NA)	If *ALK* mutational present : clonal versus subclonal (clonal >20%/sub-clonal <20%; MD; NA)	*ALK* amplification (yes; no; MD)	Any *ALK* alteration present (presence of either mutation and/or ALK amplification: yes; no alteration or no information on one or both: no)
EUPID1	No	TDS	No	NA	NA	NA	NA	No	No
EUPID2	yes	TDS	No	NA	NA	NA	NA	No	No
EUPID3	yes	TDS	no	NA	NA	NA	NA	no	no
EUPID4	yes	TDS	No	NA	NA	NA	NA	No	No
EUPID5	yes	TDS	No	NA	NA	NA	NA	No	No
EUPID6	No	TDS	yes	I1170T	93,80	4	clonal	No	yes

Bellini, Pötschger et al
1092 patients in HR NBL1

Concrete steps:

-attach EUPID to ALK data record : ☑

-reformat to adapt to INRG/PCDC data dictionary

MOLECULAR_ABNORMALITY_RESULT	Code	Molecular Abnormality Res	Wild type Mutation Unknown
MUTATION_TYPE	Code	Mutation Type	Somatic Germline Unknown
VARIANT_TYPE	Code	Variant Type	Amplification Rearrangement Unknown
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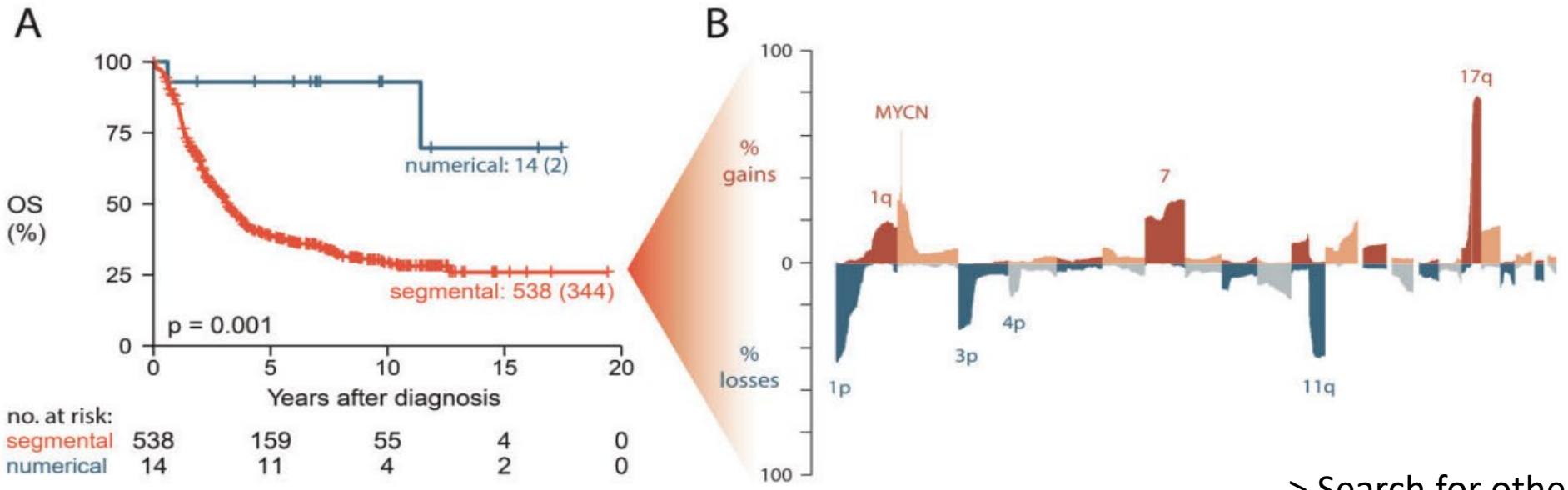
Overall tumor copy number profile Some prospective clinical trials are stratifying treatment according to the overall genomic profile.	Common definition for the nomenclature for the overall genomic profile (INRG biology white paper)
other genetic SVs/SNVs/alterations: TMM/ TERT, ATRX alterations Other genes (e.g. RAS/MAPK, p53)	Currently only studied in a subset of patients in most collaborative groups Data dictionary to be validated

Which new genomic data in INRG data commons: other data

Data type:	Proposition
All other somatic genetic data (NGS techniques; WES, WGS)	
Coding gene expression profiles miRNA and non coding gene expression profiles	
Methylation and other epigenetic profiles	-> catalogue
Genomics of cell free tumor DNA (ctDNA) Peripheral blood Bone marrow	
Germline genomics	

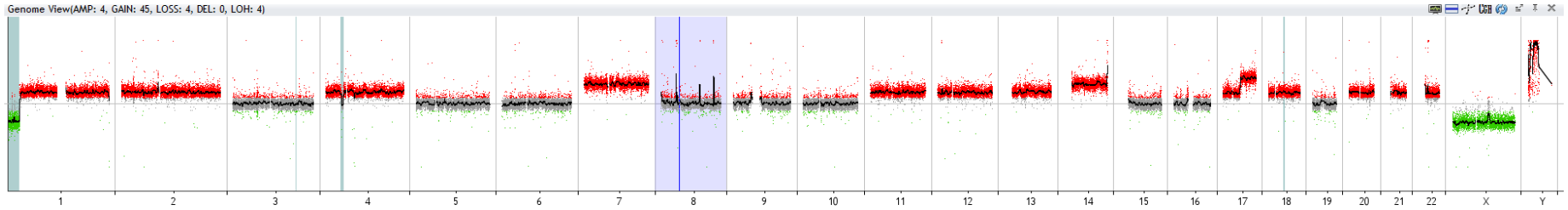
Genomic copy number profiles revisited

Depuydt et al, 2018



98% have SCA/MNA

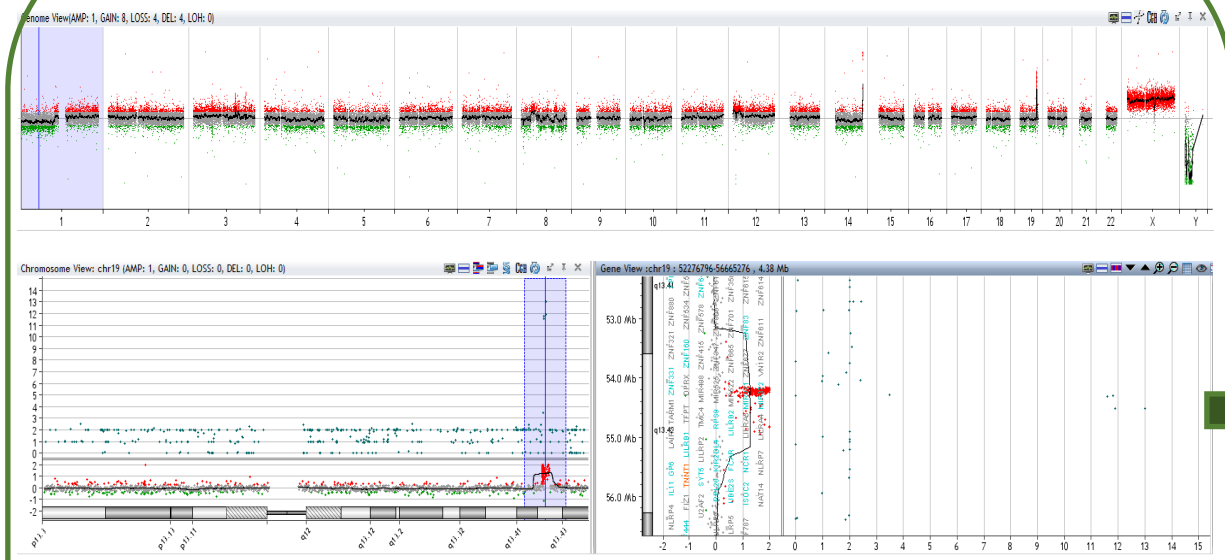
-> Search for other prognostic markers



CGH results :

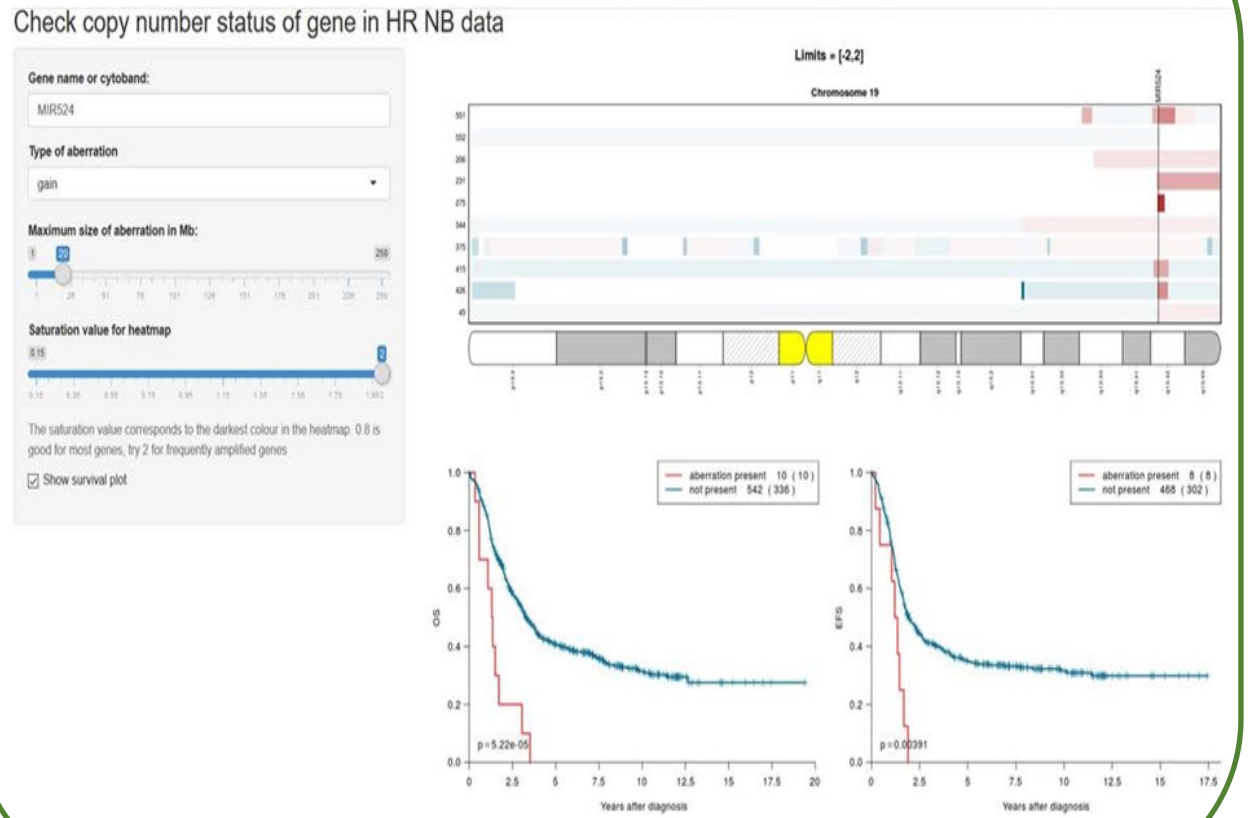
- Over-represented chromosomes : 2 ; 4 ; 7 ; 11 ; 12 ; 13 ; 14 ; 17 ; 18 ; 20 ; 21 ; 22
- Chromosomal imbalances : 1p(1-30,03Mb)- ; 1pq(30,09-249,19Mb)+ ; 17q(42,08-81,15Mb)+
- Amplicons : 8p(36,52-37,11Mb) ; 8q(94,84-95,15Mb) ; 8q(128,52-128,77Mb) including MYC
- MYCN not amplified
- ALK not amplified
- **MYC amplified**

Tools to interrogate prognostic impact of rare CNA events



amplicon on **19q13.42** harboring the **C19MC miRNA cluster** which is typically observed in ETMR (embryonal tumor with multilayered rosettes) : prognostic impact in NB?

ttps://padpuydt.shinyapps.io/check_cn_in_hr_nb/



Integration of annotations directly in INRG?

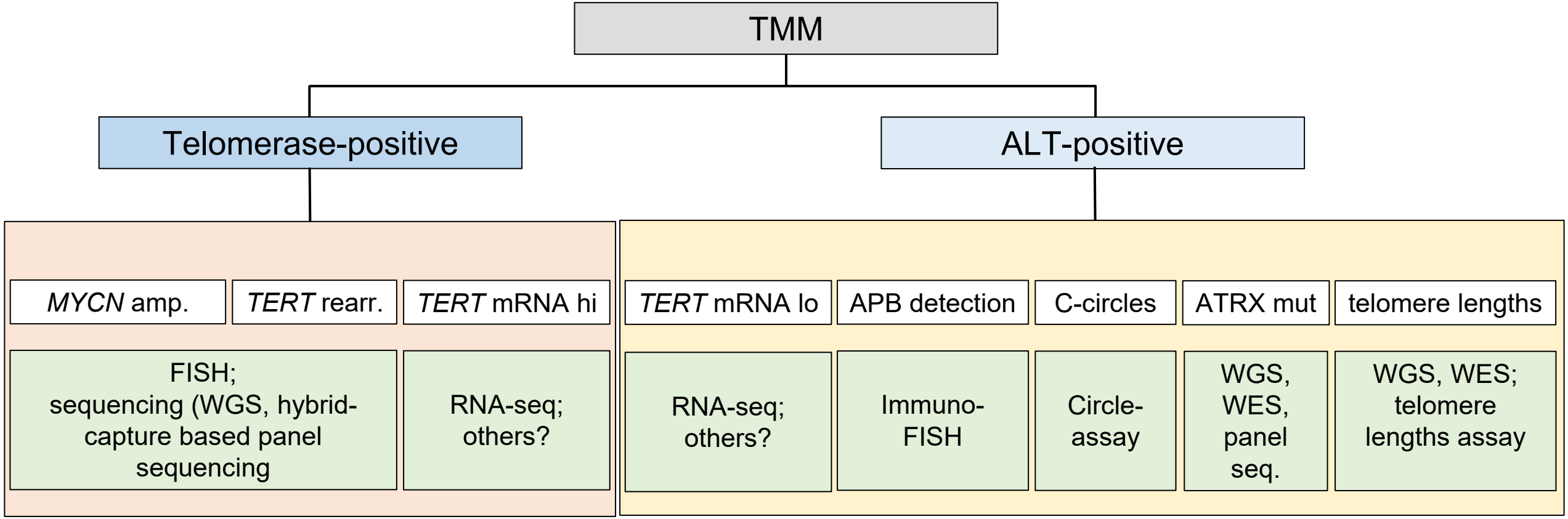
Class	case = patients that die within 1.5 years, controls = patients that survive with at least 5 years follow up, other = not meeting either criterion
Age	age in days
Stage	INSS disease stage
MYCN	1 = MYCN-amplified, 0 = non-MYCN amplified
OStime	overall survival time in days
OS	overall survival, 1 = death from any cause, 0 = censored
EFStime	event-free survival time in days
EFS	event-free survival, 1 = disease progression/relapse/death, 0 = censored
Platform	array platform including resolution. Note: the Agilent custom design used for a subset of samples is enriched for regions important in neuroblastoma (see Kumps et al., 2013, PLoS ONE).
Cohort	treatment cohort, 1 = SIOPEN, 2 = GPOH, 3 = COG, 4 = Japan
Numerical	1 = only whole chromosome aberrations, 0 = segmental aberrations present (can include whole chromosome aberrations)
GEO ID	corresponding GEO ID of sample, if samples were already published on GEO, samples GSM3… from series GSE12494, samples GSM6… from series GSE25771
1p loss, …	1 = aberration present, 0 = not present. Calculation: aberrations larger than 3 Mb and reaching the platform-specific cutoffs for gains and losses were taken into account, whole chromosome aberrations and amplicons are excluded, in case of aberration spanning centromere, is considered as p if part on p is longer and vice versa
	NOTE: this is a computational scoring to get a general image of abundance of aberrations, not aiming to establish a complete genomic profile for individual patients, nor to identify subclonal events (as these would not reach the defined cutoffs)
Amplicon	1 = amplicon other than MYCN present, 0 = no amplicon other than MYCN present, NA = not evaluated because only Agilent arrays are considered for amplicons
Distal 6q loss	1 = distal 6q loss present, 0 = no distal 6q loss present

Number	Name	Class	Source	Age	Stage	MYCN	OStime	OS	EFStime	EFS	Platform	Cohort	Numerical	GEO ID	1p loss	3p loss	4p loss	11q loss	14q loss	1q gain	2p gain	17q gain	Amplicon	Distal 6q loss
1	20979-08845-00373-hg19-Cy	control	VI	551	4	0	6369	0	6369	0	Affymetrix Cytoscan HD 2.6M (SNP)	1	1	NA	0	0	0	0	0	0	0	0	NA	0
2	21220-00476-00308-hg19-Cy	case	VI	3477	4	0	470	1	NA	NA	Affymetrix Cytoscan HD 2.6M (SNP)	1	0	NA	0	0	1	1	0	0	0	1	NA	1
3	21257-01085-00342-hg19-Cy	control	VI	1079	4	0	3680	0	2680	0	Affymetrix Cytoscan HD 2.6M (SNP)	1	0	NA	0	1	1	1	0	0	1	1	NA	0
4	21516-00089-00611-hg19-Cy	case	VI	470	4	1	203	1	NA	NA	Affymetrix Cytoscan HD 2.6M (SNP)	1	0	NA	0	0	0	0	0	0	0	1	NA	0
5	21773-01545-00554-hg19-Cy	control	VI	1435	4	1	5354	0	5354	0	Affymetrix Cytoscan HD 2.6M (SNP)	1	0	NA	1	0	0	0	0	1	0	1	NA	0
6	22332-08652-00529-hg19-Cy	control	VI	517	4	1	6209	0	6209	0	Affymetrix Cytoscan HD 2.6M (SNP)	1	0	NA	1	0	0	0	0	0	0	1	NA	0

N=556 patients

Depuydt et al, JNCI 2018

Determining TMM: consensus is required!



Sensitivity? Specificity? Comparability of methods?

M Fischer

Identification of (molecular) targets at relapse : precision medicine programs

RESEARCH ARTICLE

The European MAPPYACTS Trial: Precision Medicine Program in Pediatric and Adolescent Patients with Recurrent Malignancies

Pablo Berlanga[1], Gaelle Pierron[2], Ludovic Lacroix[3], Mathieu Chicard[4], Tiphaine Adam de Beaumais[5], Antonin Marchais[6], Anne C. Harttrampf[1], Yasmine Iddir[4,7], Alicia Larive[8], Aroa Soriano Fernandez[9], Imene Hezam[1], Cecile Chevassus[8], Virginie Bernard[10], Sophie Cotteret[3], Jean-Yves Scoazec[3], Arnaud Gauthier[11], Samuel Abbou[1], Nadege Corradini[12], Nicolas André[13,14], Isabelle Aerts[15], Estelle Thebaud[16], Michela Casanova[17], Cormac Owens[18], Raquel Hladun-Alvaro[19], Stefan Michiels[8], Olivier Delattre[4,10,15], Gilles Vassal[5], Gudrun Schleiermacher[4,15], and Birgit Geoerger[1,6]

NB 117/829

RESEARCH ARTICLE

The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets

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NB 21/519

ARTICLES
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nature medicine

Check for updates

Whole genome, transcriptome and methylome profiling enhances actionable target discovery in high-risk pediatric cancer

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Original Research

A tailored molecular profiling programme for children with cancer to identify clinically actionable genetic alterations

nature cancer

Article

https://doi.org/10.1038/s43018-022-00474-y

The clinical utility of integrative genomics in childhood cancer extends beyond targetable mutations

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Check for updates

Anita Villani[1,2], Scott Davidson[3,4,19], Nisha Kanwar[4,19], Winnie W. Lo[4,19], Yisu Li[4], Sarah Cohen-Gogo[1], Fabio Fuligni[3], Lisa-Monique Edward[3], Nicholas Light[3,5], Mehdi Layeghifard[3], Ricardo Harripaul[3], Larissa Waldman[6,7], Bailey Gallinger[6,8,9], Federico Comitani[3], Ledia Brunga[3], Reid Hayes[3], Nathaniel D. Anderson[3], Arun K. Ramani[3,10], Kyoko E. Yuki[3], Sasha Blay[3], Brittney Johnstone[6,7], Cara Inglese[8,9], Rawan Hammad[1,11], Catherine Goudie[12,13], Andrew Shuen[3], Jonathan D. Wasserman[2,14], Rosemarie E. Venier[3,6,8], Marianne Eliou[4], Miranda Lorenti[4], Carol Ann Ryan[4], Michael Braga[4], Meagan Gloven-Brown[4], Jianan Han[4], Maria Montero[4], Famida Spatare[4], James A. Whitlock[1,2], Stephen W. Scherer[3,6,15], Kathy Chun[4,16], Martin J. Somerville[4,16], Cynthia Hawkins[4,16], Mohamed Abdelhaleem[4,16], Vijay Ramaswamy[1,2], Gino R. Somers[4,16], Lianna Kyriakopoulou[4,16], Johann Hitzler[1,2,17], Mary Shago[4,16], Daniel A. Morgenstern[1,2], Uri Tabori[1,2], Stephen Meyn[18], Meredith S. Irwin[1,2], David Malkin[1,2,3,20] ✉ & Adam Shlien[3,4,20] ✉

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original reports

Actionable Tumor Alterations and Treatment Protocol Enrollment of Pediatric and Young Adult Patients With Refractory Cancers in the National Cancer Institute–Children's Oncology Group Pediatric MATCH Trial

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Original Research

Implementation of paediatric precision oncology into clinical practice: The Individualized Therapies for Children with cancer program 'iTHER'

Karin P.S. Langenberg [a,*], Michael T. Meister [a,b,1], Jette J. Bakhuizen [a,c,1]

Moving forward

New genomics data is constantly being generated

Importance of considering links to INRG upfront

Incentive for labs/clinical groups to provide « links » to clinical data (GDPR compliant)

SIOPEN BIOPORTAL Task Force 09/09/2022

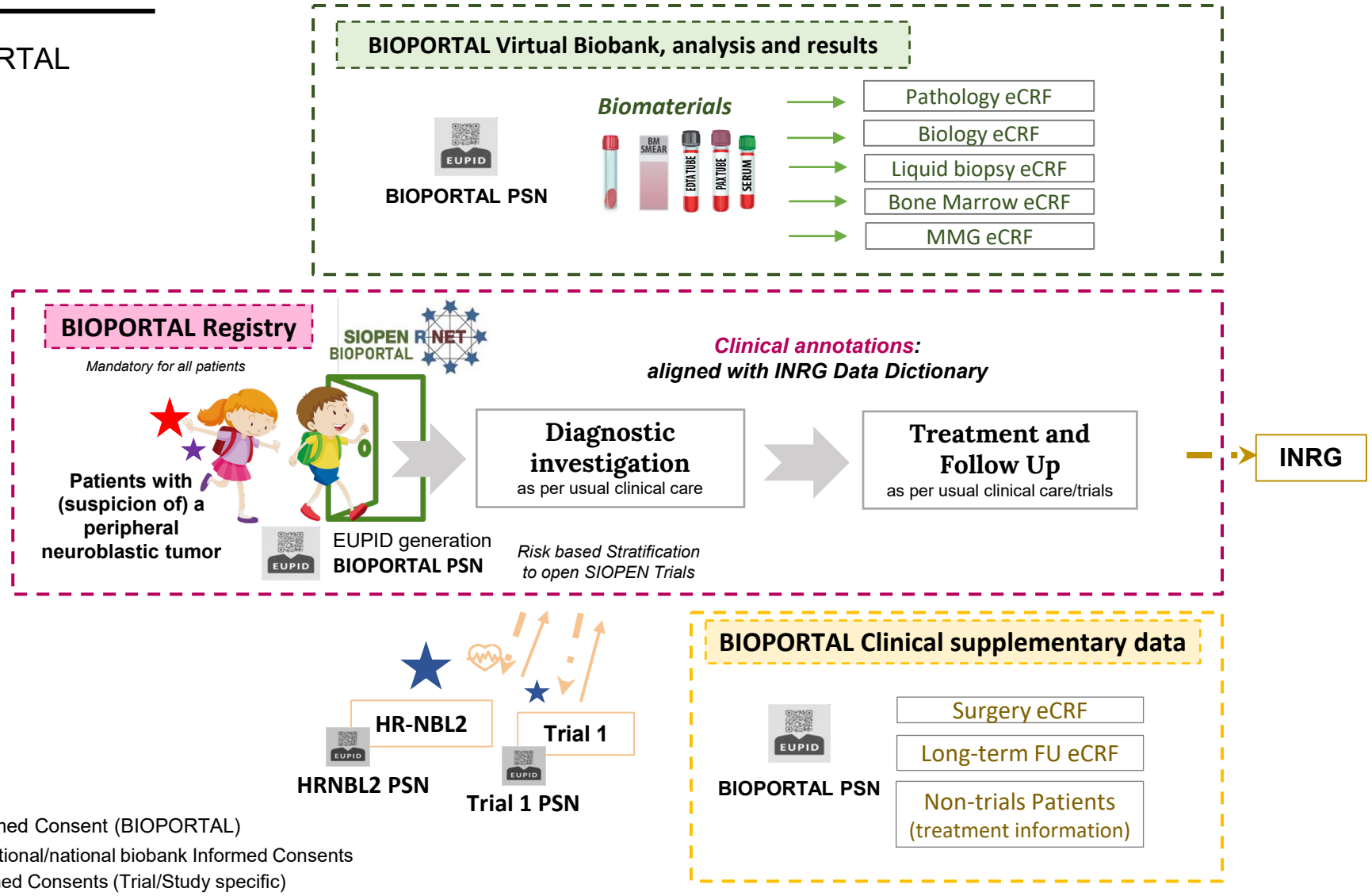
SIOPEN R-NET

BIOPORTAL Task Force
Gudrun Schleiermacher, MD,PhD
Priyanka Devi-Marulkar, PhD, MBA

WORKFLOW

SIOPEN BIOPORTAL

09/09/2022



INRG white paper

- Biomarkers and assays- summary, harmonization
  - Update of Ambros et al ,*BJC* 2009
  - Review published evidence
  - Cut-offs and data collection definitions (align with INRG db dictionary –in progress)
  - Focus on current biomarkers; include section on future
  - No new primary data
- Progress
  - Outline
  - Co-authors sent invitations for sections
  - Target end of May 2023 for drafts

INRG white paper

Section	Assays	Contributors
Tumor samples /storage/ QA and Biobanks	use SIOPEN and COG Bio study protocols/ SOPs	Alanna Church (include pathologists from COG and SIOPEN), Meredith
MYCN status	FISH, SNParray, other (exome)	Rosa Noguera, Shalini Reshmi, Meredith
Copy # (SCA, NCA)	SNP, CGH, exomes, MLPA	Gudrun, Sabine Taschner Deb Tweedle, Ruthann Pfau, Shahab Asgharzadeh
DNA sequencing (ALK, other)	NGS- panels, WGS, Sanger	Matthias, Gudrun, Yael Mosse , Ester Berko , Jan Molenaar
Future: Telomerase Maintenance Mechanisms	TERT expression and fusions- RT-PCR, RNAseq, FISH; ALT- c-circle, APB FISH;	Matthias, Pat Reynolds, Frank Westermann
Other Future- ctDNA, MRD		Lieve Tytgat, Mark Applebaum, Sue Burchill, (Gudrun)

Relapsed patient data & PCDC data dictionary

Julie Park, Wendy London, Lucas Moreno

Task Force Members

- Julie Park (co-chair)
- Lucas Moreno (co-chair)
- Wendy London
- Pablo Berlanga
- Steve Dubois
- Araz Marachelian
- Daniel Morgenstern
- Veronica Moroz
- Arlene Naranjo
- Cormac Owens
- Johannes Schulte
- Grace Holt
- Toby Trahair
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- Ulrike Potschger
- Rachid Abbas
- Angela Ernst
- Satoshi Teramukai
- Takehiko Kamijo
- Miki Ohira
- Ryuichi Sugino
- Gudrun Schleiermacher

Work to date

- Decision on data fields to be collected (first relapse/refractory, treatment assigned, fields from frontline & relapse)
- Alignment with consensus manuscript on relapse/refractory trials (Park Cancer 2022)
- Started process to incorporate the first two relapse trials (ANBL1221 & BEACON)

→ Incorporation of the new fields into the new INRG data dictionary (v4.0)

Data to be added

From frontline trials

- **Type of event** (relapse, SMN, death)
- **Treatment assigned**. Induction regimen, high dose chemo (single/double), anti-GD2, anti-ALK, MIBG, targeted agents
- **Response to frontline induction** (INRC1993 or INRC2017 from now on)
  - Metastastic, primary tumour, bone marrow & overall response

From first relapse trials

- Trial and arm assigned
- Treatment assigned. Chemo, targeted agent (TBD), antiGD2, MIBG therapy, antiALK…
- Disease status (refractory or relapsed)
- Outcomes (time to first event, time to second event, to trial entry)
- Best response on trial (INRC1993/**INRC2017**/RECIST)
  - Overall
  - Primary tumour
  - Metastatic soft tissue & bone
  - Bone marrow response
- MIBG avidity & score

Next steps

- Finalization of transition to data dictionary v4.0 (with PCDC)
- Send the additional fields to INRG statisticians for final feasibility check
- Assign dedicated statistical/programming resources:
  - to extract/reformat new data items for frontline trials (COG ANBL0532, GPOH, SIOPEN HRNBL) and relapse trials (COG ANBL1221, BEACON)
  - further programming from PCDC format to a format amenable to statistical analyses
- Data will be greatly enhanced by genomic/biomarker data from other INRG initiatives
- **Current/Future Projects:**
  - Relapse after MS pattern, Campbell PBC 2023
  - Pattern and predictors of sites of relapse, Vo PBC 2022
  - Re-analysis of relapsed patients' outcomes (as per London JCO 2011), Morgenstern & London, ongoing (approved by INRG).
  - Future projects: once data from relapsed trials & response to frontline therapy is uploaded

INRG Risk Classification 2.0

Mathias Fischer, Meredith Irwin, Wendy London,
Gudrun Schleiermacher, Julie Park, Sue Cohn and Andy Pearson

INRG Risk Classifier v2

- Objectives
  - Rationale and background
  - Methodology/Proposed cohort(s)
  - Biomarkers

INRG Risk Classification v1

VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report

Susan L. Cohn, Andrew D.J. Pearson, Wendy B. London, Tom Monclair, Peter F. Ambros, Garrett M. Brodeur, Andreas Faldum, Barbara Hero, Tomoko Iehara, David Machin, Veronique Mosseri, Thorsten Simon, Alberto Garaventa, Victoria Castel, and Katherine K. Matthay

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

-Published 2009

-Data 1990-2002, N=8,800 patients

-Treatment: pre-immunotherapy, fewer ASCTs

INRG Classifier Risk Classifier Revision v2

- **Rationale:**
  - Adoption/Change from INSS to INRG staging for majority of patients
    - (COG started collecting IDRFs in 2006)
  - **Patients treated with modern era therapy (v1 cohort was pre 2002)**
    - **Pre-immunotherapy, ASCT changes**
  - Improvement in outcomes
  - Inclusion of newer subgroups (eg observation)
  - Potential inclusion and more data for of newer biomarkers
    - Segmental Chromosome Aberrations (SCAs), ALK, TMM

COG Risk Classifier v2

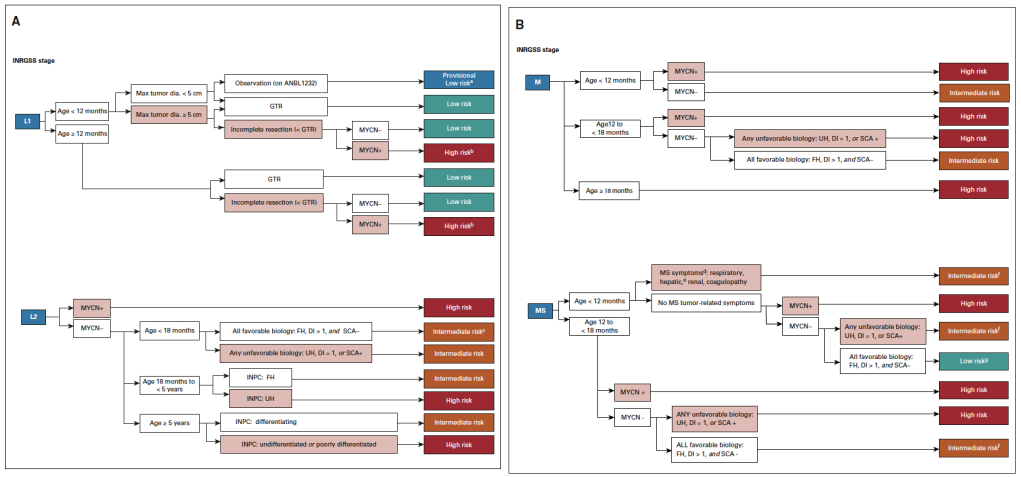
COG ANBL00B1 ~630 patients/year (2006-2016)

COG risk classifier (v1)

Stage	Age	MYCN	Ploidy	INPC Histology	Other	Risk Group
1	any	any	any	any		Low
2A/2B	any	not amp	any	any	resection ≥50%, asymptomatic	Low
2A/2B	any	not amp	any	any	resection ≥ 50%, symptomatic	Intermediate
2A/2B	any	not amp	any	any	resection <50%	Intermediate
2A/2B	any	not amp	any	any	biopsy only	Intermediate
2A/2B	any	amp	any	any	any degree of resection	High
3	<547d	not amp	any	any		Intermediate
3	≥547d	not amp	any	Fav		Intermediate
3	any	amp	any	any		High
3	≥547d	not amp	any	Unfav		High
4	<365d	amp	any	any		High
4	<365d	not amp	any	any		Intermediate
4	365-<547d	amp	any	any		High
4	365-<547d	any	DI=1	any		High
4	365-<547d	any	any	Unfav		High
4	365-<547d	not amp	DI>1	Fav		Intermediate
4	≥547d	any	any	any		High
4S	<365d	not amp	DI>1	Fav	asymptomatic	Low
4S	<365d	not amp	DI=1	any	asymp or symp	Intermediate
4S	<365d	missing	missing	missing	too sick for biopsy	Intermediate
4S	<365d	not amp	any	any	symptomatic	Intermediate
4S	<365d	not amp	any	Unfav	asymp or symp	Intermediate
4S	<365d	amp	any	any	asymp or symp	High

- Harmonize with INRG
- ANBL00B1: 2006-2016
- Map INSS to INRG stages
- New biomarkers (SCAs)
- Modern era patients/Rx
  - Prognostic factors

COG risk classifier (v2), 2021



Naranjo, Irwin…. London, JCO-CCI 2018
Irwin et al, JCO 2021

INRG risk classification, Version 1 (INRGv1)

- Vision of INRGV1 risk classification:
  - Building blocks for trial eligibility and cross-trial international treatment comparisons
- V1 : good job using prognostic factors to assign therapy.
  - Result: prognostic factors and treatment are extremely confounded

INRG risk classification, Version 2 (INRGv2)

Primary Objective:

"Within cohorts of patients homogeneously treated with modern-era therapies, to refine INRGV1, by identification of clinically and statistically distinct neuroblastoma patient subgroups on the basis of outcome, treatment, and existing and/or novel prognostic and/or predictive biomarkers."

Secondary objectives:

"To identify homogeneously treated patient subgroups with poor outcome who could potentially benefit from different therapy (e.g., targeted therapy) of a predictive biomarker."

"To identify homogeneously treated patient subgroups with good outcome who would likely benefit from a reduction of initial therapy."

Methodology

- **Analytic Cohort**
  - Dates
  - Trials (and Biology study)
    - Treatment groups
  - Need data for INRGSS stage to identify loco-regional
- **Endpoint(s)**
- **Statistical methods**

Analytic Cohort(s)

Cooperative group	COG (trials)	COG (bio only)	GPOH	SIOPEN	Japan	St Jude
	8,348	7,487	2,575	4,942	970	198

- >24,000 patients (1990-2022)
- Considerations:
  - What date range to include?
  - Consider impact of therapy
  - Stage data available as INRGSS (vs. INSS)
    - Mainly issue for loco-regional

Methods to create INRGV2

- Proposal: stick with our survival tree approach (Cox PH model with recursive partitioning)
  - allows introduction of expert subjectivity
  - has greater transparency than a multivariable model
  - Investigate use of propensity scores to deal with non-overlapping patient cohorts with known data for a given biomarker

- Primary endpoint: consider change to OS instead of EFS
  - OS captures salvageability
  - OS might improve distinction of low- and intermediate-risk

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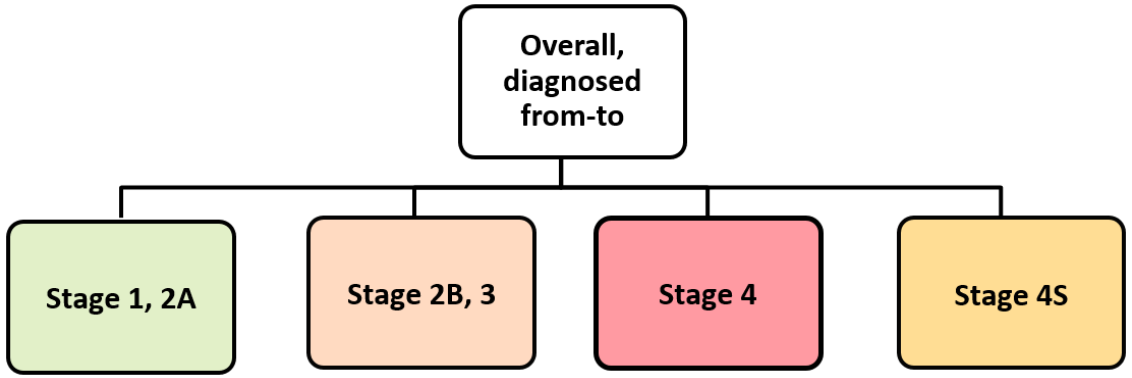

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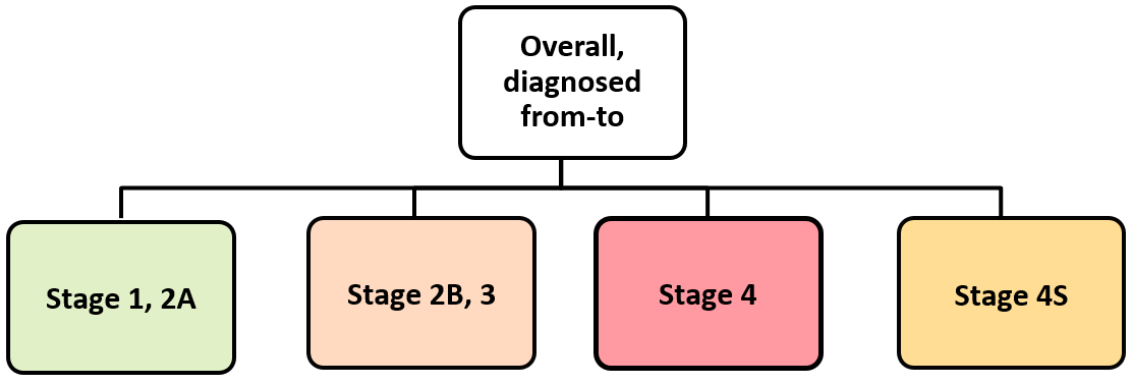

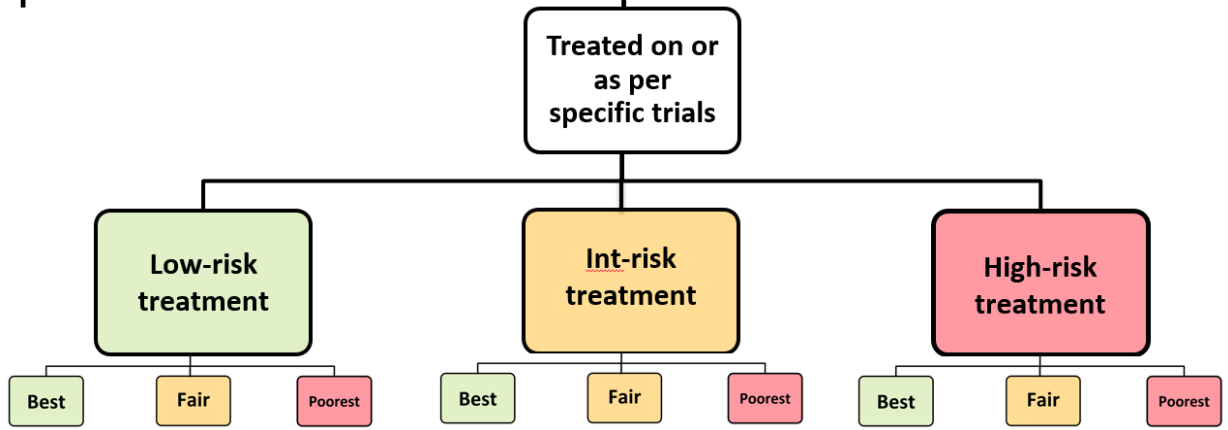

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- Analytic cohort: Don't use data cut-off. Select patients treated on or 'as per' certain trials → homogeneously treated cohorts
- Test modern cohort with "old" methods/risk: Has survival of INRGV1 risk groups and prognostic strength of risk factors changed with modern therapies/approaches?
- Create INRGV2 in two steps: 1) without; and, 2) with new genomic data (How long do we wait for new genomic data?)

Validation of INRGV2

- Randomly partition the data into test and validation sets (what ratio?)
- External validation cohort is unlikely, as the INRG Data Commons contains almost all the trial patients in the world) (high-income countries
- Compare the HR of the biomarker from INRGV2 analysis to the biomarker's published HR (if a different pt cohort).

Risk factors for INRGv2

- Prognostic strength determines variables selected for risk classification (largest hazard ratio)
- Test for 'predictive' factors: prognostic strength differs by treatment
- For this revised classifier we predict the following biomarkers will be available in sufficient #:
  - **ALK** –mutation, amplification status
    - - Gabriella Miller (n=1200); SIOPEN HR-NBL data (n~1000); GPOH (n>700), COG
  - **SCAs** (1p, 11q, 17q, other loci less common, but increasingly available
- Continue to work towards collecting additional biomarkers for INRG data commons
  - Expression data
  - NGS data with focus on genes/ pathways with strongest evidence to data
    - TERT fusions, RNA levels, ALT data - GPOH, COG ANBL0532, TARGET
    - ATRX – COG ANBL0532, St. Jude
    - Other to be determined (including RAS- and p53-pathway genes)

Conclusions

- Next steps:
  - Final discussion of cohort eligibility
    - Incorporate decisions from project of change in outcome over time (Decarolis, London, Pearson, Cohn)
      - Update treatment group classification
      - Classify trials/arms/risk groups into new treatment group classification
  - Finalize biomarkers available
- Updated INRGv2 (2009-2020?) risk classifier will:
  - incorporate pts treated with more modern therapy vs 1990-2002 (INRGv1)
  - Include additional biomarkers

In conclusion

Andy Pearson, Sue Cohn

Closing remarks

- We have come a long way and we still have more to do
- We have built a vibrant international community
- We have amassed data and data commons tools that provide more power for our research community
- Using the INRG data commons, the INRG Task Force has the way to change the way we think and the way we treat our patients with neuroblastoma

We gratefully acknowledge and thank

Mr. Daniel Tierney

US Department
of the Interior