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Commentary

International neuroblastoma risk group consortium: a model of networking for rare cancers

Susan L. Cohn, MD[1,‡], Wendy B. London, PhD[2,‡], Gudrun Schleiermacher, MD, PhD[3], Lucas Moreno, MD, PhD[4], Inge M. Ambros, PhD[5], Peter F. Ambros, PhD[6], Rochelle Bagatell, MD[7,8], Maja Beck Popovic, MD[9], Klaus Hermann Beiske, MD, PhD[10,11], Frank Berthold, MD[12], Suzi Birz, MScMI[13], Hervé J. Brisse, MD[14], Garrett M. Brodeur, MD[7,8], Penelope R. Brock, MD[15], Susan Burchill, PhD[16], Angelika Eggert, MD[17,18], Sara M. Federico, MD[19], Matthias Fischer, PhD[20], Brian T. Furner, MS[13], Barbara Hero, MD[21], David Machin, PhD[22], Takehiko Kamijo, MD[23], Katherine K. Matthay, MD[24], Akira Nakagawara, MD, PhD[25], Arlene Naranjo, PhD[26], Ulrike Pötschger, PhD[27], Dominique Valteau-Couanet, MD[28], Michael T. Watkins, PhD[13], Meredith S. Irwin, MD[29], Samuel L. Volchenboum, MD, PhD[13], Julie R. Park, MD[19], Andrew D.J. Pearson, MD[30,*]

[1]Department of Pediatrics, Comer Children's Hospital and University of Chicago, Chicago, IL, United States
[2]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Division of Hematology and Oncology, Department of Pediatrics, Harvard Medical School, Boston, MA, United States
[3]SIREDO Integrated Pediatric Oncology Center and U1330 Institut national de la santé et de la recherche médicale (INSERM), Institut Curie Research Center, PSL Research University, Institut Curie, Paris, France
[4]Department of Pediatric Oncology, Vall d'Hebron Hospital, Barcelona, Spain
[5]Children's Cancer Research Institute, Vienna, Austria (retired)
[6]Children's Cancer Research Institut, Vienna, Austria (emeritus)
[7]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[8]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States
[9]Faculty of Biology and Medicine, University Hospital CHUV, Lausanne, Switzerland
[10]Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway
[11]Department of Pathology, Oslo University Hospital Radiumhospitalet, Oslo, Norway
[12]Department of Pediatric Oncology and Hematology, University of Cologne, Cologne, Germany (retired)
[13]Department of Pediatrics, Data for the Common Good, University of Chicago, Chicago, IL, United States
[14]Imaging Department, Institut Curie and Université Paris Sciences et Lettres, Paris, France
[15]Department of Paediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom (retired)
[16]Children's Cancer Research Group, Leeds Institute of Medical Research, St James's University Hospital, Leeds, United Kingdom
[17]Department of Pediatric Oncology/Hematology, Charité - Universitätsmedizin, Berlin, Germany
[18]German Cancer Consortium (DKTK), partner site Berlin, and German Cancer Research Center (DKFZ), Heidelberg, Germany
[19]Department of Oncology, St Jude Children's Research Hospital, Memphis, TN, United States
[20]Department of Experimental Pediatric Oncology, University Children's Hospital, Medical Faculty, Center for Molecular Medicine Cologne, University of Cologne, Germany
[21]Department of Pediatric Oncology and Hematology, University Children's Hospital, Medical Faculty University of Cologne, Köln, Germany
[22]University of Leicester, United Kingdom (retired)
[23]Research Institute for Clinical Oncology, Saitama Cancer Center, Saitama, Japan
[24]Department of Pediatrics, University of California San Francisco (UCSF) School of Medicine and UCSF Benioff Children's Hospital, San Francisco, CA, United States
[25]Saga International Carbon Particle Beam Radiation Cancer Therapy Center, Saga HIMAT Foundation, Saga, Japan
[26]Department of Biostatistics, University of Florida Children's Oncology Group Statistics and Data Center, Gainesville, FL, United States
[27]St Anna Children's Cancer Research Institute, Vienna, Austria
[28]Department of Pediatric and Adolescent Oncology, Gustave Roussy Cancer Campus Grand-Paris, Villejuif Cedex, France (retired)
[29]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada
[30]The Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom (retired)

[‡]Author Contributions: Susan L. Cohn and Wendy B. London are co-first authors and are joint first authors.

*Corresponding author: Andrew D.J. Pearson, MD, The Royal Marsden Hospital and The Institute of Cancer Research, London, Downs Rd, Sutton SM2 5PT UK (andy1pearson@btinternet.com).

Abstract

It is critical to share knowledge and harmonize approaches to optimize progress in rare cancers. The International Neuroblastoma Risk Group (INRG) Task Force was formed by the 4 major neuroblastoma cooperative groups in 2004 to achieve this goal. Strategies developed for neuroblastoma are an exemplar for other rare malignancies. Data from an initial cohort of 8800 patients were transferred to the INRG Data Commons, and a data-sharing model was developed. Currently, information on more than 25 000 patients is available to the research community. The INRG staging and risk classification systems have led to harmonized approaches for therapeutic groupings. INRG consensus manuscripts have led to uniform criteria for classifying biological data, evaluating the extent of disease, and defining treatment response. More than 40 INRG research studies have been performed by investigators from around the world, including analyses of rare patients, which would not otherwise be possible. The success of this approach for

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neuroblastoma has been leveraged to create the Pediatric Cancer Data Commons and the Data for the Common Good. Efforts to enrich the INRG Commons with additional genomic and biomarker data, extracted electronic health records, and digital medical images are ongoing. The international networking model developed by the INRG Task Force has led to new research discoveries and progress in neuroblastoma. The approach has now been applied to 16 other cancers and conditions, including rhabdomyosarcoma, germ cell tumor, Lynch syndrome, and cancer predisposition. This framework of international collaboration and data sharing serves as a model for advancing rare adult malignancies.

Introduction

Neuroblastoma is a rare childhood cancer with 5560 patients presenting worldwide in 2021.[1] The clinical behavior of neuroblastoma is diverse, ranging from spontaneous regression and maturation to rapid progression despite intensive multimodality therapy.[2,3] Accordingly, modern treatment is tailored based on a combination of prognostic clinical factors and biomarkers.[4] However, for decades, the criteria defining risk were not uniform. The International Neuroblastoma Risk Group (INRG) Task Force was formed in 2004 to establish a consensus approach for pretreatment risk stratification.[5,6] In addition to achieving this goal, the data collected presented a resource for research studies. Moreover, the Task Force recommended procedures for molecular diagnostic testing[7] and evaluating metastatic disease.[8,9] In this review, we highlight the wide-reaching impact of the Task Force's approach to advance neuroblastoma research and treatment. This networking strategy serves as a model for other pediatric cancers and rare adult malignancies.

The INRG classification system

The INRG Task Force recognized that an international neuroblastoma classification system with consensus definitions of pretreatment risk groups would facilitate comparison of clinical trial results thereby accelerating progress in neuroblastoma treatment. Leaders from the cooperative groups (Children's Oncology Group [COG], International Society of Paediatric Oncology Europe Neuroblastoma Group [SIOPEN], German Paediatric Oncology and Hematology Group, Japanese Advanced Neuroblastoma Study Group, and Japanese Infantile Neuroblastoma Cooperative Study Group) nominated multidisciplinary neuroblastoma investigators to attend 4 conferences, including a meeting sponsored by the William Guy Forbeck Research Foundation in 2005, to define the methodology for the INRG classification (Table S1).

Data used to establish the INRG classification system

De-identified diagnostic patient data (demographic, clinical, biologic, genomic factors) from completed cooperative group clinical trials or biology registries were collected to create the initial INRG cohort of 8800 patients, diagnosed between 1990 and 2002 (Table S2). The analytic objective was to stratify patients into statistically and clinically distinct pretreatment subgroups—very low, low, intermediate, and high risk—according to the most strongly prognostic factors. The biggest challenge was missing data in more than 50% of patients for some risk factors. The primary endpoint was event-free survival, chosen because overall survival (a secondary endpoint) was influenced by postrelapse treatment. Supervised recursive partitioning (survival-tree regression) was performed. Testing each prognostic marker in a univariate Cox proportional hazards regression model of event-free survival,[10] the biomarker with the largest hazard ratio was chosen to create a split or branch in the tree.[11,12] For a given split/branch, if several biomarkers had similarly high hazard ratios, clinical judgment and the likely treatment received played a role in selecting the biomarker for a split/branch. Adjustment for treatment was not made in the statistical models. The resulting INRG classification schema (Version 1 2009) had 16 pretreatment risk groups, defined by stage, age, tumor histological features, differentiation grade, *MYCN* amplification, 11q aberration, and DNA ploidy[5] (Figure 1).

Current implementation of the INRG classification system in the cooperative groups

The Low and Intermediate Risk Neuroblastoma European study (NCT01728155) was the first to implement the INRG staging system.[6] Today, all actively accruing SIOPEN and COG clinical trials have incorporated the INRG staging system to define extent of disease. SIOPEN and COG have also implemented that INRG classifier[5] to assign risk with some modifications.[13] The main challenges to implementing new risk classification systems include (1) synchronization with cooperative group trial activation, as new classifications can only be implemented at the time of new trial development; (2) availability and consistency of biomarker assays across different groups, allowing for inclusion in an international classifier; and (3) lack of access to these biomarkers in countries with limited resources, hampering global implementation.

Building the future INRG classification system

The rationale for a new INRG risk classification system (INRG 2.0) is to refine risk group assignment through comparisons of the prognostic strength of new vs currently used factors. Treatment is known to impact the prognostic strength of markers, and the new analytic cohort will consist of approximately 15 000 patients diagnosed after 2002 who received more modern therapy than the original cohort. Furthermore, most patients in the new cohort were prospectively staged using the INRG staging system. Collection and inclusion of new biomarkers discovered over the last 2 decades such as genomic copy number alterations, single gene alterations (eg, anaplastic lymphoma kinase [ALK]), expression signatures, and markers of telomere maintenance mechanisms[14-20] are high priorities. Challenges to address during the development of INRG 2.0 include the confounding prognostic biomarkers with efficacious treatment(s) and small sample size with available new biomarker data. To make effective use of these new biomarkers and address "missingness," the Task Force will utilize a propensity score approach to address the small sample size of patients with known data for the new biomarkers. Discussions are ongoing regarding whether survival vs event-free survival should be used in this analysis and the magnitude of survival difference (as quantified by the hazard ratio) required to integrate a new prognostic biomarker into the INRG Classification System 2.0. Only the prognostic (not the predictive) ability of a biomarker is used to assign INRG very-low, low-, intermediate-, or high-risk group.

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INRG Stage	Age months	Histological Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pre-treatment 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 m	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥18 m	GNB nodular Neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate*
			Poorly differentiated or Undifferentiated	NA			H Intermediate*
				Amp			N High
M	<18 m			NA		Hyperdiploid	F Low
	<12 m			NA		Diploid	I Intermediate
	12 – <18m			NA		Diploid	J Intermediate
	<18 m			Amp			O High
	≥18 m						P High
MS	<18 m			NA	No		C Very Low
					Yes		Q High
				Amp			R High

Figure 1. The International Neuroblastoma Risk Classification, Version 1 (JCO 2009[5]). INRG Consensus Pretreatment Classification schema. Abbreviations: amp = amplified; EFS = event-free survival; GN = ganglioneuroma; GNB = ganglioneuroblastoma; INRG = International Neuroblastoma Risk Group; NA = not amplified. Copyright 2009 American Society of Clinical Oncology. Reprinted with permission from Wolters Kluwer Health, Inc.[5]

International harmonization and consensus statements

Harmonization of biomarker assays and standardization of criteria for staging and response assessment make neuroblastoma an ideal model to develop an integrated system guiding clinical trial eligibility, implementation, and outcome.

Molecular diagnostics

Neuroblastoma serves as an ideal model for integrating biomarkers into trial eligibility and treatment decisions.[4] In 2009, the INRG Biology Committee published a consensus paper[7] recommending assay standards and technique-specific cutoffs for biomarkers (*MYCN*, 1p, 11q, DNA index). Over the past 15 years, new biomarkers have been identified,[3,15] and the most clinically relevant have been implemented in therapeutic decision making (eg, copy number profiles, *ALK* gene status, expression profiles, and telomere maintenance mechanisms).[13,16-18,21] Diverse assays are used worldwide to assess these genomic alterations. The Biology Committee is developing an updated consensus for current biomarker standards and reporting recommendations. The goal is to align and harmonize result reporting, ensuring comparability between gold standard assays and newer genomic techniques.[22] This includes analyses of tumor tissue and other samples such as circulating tumor DNA. This framework aims to harmonize results for data sharing that can be combined with existing INRG data for analyses and provide guidance to interpret results.

Guidelines for imaging and staging

Imaging of all sites of neuroblastoma is critical for initial staging, evaluating response to therapy, and surveillance. Computed tomography or magnetic resonance imaging is mandatory at diagnosis for imaging the primary tumor and addressing its precise anatomic location, size, and image-defined risk factors.[3,6,23] The legacy International Neuroblastoma Staging System (INSS),[24] revised in 1993,[25] was based on extent of surgical resection at diagnosis with local or locoregional tumors. The INRG staging system was developed for the pretreatment INRG Risk Classification System,[6] which required nonsurgical staging. Image-defined risk factors defined localized tumors as L1, without image-defined risk factors, usually correlating with INSS stage 1 and 2a, and L2 tumors, with 1 or more image-defined risk factors, usually correlating with INSS stage 2b and 3.[13,23,26] Preoperative reanalysis of image-defined risk factors after neoadjuvant chemotherapy has demonstrated its value.[27] Metastatic evaluation must include bilateral bone marrow aspirates and biopsies[9] and ^{123}I-metaiodobenzylguanidine (mIBG) imaging for visualization of metastases[6] or ^{18}F-fluorodeoxyglucose positron emission tomography, a less specific substitute.[28]

Criteria for evaluation of extent of disease by mIBG scans

Neuroblastoma presents with metastatic disease in more than half of patients, with osteomedullary involvement in 70%.[29] 123 I-mIBG provides a sensitive and specific method of assessing tumor in soft tissue and bone sites. A working group developed international consensus guidelines for mIBG scans in staging, response assessment, and surveillance, including validated scoring systems for prognosis and response assessment.[8] These scoring systems, including Curie and SIOPEN scores, were derived from planar images and were subsequently validated for response using data from high-risk SIOPEN and COG protocols.[30-32] The value of single-photon emission computed tomography images, which are more sensitive, in the semiquantitative score and grading the

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uptake in the primary tumor is to be determined. More sensitive imaging methods using positron emission tomography either via the norepinephrine transporter (eg, [(18)F]MFBG PET/CT) or the somatostatin receptor are under investigation.[33-35]

Criteria for detection of minimal disease in the bone marrow

To identify minimal disease in blood, bone marrow, or stem cell preparations, an INRG working group recommended using immunocytology and quantitative reverse transcriptase-polymerase chain reaction to detect disialoganglioside and tyrosine hydroxylase mRNA, respectively.[36] Sampling times, methods for collection, processing, and analysis were also described. In 2017, recommendations for the accurate evaluation of bone marrow disease (aspirates and biopsies) after treatment and antibodies to target antigens including synaptophysin, tyrosine hydroxylase, chromogranin A, and paired-like homeobox 2B were published.[9] Quantitative reverse transcriptase-polymerase chain reaction analyses of both paired-like homeobox 2B and tyrosine hydroxylase more strongly predicted outcome than either alone.[37] These quantitative methods assessing bone marrow involvement were incorporated into the International Neuroblastoma Response Criteria (INRC).[38]

International neuroblastoma response criteria

A National Cancer Institute (NCI)–sponsored Clinical Trials Planning Meeting was held in 2011 to develop international guidelines for revisions to the INRC.[38] To support these guidelines, the assessment of primary tumor response was developed.[39] This work represented an evolution of the INRC with the incorporation of functional imaging using mIBG scintigraphy, the quantitative analysis of marrow involvement, and the recognition that clinically significant minimal bone marrow disease can be assessed. To complement the revised INRC, additional recommendations for collection of patient and tumor characteristics, eligibility criteria, and defined evaluable sites of disease for patients with refractory, progressive, or recurrent high-risk neuroblastoma enrolled onto early phase clinical trials have been made.[40] These international consensus criteria provide a common language for assessment of clinical trial outcomes in patients with high-risk neuroblastoma and an improved ability to understand data across clinical trials. They have also facilitated the development of international collaborative clinical trials.

INRG data and research studies

Recognizing that the data collected to establish the INRG classifier[5] provided an unprecedented resource for the research community, the Task Force developed a data-sharing model. Information about the INRG and the process to request data for research studies was disseminated at national and international meetings. Applications for the INRG data by teams of investigators reflected the collaborative efforts to share the data. Clinical investigators and statisticians, selected by the cooperative group chairs, worked with primary investigators on INRG studies. Twelve studies analyzing data from the original 8800-patient cohort have been published,[41-52] including 4 studies evaluating rare cohorts. In 2013, the INRG data were transferred to the INRG Data Commons at the University of Chicago.[2,53] New patient data have prospectively been added to the Commons by cooperative groups and, more recently, St Jude Children's Research Hospital. Today, data from more than 25 500 patients are available for research studies, and 25 research studies have been published. As shown in Table S3, there are 2 groups of patients contributed by COG: those enrolled only on the COG biology study (INRG Data Commons submission limited to demographic and biological data; $n = 8255$) and patients who were enrolled on a therapeutic clinical trial ($n = 8571$). SIOPEN, GPOH, and the Japanese cooperative groups only contributed data from patients enrolled on clinical trials ($n = 8487$). Thus, similar proportions of patients enrolled on clinical trials were contributed by COG compared with the other cooperative groups. Therefore, the INRG Data Commons is representative of clinical trial international efforts. A recent analysis of COG data in the INRG Data Commons demonstrated that enrollment in a clinical trial was not associated with a superior overall survival and, therefore, indicates that data from the COG biology study is represenative.[54]

Building the INRG Data Commons

The initial dataset has been augmented through the addition of more patients, new data elements, and linkage to datasets in external large repositories (Figure 2). The COG Universal Specimen Identifier (USI), a publicly linkable participant identifier for COG patients, has made it possible to connect INRG clinical data and genomic data housed in the NCI Genomics Data Commons and the Gabriella Miller Kids First Data Resource, enabling research evaluating the clinical significance of genomic variants and expression signatures in neuroblastoma.[55,56] The USI also allows the Commons to determine availability of biospecimens in the COG Biopathology Center biorepository. SIOPEN has linked INRG clinical and genomic data housed in Gene Expression Omnibus.

Data on the initial neuroblastoma cohort in the Commons were harmonized to 68 fields, encompassing a high-level baseline of data. Since initial data contribution, the number of fields has substantially increased to accommodate several strategic areas. Radiographic images and associated radiology reports have been incorporated into the Commons through an NCI-funded Data Integration and Imaging informatics initiative. The Data Integration and Imaging Informatics data include mIBG scans alongside other modalities and redacted radiology reports for 2 COG trials (ANBL1221 NCT01767194 and ANBL12P1 NCT01798004). Fields for *ALK* copy number and mutational status have been developed, and the Commons now houses *ALK* data on 1538 patients. Additional new fields were created for data from trials that included patients with relapsed and refractory disease, and data from patients enrolled on the BEACON Neuroblastoma trial (EudraCT 2012-000072-42) and COG ANBL1221 will be uploaded in the Commons. Work is ongoing to develop new fields for additional clinical data, molecular biomarker data, digital medical images, and extracted electronic health record data.[57] New patient data are deposited in the Commons following publication of the primary clinical trial results. The Commons also receives updated survival data every year for COG patients not enrolled on an active therapeutic trial.

In the European context, there are several large data resources that house genomics data, including the European Genome-phenome Archive and the Genomic Data Infrastructure. Current linkage between the Pediatric Cancer Data Commons (PCDC) data and these resources is constrained by several factors, both technical and regulatory. First, although the European Patient Identity (EUPID) functions in much the same way as the USI and can enable record linkage across studies and resources, its adoption is recent and, therefore, not present in retrospective datasets and is not universal, limiting its impact for linkage across systems. Second, resources like the European Genome-phenome

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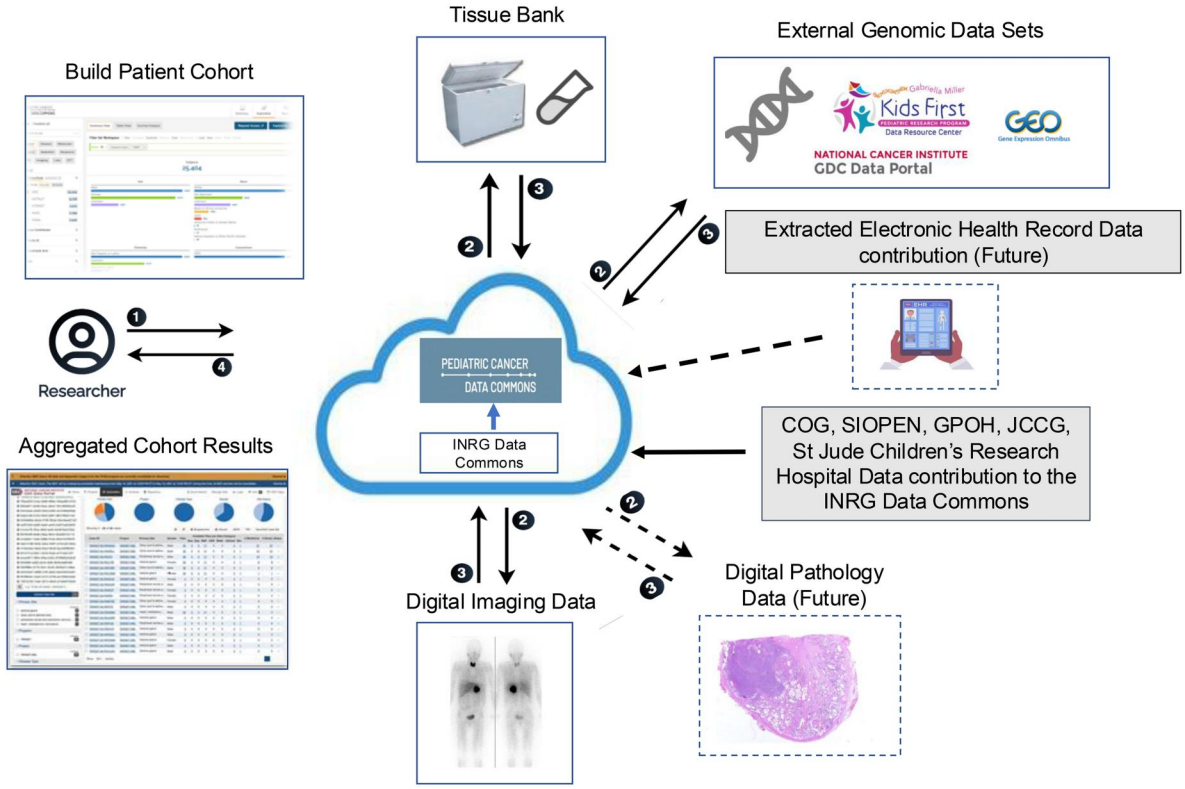


Figure 2. Workflow for cohort discovery using the PCDC data portal and data contribution to the INRG Data Commons. (1) Researcher conducts patient cohort discovery using the PCDC interface. (2) Patient data can be linked to external data sources via common identifier. (3) Matched results are assembled in the PCDC data portal. (4) Aggregated results are presented to researcher. Data on patients enrolled on cooperative group or institutional clinical trials and registries are contributed to the INRG Data Commons, contained in the PCDC. Efforts to contribute extracted electronic health record data to the INRG Data Commons and digital pathology data are ongoing. Abbreviations: COG = Children's Oncology Group; INRC = International Neuroblastoma Risk Group; PCDC = Pediatric Cancer Data Commons; SIOPEN = International Society of Paediatric Oncology Europe Neuroblastoma Group.

Archive do not expose application programming interfaces (APIs) that enable queries supporting cross-system record linkage such as "which patients identified by EUPIDs have available genomics data?" Third, interpretation and implementation of regulations like the General Data Protection Regulation (GDPR) can vary by country and region, making broad agreement on record linkage practices challenging. As a result, some of the data contributor agreements executed between the PCDC and European data contributors have allowed for pseudonymized data, which would be potentially linkable, whereas other data contributor agreements have required fully anonymized data, which, by definition, are not linkable. Although there is reason to be optimistic about both broader use of the EUPID and agreements to share pseudonymized data to support record linkage, currently the ability to do so is constrained by the factors outlined above.

Cohort discovery and visualization tools

The INRG Data Commons is included in the PCDC.[58] The PCDC data portal allows users to browse aggregate-level data to identify potential cohorts of interest and provides in-browser analytic tools for preparatory research, including Kaplan–Meier survival curve generation.

Governance

The INRG Data Commons is built on a foundation of trust that serves as the guiding principle to protect data contributors and research participants. The central element of governance is a Memorandum of Understanding, which affirms the PCDC's commitment to share data and details the members and responsibilities of the INRG Executive Committee. The INRG Task Force adopted a publication policy and continues to refine the policy as contributors and data increase. The policy ensures that representatives from all data contributors have an opportunity to review all project requests and participate in approved projects using data from their studies. The University of Chicago executes legal data contributor and data use agreements to ensure compliance with all applicable regulations.

Strategies for involving new investigators

In 2018, the Strategy Development Committee (SDC) was formed to (1) increase new and young investigator–initiated projects and involvement in ongoing projects, (2) mentor young investigators, and (3) generate ideas for young investigator projects. The members work closely with young investigator cooperative group leads and have disseminated information about INRG studies at international meetings. The SDC also hosts educational hands-on meetings to demonstrate how to initiate INRG projects and use the cohort-discovery tool (Figure S1). There is a young investigator email (mentorship@inrgdb.org) and information at https://inrgdb.org/get-involved/. A prioritized list of new projects, including proposals to re-address previous study questions using more recent data, has been developed. Since initiation of SDC, 7 applications have been approved from young investigators from 7 different countries. Important enablers include mentorship from senior investigators with previous INRG project experience, the cohort discovery tool, training provided to young

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investigators, availability of statisticians, and the INRG publication guidelines recommending young investigator inclusion on all new projects.

INRG research studies

The availability of clinical data on thousands of patients with neuroblastoma has enabled studies evaluating rare patient subsets with unusual clinical presentations[41,43,44,47,50,55,59] (Table 1). Studies have identified markers of survival after relapse[48] and revealed changes in patient outcome during different treatment eras.[49] Analysis of digital mIBG imaging data in the Commons has demonstrated the feasibility of using machine-learning tools to predict response to induction chemotherapy.[60] Linkage of clinical INRG data with external genomic data has shown that high-risk patients with T-cell–inflamed tumors have superior outcome compared with those with non–T-cell–inflamed signatures.[56]

Data for the Common Good

Data for the Common Good (D4CG) is an academic research laboratory at the University of Chicago.[61] The mission of D4CG is to maximize the potential of data to drive discovery and improve human health (https://commons.cri.uchicago.edu/). This requires a 3-tiered approach: governance (legal framework and considerations for data sharing across collaborating institutions), modeling (finding consensus in data representation and ensuring adherence to clinical data standards), and technology (hosting and releasing the data and facilitating hypothesis generation/cohort discovery). The INRG's data were the first in the PCDC—the flagship project of D4CG. Since the first INRG neuroblastoma dataset was contributed, the PCDC has grown to be the world's largest set of harmonized pediatric cancer clinical data. The PCDC network now includes 16 rare cancers, with expertise and data being provided from stakeholders spanning over 40 countries. D4CG initiatives include clinical trial matching and data

Table 1. Rare patient cohort INRG studies

INRG study	Neuroblastoma cohort analyzed	Major findings

Lung metastases in neuroblastoma at initial diagnosis: A report from the International Neuroblastoma Risk Group (INRG) project (DuBois et al., *Pediatr Blood Cancer*, 2008)[41]	Patients with lung metastases at diagnosis	• Lung metastasis associated with
		  • *MYCN* amplification;
		  • elevated LDH levels; and
		  • inferior survival but was not independently predictive of outcome in multivariable analysis.

Significance of *MYCN* amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma (Bagatell et al., *J Clin Oncol.*, 2009)[43]	Patients with *MYCN*-amplified, localized tumors	• Patients with *MYCN*-amplified, low-stage tumors had inferior survival compared with patients with nonamplified localized tumor. • Event-free survival and overall survival were statistically significantly higher for patients with *MYCN*-amplified hyperdiploid vs diploid tumors.
Characteristics and outcome of patients with ganglioneuroblastoma, nodular subtype (Angelini et al., *Eur J Cancer*, 2012)[47]	Patients with ganglioneuroblastoma nodular tumors	• Patients with ganglioneuroblastoma nodular tumors were significantly older than patients diagnosed with neuroblastoma. • Overall survival was excellent for patients aged younger than 18 months, those with stages 1, 2, 3, and 4S tumors, but poor among patients with stage 4 disease.
Neuroblastoma in older children, adolescents and young adults (Mosse et al., *Pediatr Blood Cancer*, 2014)[44]	Patients aged 18 months and older	• Outcome gradually worsening with increasing age at diagnosis. • No optimal age cutoff beyond 18 months. • Following relapse, older patients had prolonged overall survival compared with those aged 18 months and older to younger than 5 years.
Metastatic neuroblastoma confined to distant lymph nodes (stage 4N) predicts outcome in patients with stage 4 disease (Morgenstern et al., *J Clin Oncol.*, 2014)[50]	Patients with stage 4 N	• Event-free survival and overall survival were statistically significantly higher for stage 4N patients compared with stage 4. • Stage 4N patients were more likely to have prognostically favorable characteristics. • Stage 4N disease remained a statistically significant predictor of outcome in multivariable analysis.
Neuroblastoma survivors are at increased risk for second malignancies (Applebaum et al., *Eur J Cancer*, 2017)[55]	Patients who developed second malignant neoplasms	• Ten-year cumulative incidence of second malignant neoplasms among high-risk patients was statistically significantly higher compared with low-risk patients. • High-risk patients had an almost 18-fold higher incidence of second malignant neoplasms compared with age- and sex-matched controls.
Persistence of racial and ethnic disparities in risk and survival for patients with neuroblastoma over two decades (Chennakesavalu et al., *EJC Paediatric Oncology*, 2023)[59]	Racial and ethnic minority patients	• Compared with White patients, Black patients diagnosed 2001-2009 or 2010-2019 had a higher proportion of high-risk disease and worse event-free survival and overall survival. • No significant survival disparities were observed for low- or intermediate-risk patients. • Statistically significantly worse overall survival, but not event-free survival, was observed among Black and Hispanic patients assigned to receive postconsolidation dinutuximab on clinical trials.

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Box 1. Approach for collecting International Neuroblastoma Risk Group (INRG) data for the classifier and research: lessons learned, challenges, and future developments

Approach for collecting INRG data for the classifier and research: lessons learned

- A common data dictionary was established.
- Patient data without protected health information were collected from institutions and cooperative groups from around the world and collated in an INRG database.
- A consensus international risk classifier for treatment stratification was developed based on analysis of the data.
- A data-sharing model was established to provide data to investigators for research studies.
- INRG data were transferred from the flat filed database to a data commons with cohort discovery and visualization tools and an application programming interface to connect to external datasets.
- A governance with a Memorandum of Understanding that affirms the commitment to share data and contracts for data use and data contribution was developed.
- A publication policy that ensures representatives from all data contributors have an opportunity to review project requests and participate in approved projects using data from their studies was created.
- Strategies for mentoring and involving new investigators were developed.
- Manuscripts describing uniform approaches for assessing disease and treatment response were published, consolidating international consensus strategies.

Challenges experienced by the INRG

- Connections between INRG clinical data and external genomic datasets are limited because of lack of common identifiers and access.
- Legal and administrative frameworks from different regions around the world, such as the European General Data Protection Regulation, have restricted sharing of genomic data and updated clinical data.
- Data was missing.
- Detailed information about the therapy patients received was not collected.

Future developments

- Expand data collection for the INRG Data Commons including new molecular biomarkers, digital medical images, and extracted electronic health record data.
- Increase connections between the INRG data and external data in large repositories.
- Build the next-generation INRG classifier (INRG 2.0) with additional prognostic markers to further refine risk group assignment.

commons development in monogenic epilepsy, monogenic diabetes, and social determinants of health. The D4CG seeks to facilitate a "big tent" philosophy of community consensus.

Lessons learned, challenges, and opportunities

Lessons learned by the Task Force during the past 20 years, challenges encountered, and future goals are highlighted in Box 1. Speaking the same language with a common data dictionary, housing the data in a data commons ecosystem, and developing governance policies and contracts with legal experts with knowledge of country-specific data-sharing laws were critical for establishing the INRG international, multidisciplinary collaborative framework for collecting, sharing, and analyzing data to advance research and treatment for children with neuroblastoma. The main error was not anticipating the substantial barrier that GDPR in Europe would pose for collection and linkage of international data and the challenges of incorporating genomic data. Recent and ongoing technological advances, as well as the rising possibilities of complex algorithms and artificial intelligence, have led to an exponential rise of novel information for treatment stratification and more individualized therapeutic options. Simple genomic tumor characterization is evolving toward multiomics characterization of tumor tissue and other patient-derived biological material, focusing not only on tumor-cell specific information but also the tumor microenvironment, immunological, and germline analyses including pharmacogenomics. Liquid biopsies will pave the way toward integration of sequential analyses. Novel treatment strategies will aim to develop more effective local and systemic therapies including immunotherapy strategies. Important advances will also aim to reduce treatment for specific patient subgroups to avoid long-term toxicities. With an increasing number of biomarkers used for treatment stratification and more patient subgroups, expanding the data in the INRG Data Commons will be crucial to enable large-scale data analyses. It will be necessary to implement these comprehensive large-scale data collections while considering legal and administrative frameworks from different regions around the world, such as the GDPR.[62] Future studies evaluating expanded INRG data, enriched with medical records data, could identify new prognostic factors, optimizing risk classification and enabling future individualized treatment strategies.

Conclusions

The INRG classification system has led to consensus risk-based therapeutic groupings. There has been international harmonization of the criteria for classifying biological data and evaluating the extent of disease and treatment response. Furthermore, the INRG data-sharing practices have enabled seminal large cohort research studies. The key drivers in motivating data sharing are the benefit to all cooperative groups of the INRG classifier, the opportunities for any investigator to mine the rich INRG data resource, and the publication policy regarding co-authors from contributor groups. However, perhaps the Task Force's greatest

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achievement has been to increase international and intercontinental collaboration by forming a framework for investigators focused on neuroblastoma. This approach to collaborate and share data has been expanded to other pediatric cancers leading to the creation of the PCDC and the D4CG. The INRG risk classifier and data collection will continue to evolve based on new discoveries and the needs of investigators. Enriching the Commons with digital medical images, extracted electronic health record data, and expanded connections to external datasets with tumor and host molecular information is crucial. The INRG Task Force has demonstrated the great benefits of international collaboration and data sharing. The networking framework developed for neuroblastoma serves as a model approach for advancing other childhood cancers and rare adult malignancies.

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Author contributions

Susan L. Cohn (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Wendy B. London (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Gudrun Schleiermacher (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Lucas Moreno (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Inge M. Ambros (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Peter F. Ambros (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Rochelle Bagatell (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Maja Beck Popovic (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Klaus Hermann Beiske (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Frank Berthold (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Suzi Birz (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Herve J. Brisse (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Garrett M. Brodeur (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Penelope R. Brock (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Susan Burchill (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Angelika Eggert (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Sara M. Federico (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Matthias Fischer (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Brian T. Furner (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Barbara Hero (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), David Machin (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Takehiko Kamijo (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Katherine K. Matthay (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Akira Nakagawara (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Arlene Naranjo (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Ulrike Potschger (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Dominique Valteau-Couanet (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Michael T. Watkins (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Meredith S. Irwin (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Samuel L. Volchenboum (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Julie R. Park (Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), and Andrew D.J. Pearson (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing)

Supplementary material

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Conflicts of interest

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Data availability

This is a commentary, no new scientific data were generated, and all data are within the manuscript. The data are available by request from the INRG Data Commons (https://inrgdb.org).

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Commentary

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