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The international diffuse intrinsic pontine glioma registry: an infrastructure to accelerate collaborative research for an orphan disease

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Abstract

Diffuse intrinsic pontine glioma (DIPG), a rare, often fatal childhood brain tumor, remains a major therapeutic challenge. In 2012, investigators, funded by the DIPG Collaborative (a philanthropic partnership among 29 private foundations), launched the International DIPG Registry (IDIPGR) to advance understanding of DIPG. Comprised of comprehensive de identified but linked clinical, imaging, histopathological, and genomic repositories, the IDIPGR uses standardized case report forms for uniform data collection; serial imaging and histopathology are centrally reviewed by IDIPGR neuro-radiologists and neuro-pathologists, respectively. Tissue and genomic data, and cell cultures derived from autopsies coordinated by the IDIPGR are available to investigators for studies approved by the Scientific Advisory Committee. From April 2012 to December 2016, 670 patients diagnosed with DIPG have been enrolled from 55 participating institutions in the US, Canada, Australia and New Zealand. The radiology repository contains 3558 studies from 448 patients. The pathology repository contains tissue on 81 patients with another 98 samples available for submission. Fresh DIPG tissue from seven autopsies has been sent to investigators to develop primary cell cultures. The bioinformaticsrepository contains next-generation sequencing data on 66 tumors. Nine projects using data/tissue from the IDIPGR by 13 principle investigators from

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around the world are now underway. The IDIPGR, a successful alliance among philanthropic agencies and investigators, has developed and maintained a highly collaborative, hypothesis-driven research infrastructure for interdisciplinary and translational projects in DIPG to improve diagnosis, response assessment, treatment and outcome for patients

Keywords

Brain tumor; Diffuse intrinsic pontine glioma; Registry

Background

Diffuse intrinsic pontine glioma (DIPG) is an aggressive childhood brainstem tumor with a dismal prognosis. [1, 2] The diagnosis of DIPG has, hitherto, been based on imaging and clinical findings. The reluctance to conduct brainstem biopsies, a paradigm which has recently been challenged, [3–6] long hindered understanding of this fatal disease. Radiation therapy prolongs survival by only 2–3 months and remains the standard of care,[7] while chemotherapy has proven ineffective [8].

In 2012, next-generation sequencing studies using autopsy and some biopsy tissue elucidated the genomic landscape of DIPG [9, 10]. Despite these discoveries, DIPG research remains challenging, due to the tumor's relative rarity, the limited power of single-institution or small-scale studies, presence of inter- and intra-tumoral heterogeneity, and a lack of understanding of mechanisms of therapy resistance [11, 12].

In 2011, physicians, scientists, and patient advocacy groups met at the first International DIPG Symposium, and advocated for the establishment of a focused international effort to develop uniform criteria for diagnosis, classification, disease assessment, and to study DIPG biology and therapeutic strategies through the development of in vitro and in vivo models. In 2012, with financial support from the DIPG Collaborative, a philanthropic partnership which now includes 29 private foundations, and international investigators banded together to establish the International DIPG Registry (IDIPGR) and a parallel European SIOPE Registry. The IDIPGR continues to expand and maintains a highly-collaborative, hypothesis-driven research infrastructure to support a wide spectrum of interdisciplinary and translational projects in DIPG. Here, we report the logistical challenges, pitfalls, and successes of developing this registry, which we hope will serve as a model for other orphan disease registries.

Methods

Structure of the DIPG registry

The IDIPGR consists of the Operations Center (OC), a Steering Committee (SC), Scientific Advisory Committee (SAC), Research Ethics Panel, Quality Assurance Group, and collaborating institutions. An organizational chart is provided in Fig. 1.

Cincinnati Children's Hospital Medical Center (CCHMC) is the Operations Center and repository for all clinical and neuroimaging data and pathology specimens from

collaborating institutions. Tissue from Canada is stored in a separate biobank at The Hospital for Sick Children.

The SC serves as the governing board, providing oversight of the IDIPGR. SC consists of experts in the field of DIPG, and one patient/family representative. Non-voting members include two registry staff members: the IDIPGR project coordinator and the regulatory and ethics officer. The SAC consists of senior basic, translational and clinical experts in DIPG research, including two external reviewers, and is responsible for evaluating and prioritizing submitted research proposals. The Registry's policies and detailed organizational information are outlined in the DIPG Registry and Repository constitution. The SC meets semi-annually by teleconference or in-person. Biannually, an in-person meeting of the SC and SAC is conducted.

Registry website (http://www.dipgregistry.org)

A website, http://www.dipgregistry.org, representing the International and SIOPE DIPG Registries, serves as a direct link between families/medical professionals and registry personnel, providing a list of registry-affiliated oncologists around the world, clinical trials and research updates, investigator profiles and educational information about DIPG, palliative care and autopsy. The website also facilitates consultations or self-referrals to the registries. Information on the website is updated monthly by the registry coordinators and the Principle Investigator to reflect the most up-to-date information available.

Recruitment and data collection

There are two principal mechanisms for identification and recruitment of participants (a) self-referral by patients and their families via the DIPG Registry website or (b) procurement of deceased patient records from participating institutions, after Institutional Review Board (IRB) approval or non-humansubjects determination. All patients, regardless of age, with an institutional diagnosis of DIPG are eligible for enrolment in the International DIPG Registry.

Self-referral—Prospective patients and their families may self-refer by contacting the IDIPGR office directly at http://www.dipgregistry.org or by phone. Physicians and medical staff may also provide prospective patients with the IDIPGR brochure. Once self-referral is made, registry staff contact the patient or parent/guardian (for minor patients) to obtain consent for registry participation. When possible, written assent to participate is also obtained from patients ≥11 years old. Once written consent has been obtained, registry staff work directly with the treating medical team to collect information, imaging, and tissue samples, if available.

Parents/legal guardians of deceased patients may also self-refer to the IDIPGR and grant registry personnel access to the decedent's medical information by signing a HIPAA release form.

Institutional referral—Each collaborating institution is responsible for providing source documentation for registry personnel to abstract data from medical records of their DIPG patients. The IDIPGR coordinator works with a designee from each collaborating institution

to obtain source documentation, including medical records, radiographic imaging on CD-ROM, available pathological material. Data are abstracted from the medical record by the IDIPGR coordinator, who is solely responsible for completing case report forms (CRF) and entering into the Registry database. If release of individually identifiable medical records of deceased patients is not permissible from a collaborating institution, the CRFs may be completed on site using a data abstraction guide developed to ensure uniform interpretations and collection of variables/data points. Radiographic images submitted on CD-ROM are de-identified, uploaded, and stored in the research picture archiving and communication systems (PACS) system housed at CCHMC. All paraffin blocks/slides or frozen tissue for central pathology review and/or future research are de-identified and sent to CCHMC, or The Hospital for Sick Children (HSC) for Canadian sites.

Collaborating institutions can inform prospective, living patients about the IDIPGR, either verbally or by providing IRB-approved brochures. Interested patients or families may then self-refer to the IDIPGR for enrolment. For international sites, local staff may obtain informed consent per institutional and country policies using site-specific consent forms approved by their ethics committee based on the IRB-approved consent template provided by the IDIPGR.

Data inclusion moratorium—Investigators at each institution may elect to place a 1-year moratorium on inclusion of their data (clinical, imaging, pathology/tissue) as part of any research or publications from the IDIPGR. The moratorium begins when the first patient records are accessed. The collaborating institution may request an extension of the moratorium if needed for projected publication of institutional data donated to the registry.

Regulatory strategies

Institutions in the United States—The IRB approval for the IDIPGR is maintained at the CCHMC operations center. According to HIPAA regulation 45 CFR 164.512, the request for and release of decedent personal health information (PHI) for research purposes is permitted and HIPAA requirements are fulfilled as part of a decedent PHI request form (available on request). All PHI received by the IDIPGR is coded. The IDIPGR research personnel function as the honest brokers ensuring that no identifying information is released to researchers. Many collaborating institutions have consulted with their IRB and acted in accordance with institutional policy. Some of the submissions to IRBs have included the decedent request form and brief explanation of use of PHI through completion of their IRB application. Most IRBs have granted a non-human subjects research determination and grant HIPAA waivers. Since the informed consent is obtained by Registry staff, institutions should not need to obtain full IRB approval.

International institutions—For international sites, local staff may obtain informed consent of living participants according to institutional and country policies using a site-specific consent form approved by their Research Ethics Board. Privacy laws do not typically permit release of PHI, requiring most international sites to submit data on CRFs and maintain source documents, including consent forms, on-site.

Protocols and procedures

Clinical database—Demographic, clinical, treatment, and outcome data are abstracted from existing clinical records, pathology and imaging reports by the two IDIPGR coordinators using standardized case report forms (CRFs). Clinical CRFs have been developed in conjunction with investigators from the SIOPE DIPG Registry for collection of identical data that would enable facile collaboration. Data are coded and stored in Oncore, a clinical trials management software system. Abstracted data elements include: demographics, diagnosis, date of diagnosis, imaging, signs and symptoms and physical exam at diagnosis, treatment, response evaluations, central pathology review characteristics, central imaging review characteristics, and molecular profile. All source documentation is maintained at the operations center in patient binders for access for future studies and quality assurance. Annually, members of the oncology quality assurance team at CCHMC review 10% of all patient data for completion and accuracy and provide formal reports regarding their findings.

Imaging repository—All available imaging on each enrolled subject is submitted to the central imaging repository at the OC on CD, and loaded onto a dedicated, research-only, picture archiving and communication system (PACS). Data are reviewed prior to placement in the research PACS to ensure all patient identifiers are removed from images, and a study ID generated, linkable to the subject identity only by DIPG Registry staff.

MR imaging is reviewed by the study primary neuroradiologists (BVJ, JLL) at diagnosis, post-radiation, best response to each therapy, and at the time of progression with each therapeutic intervention. An international central neuroimaging review panel is available as needed to define/ cross validate evaluation parameters. All cases are reviewed by both primary neuroradiologists and consensus opinions utilized in cases in which there is disagreement. The primary goal of central review is to confirm the imaging diagnosis of DIPG, provide measurements of tumor extent, and basic descriptive assessments of imaging appearance. Each case is evaluated and classified as: (1) typical DIPG imaging appearance, (2) some atypical features, but likely DIPG, and (3) unlikely DIPG, other diagnosis suspected. A tumor is considered a typical DIPG if it arises from the pons, exhibits a diffuse pattern of involvement, and involves ≥50% of the pons at diagnosis. Each case classified as unlikely DIPG by consensus opinion of both neuroradiologists will be designated as such in the IDIPGR database and excluded from analyses. Imaging features suggestive of an alternative diagnosis may include: tumor not arising from the pons (medulla or midbrain origin), a primarily focal exophytic morphology, very sharply defined margins, or marked diffusion restriction of the majority of the lesion. Cases in which there is secondary brainstem involvement by a tumor centered in the thalami, cerebral hemispheres, or cerebellar hemispheres are excluded. Only tumors that appear to originate in the brainstem are included in the registry. After consensus review, MR imaging data will be entered into the registry database for use by approved research studies.

Biospecimen repository—If biopsy or autopsy materials are available, submission is requested at the time of enrolment. The Division of Pathology at CCHMC archives and digitizes all pathology cases using Biomaterial Tracking and Management Research (BTM).

De-identified pathology images and reports are centrally reviewed by the study primary neuropathologists at CCHMC (CF) or HSC (CH) in Canada for Canadian patients. Frozen specimens originating from referring institutions in Canada are sent to HSC for long-term storage. Frozen specimens originating from all other institutions around the world are stored at CCHMC.

Genomics repository—Molecular data, including genome-wide DNA copy number, karyotyping, expression profiling (mRNA and miRNA), methylation analysis, and DNA or RNA sequencing is collated into an International DIPG Bioinformatics Repository. Both original raw data and processed files are requested, and can be uploaded along with annotation files to a secure ftp site. For autopsy tissue that has been donated to the IDIPGR, if molecular/genomics testing have not been conducted or are not available, next generation sequencing consisting of whole genome sequencing, RNA sequencing, paid for through IDIPGR funds are being conducted by core facilities or commercial vendors and deidentified, raw data are then deposited in the genomics repository. Investigators who have donated tissue to the IDIPGR can receive raw NGS data generated from specimens submitted to the IDIPGR.

Researchers are invited to contribute any relevant data in addition to that which may be found in the published literature or databases. Investigators known to have unpublished data are approached to contribute pre-publication. Data may be held in this context in a non-public (password-controlled) area. Data generated from biospecimens contributed to the Registry are also incorporated into the repository in a prospective manner.

Sample identifiers are linked to those in the IDIPGR to allow correlation of molecular and clinico-pathological variables. The IDIPGR staff maintain the link. The repository is held at the genomic data facility in the Bioinformatics Division at CCHMC. By combining these data, we intend to generate a comprehensive, accessible database of the molecular profiles of DIPG for the academic community.

Results

Current status

The IDIPGR has enrolled 670 patients, from 55 collaborating institutions in the United States, Canada, and Australia, and New Zealand with an additional 500 patients committed from 25 other sites in these countries, which are at various points in their approval and data submission processes. Data have been abstracted on all enrolled patients. A summary of available clinical, radiographic, genomics data and biospecimens are summarized in Table 1. Currently, 81 tumor specimens are housed in the pathology biorepository with approximately 98 more specimens committed for sub-mission on enrolled patients. Next Generation Sequencing data from tumor and germline are currently available on 66 patients.

Registry research studies

Nine studies, from various investigators in the US, Canada and Europe have been approved by the SAC utilizing registry resources. Several of these studies have external funding,

including funding from the DIPG Collaborative. The studies are in various stages of conduct and analysis and include:

1. Joint International and SIOP-E DIPG Registry long-term survivor project. To describe the clinical, radiographic, pathological and biologic characteristics of long-term survivors with DIPG and correlate key variables with outcome.
2. An epidemiological study to determine incidence patterns of DIPG in North America. Our Canadian collaborators have presented the Canadian epidemiology data and we plan to expand this study to examine incidence of DIPG in other countries.
3. External validation of the Survival Prediction Model for Diffuse intrinsic pontine glioma. A survival prediction model, developed within a cohort of European DIPG patients is being validated using the International DIPG Registry cohort.
4. DIPG: Contemporary Survival Endpoints. A study examining reported survival endpoints in order to better define progression and aid the development of objective measures for robust clinical trials.
5. Establishment of in vitro and in vivo Models. Fresh tissues from autopsy are being shared to establish in vitro and in vivo models for drug screening.
6. Comprehensive Molecular-Based Cross-Species Comparison of DIPG Biology examines overlapping genetic alterations between mouse and human DIPG, allowing for identification of novel subtype-specific oncogenic pathways.
7. Imaging Phenotype and Survival in DIPG. This proposal seeks to identify specific imaging features at baseline that significantly correlate with overall survival and assess multi-reader agreement and concordance with imaging features of the DIPG registry.
8. DIPG as a complication of Medulloblastoma Therapy. This proposal seeks to study the incidence of brainstem glioma as a complication of therapy for medulloblastoma.
9. Radiogenomic Evaluation in Diffuse Intrinsic Pontine Glioma.

Consultations, second opinions and education via (http://www.dipgregistry.org)

Since the website launched in April 2012, over 218,000 people have visited the site from 183 countries. Dipgregistry.org is now an established centralized resource for patients, families and physicians around the world in search of up-to-date information regarding DIPG including DIPG education, currently open clinical trials, latest literature and research developments, access to an international network of oncologists for consultations. To date, 283 consultations have been provided to patients, families and physicians around the world. These consultations are provided by DIPG Registry participating investigators from around the world depending on the origin of the consult requests. Since the IDIPGR is housed at CCHMC, initial review of consult requests is conducted by Registry Coordinators, IDIPGR PI (MF) and triaged accordingly. Consultation by the IDIPGR PI, review of imaging by IDIPGR neuroradiologists (JL and BVJ) is provided free of charge to patient.

Tissue procurement efforts

Recently, greater acceptance of the safety of DIPG biopsy, [3–5, 13] development of autopsy-based protocols, [14–16] and next generation sequencing (NGS) efforts have advanced our understanding of the molecular basis of DIPG, identifying aberrations such as the highly recurrent histone mutations (*H3F3A* or *HIST1H3B/C/I*) [9, 10, 17] and *ACVR1* [18–20]. The IDIPGR repository contains tissue specimens on 81 enrolled patients and NGS data on 66 enrolled patients. Registry funding supports conduct of comprehensive whole genome sequencing, RNA sequencing and 850 K methylation array on all available specimens. Spurred on by the explosion of knowledge about this disease through tissue donations, many patients and families have contacted the IDIPGR to assist in organizing autopsies at participating institutions to donate tissue for research to the Registry. Registry staff have organized 24 autopsy donations to the Registry. Tumor specimens from seven patients have been sent to registry investigators to establish patient-derived cell culture and xenograft models for drug screening and other studies. To date, one cell culture has been successfully established.

Funding strategies

One of the major obstacles to establishing and maintaining registries for rare cancers is the lack of sustained funding opportunities to support such efforts. The IDIPGR has been generously supported by the DIPG Collaborative from 2012 to 2018 for a total of $1.4 million. The DIPG Collaborative also fully funds SIOPE DIPG Registry. The DIPG Collaborative and IDIPGR formed in parallel in 2012, when the need for collaborative research and funding became evident. The DIPG Collaborative is comprised of 29 foundations supporting DIPG research world-wide. The growth of the DIPG Collaborative has been vital to sustaining the International DIPG Registry and this relationship remains an integral part of maintaining and improving research for this orphan disease.

Discussion

In a rare orphan disease like DIPG, scientific progress and development of effective therapies have often been impeded by the lack of large scale, well-annotated, clinico-radiologic and biologic data available about the disease. The IDIPGR provides the infrastructure for acquisition of biological specimens, imaging, and correlative clinical and genomics data to facilitate basic and translational research studies in this rare disease. The increased availability and centralization of data and specimens from DIPG patients, and the effective collaboration among clinical, translational and basic researchers as well as philanthropic foundations represent a welcome paradigm shift in DIPG research in which data and tumor specimens are no longer rate-limiting resources.

The highly collaborative, international, hypothesisdriven and hypothesis-generating research infrastructure of the IDIPGR can support a wide spectrum of interdisciplinary and translational research that will be critical to improving diagnosis, classification, response assessment and treatment options for this vulnerable population. Centralized, standardized and linked pathologic, clinical, genomics and radiological data enable investigators to

develop new approaches to DIPG diagnosis, classification and response assessment that will inform the development and conduct of future clinical trials.

Tissue acquisition from autopsies on the DIPG Registry has led to critical collaborations among basic science and translational investigators to develop primary cell cultures and xenografts to support assay development and high throughput screening of novel agents for the treatment of DIPG. Keys to these discovery efforts are the ability to integrate analysis of relevant genes and pathways and assess potential biomarkers. Comprehensive genomics and functional proteomics efforts are already on the way through international collaborations by scientists utilizing the IDIPGR infrastructure and biorepository. Promising drugs can then be tested in the animal models and cell lines developed from registry tissue and provide the rationale for scientifically-sound clinical trials to improve outcome. Dipgregistry.org provides a platform to disseminate results and aid recruitment of patients for future studies.

Data requests and research proposals

Data and samples from the registry are available to researchers affiliated with the registry and to external researchers world-wide. Research proposals (application available on the DIPG registry website) from participating investigators are evaluated by the SAC for scientific merit, prioritization, feasibility and appropriate use of resources before approval. If approved, de-identified clinical, radiographic, pathologic, genomic data and biological specimens may be released to investigators. IDIPGR statistician and bioinformaticians perform and provide detailed analyses to the investigators for manuscript preparation.

Future directions

The ready availability of the IDIPGR resources to external investigators has promoted robust, hypothesis-driven international and interdisciplinary collaborative research on all aspects of DIPG. Areas of focus for the IDIPGR are: to prospectively enrol patients diagnosed with DIPG, expand participation to other regions around the world, develop supplemental web-based educational materials for families and medical teams to improve awareness and treatment of DIPG. Ultimately, the IDIPGR's extensive and robust infrastructure for collaborative research may serve as a platform to develop and conduct innovative, multi-institutional trials to improve the outcome for patients with DIPG.

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References

1. Hargrave D, Bartels U, Bouffet E (2006) Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 7:241–248. doi:10.1016/s1470-2045(06)70615-5 [PubMed: 16510333]
2. Jansen MH, van Vuurden DG, Vandertop WP, Kaspers GJ (2012) Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev 38:27–35. doi:10.1016/j.ctrv.2011.06.007 [PubMed: 21764221]
3. Walker DA, Liu J, Kieran M, Jabado N, Picton S, Packer R, St Rose C, Group CPNPCC (2013) A multi-disciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neurooncol 15:462–468. doi:10.1093/neuonc/nos330
4. Kieran MW (2015) Time to rethink the unthinkable: upfront biopsy of children with newly diagnosed diffuse intrinsic pontine glioma (DIPG). Pediatric Blood Cancer 62: 3–4 doi:10.1002/pbc.25266 [PubMed: 25284709]
5. Puget S, Beccaria K, Blauwblomme T, Roujeau T, James S, Grill J, Zerah M, Varlet P, Sainte-Rose C (2015) Biopsy in a series of 130 pediatric diffuse intrinsic Pontine gliomas. Child Nerv Syst 31:1773–1780. doi:10.1007/s00381-015-2832-1
6. Wang ZJ, Rao L, Bhambhani K, Miller K, Poulik J, Altinok D, Sood S (2015) Diffuse intrinsic pontine glioma biopsy: a single institution experience. Pediatric Blood Cancer 62: 163–165 doi:10.1002/pbc.25224 [PubMed: 25263768]
7. Warren KE (2012) Diffuse intrinsic pontine glioma: poised for progress. Front Oncol 2:205. doi:10.3389/fonc.2012.00205 [PubMed: 23293772]
8. Morales La Madrid A, Hashizume R, Kieran MW (2015) Future clinical trials in DIPG: bringing epigenetics to the clinic. Front Oncol 5:148. doi:10.3389/fonc.2015.00148 [PubMed: 26191506]
9. Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, Qu C, Ding L, Huether R, Parker M, Zhang J, Gajjar A, Dyer MA, Mullighan CG, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Ellison DW, Baker SJ (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 44:251–253. doi:10.1038/ng.1102 [PubMed: 22286216]
10. Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, Sturm D, Fontebasso AM, Quang DA, Tonjes M, Hovestadt V, Albrecht S, Kool M, Nantel A, Konermann C, Lindroth A, Jager N, Rausch T, Ryzhova M, Korbel JO, Hielscher T, Hauser P, Garami M, Klekner A, Bognar L, Ebinger M, Schuhmann MU, Scheurlen W, Pekrun A, Fruhwald MC, Roggendorf W, Kramm C, Durken M, Atkinson J, Lepage P, Montpetit A, Zakrzewska M, Zakrzewski K, Liberski PP, Dong Z, Siegel P, Kulozik AE, Zapatka M, Guha A, Malkin D, Felsberg J, Reifenberger G, von Deimling A, Ichimura K, Collins VP, Witt H, Milde T, Witt O, Zhang C, Castelo-Branco P, Lichter P, Faury D, Tabori U, Plass C, Majewski J, Pfister SM, Jabado N (2012) Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 482:226–231. doi:10.1038/nature10833 [PubMed: 22286061]
11. Hoffman LM, DeWire M, Ryall S, Buczkowicz P, Leach J, Miles L, Ramani A, Brudno M, Kumar SS, Drissi R, Dexheimer P, Salloum R, Chow L, Hummel T, Stevenson C, Lu QR, Jones B, Witte D, Aronow B, Hawkins CE, Fouladi M (2016) Spatial genomic heterogeneity in diffuse intrinsic pontine and midline high-grade glioma: implications for diagnostic biopsy and targeted therapeutics. Acta Neuropathol Commun 4:1 doi:10.1186/s40478-015-0269-0 [PubMed: 26727948]
12. Nikbakht H, Panditharatna E, Mikael LG, Li R, Gayden T, Osmond M, Ho CY, Kambhampati M, Hwang EI, Faury D, Siu A, Papillon-Cavanagh S, Bechet D, Ligon KL, Ellezam B, Ingram WJ, Stinson C, Moore AS, Warren KE, Karamchandani J, Packer RJ, Jabado N, Majewski J, Nazarian J (2016) Spatial and temporal homogeneity of driver mutations in diffuse intrinsic pontine glioma. Nat Commun 7:11185. doi:10.1038/ncomms11185 [PubMed: 27048880]
13. Grasso CS, Tang Y, Truffaux N, Berlow NE, Liu L, Debily MA, Quist MJ, Davis LE, Huang EC, Woo PJ, Ponnuswami A, Chen S, Johung TB, Sun W, Kogiso M, Du Y, Qi L, Huang Y, Hutt-Cabezas M, Warren KE, Le Dret L, Meltzer PS, Mao H, Quezado M, van Vuurden DG, Abraham J, Fouladi M, Svalina MN, Wang N, Hawkins C, Nazarian J, Alonso MM, Raabe EH, Hulleman E, Spellman PT, Li XN, Keller C, Pal R, Grill J, Monje M (2015) Functionally defined therapeutic

targets in diffuse intrinsic pontine glioma. Nat Med 21:555–559. doi:10.1038/nm.3855 [PubMed: 25939062]

14. Broniscer A, Baker JN, Baker SJ, Chi SN, Geyer JR, Morris EB, Gajjar A (2010) Prospective collection of tissue samples at autopsy in children with diffuse intrinsic pontine glioma. Cancer 116:4632–4637. doi:10.1002/cncr.25405 [PubMed: 20589749]
15. Kambhampati M, Perez JP, Yadavilli S, Saratsis AM, Hill AD, Ho CY, Panditharatna E, Markel M, Packer RJ, Nazarian J (2015) A standardized autopsy procurement allows for the comprehensive study of DIPG biology. Oncotarget 6:12740–12747. doi:10.18632/oncotarget.3374 [PubMed: 25749048]
16. Angelini P, Hawkins C, Laperriere N, Bouffet E, Bartels U (2011) Post mortem examinations in diffuse intrinsic pontine glioma: challenges and chances. J Neurooncol 101:75–81. doi:10.1007/s11060-010-0224-7 [PubMed: 20473723]
17. Wu G, Diaz AK, Paugh BS, Rankin SL, Ju B, Li Y, Zhu X, Qu C, Chen X, Zhang J, Easton J, Edmonson M, Ma X, Lu C, Nagahawatte P, Hedlund E, Rusch M, Pounds S, Lin T, Onar-Thomas A, Huether R, Kriwacki R, Parker M, Gupta P, Becksfort J, Wei L, Mulder HL, Boggs K, Vadodaria B, Yergeau D, Russell JC, Ochoa K, Fulton RS, Fulton LL, Jones C, Boop FA, Broniscer A, Wetmore C, Gajjar A, Ding L, Mardis ER, Wilson RK, Taylor MR, Downing JR, Ellison DW, Zhang J, Baker SJ, St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome P (2014) The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet 46: 444–450 doi:10.1038/ng.2938 [PubMed: 24705251]
18. Fontebasso AM, Papillon-Cavanagh S, Schwartzentruber J, Nikbakht H, Gerges N, Fiset PO, Bechet D, Faury D, De Jay N, Ramkissoon LA, Corcoran A, Jones DT, Sturm D, Johann P, Tomita T, Goldman S, Nagib M, Bendel A, Goumnerova L, Bowers DC, Leonard JR, Rubin JB, Alden T, Browd S, Geyer JR, Leary S, Jallo G, Cohen K, Gupta N, Prados MD, Carret AS, Ellezam B, Crevier L, Klekner A, Bognar L, Hauser P, Garami M, Myseros J, Dong Z, Siegel PM, Malkin H, Ligon AH, Albrecht S, Pfister SM, Ligon KL, Majewski J, Jabado N, Kieran MW (2014) Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma. Nat Genet 46:462–466. doi:10.1038/ng.2950 [PubMed: 24705250]
19. Taylor KR, Mackay A, Truffaux N, Butterfield YS, Morozova O, Philippe C, Castel D, Grasso CS, Vinci M, Carvalho D, Carcaboso AM, de Torres C, Cruz O, Mora J, Entz-Werle N, Ingram WJ, Monje M, Hargrave D, Bullock AN, Puget S, Yip S, Jones C, Grill J (2014) Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma. Nat Genet 46:457–461. doi:10.1038/ng.2925 [PubMed: 24705252]
20. Buczkowicz P, Hoeman C, Rakopoulos P, Pajovic S, Letourneau L, Dzamba M, Morrison A, Lewis P, Bouffet E, Bartels U, Zuccaro J, Agnihotri S, Ryall S, Barszczyk M, Chornenkyy Y, Bourgey M, Bourque G, Montpetit A, Cordero F, Castelo-Branco P, Mangerel J, Tabori U, Ho KC, Huang A, Taylor KR, Mackay A, Bendel AE, Nazarian J, Fangusaro JR, Karajannis MA, Zagzag D, Foreman NK, Donson A, Hegert JV, Smith A, Chan J, Lafay-Cousin L, Dunn S, Hukin J, Dunham C, Scheinemann K, Michaud J, Zelcer S, Ramsay D, Cain J, Brennan C, Souweidane MM, Jones C, Allis CD, Brudno M, Becher O, Hawkins C (2014) Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. Nat Genet 46:451–456. doi:10.1038/ng.2936 [PubMed: 24705254]

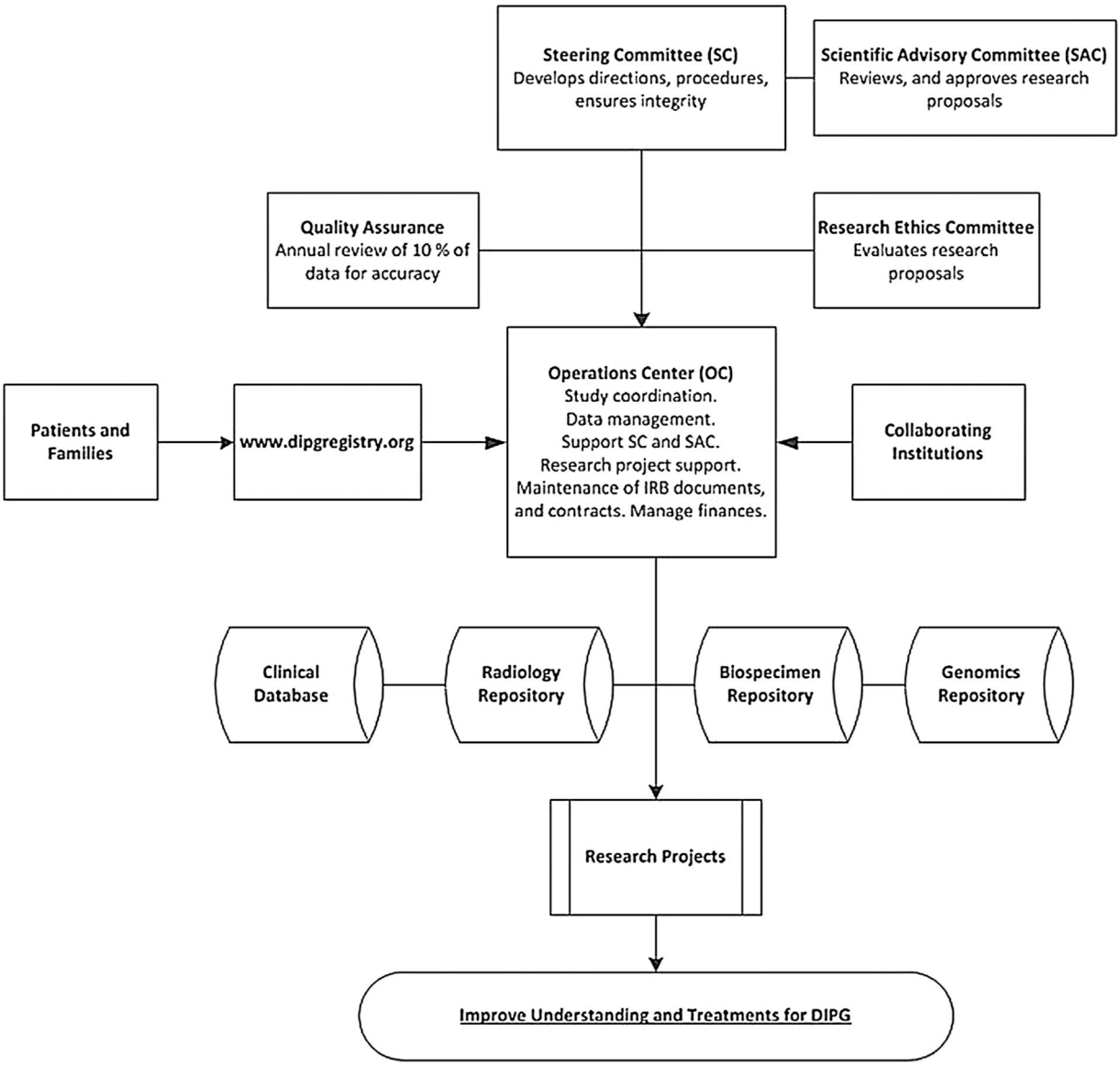

Fig. 1.
Organizational of the DIPG registry and repository

Table 1

Patient characteristics and available imaging, pathology and molecular data

Category	Subcategory	December 2016 n
Total enrollment		670
Collaborating institutions		55
Sex	Female:male	351:319
Age at diagnosis (years)	Mean age (range)	7.4 (<0.1 to 26.8 years)
Ethnicity	African American	43
	Asian	15
	Caucasian	278
	Other	11
	Unknown	323
Neuroimaging		541 (3558 studies)
	Diagnostic	448
	MRI	3182 studies
	CT	376 studies
	Central review	438
	Not DIPG	29
	Typical DIPG	300
	Some atypical features	109
Biospecimens		Targeted only
	Central review	54
	Autopsies coordinated	24
	Fresh tissue shared for in vitro and in vivo modeling	7
	Frozen	57
	FFPE	19
	Slides only	8
Molecular data		66
	Whole exome	21
	Whole genome	29
	Targeted only	16