Pediatric Blood & Cancer

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RESEARCH ARTICLE OPEN ACCESS

The HIT Network for Children and Adolescents With CNS Tumors Facilitates Improvements of Diagnostic Assessments, Multimodal Treatments, Individual Counseling, and Research in Germany, Austria, and Switzerland

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Received: 19 March 2025 | **Revised:** 18 December 2025 | **Accepted:** 22 January 2026

Keywords: brain tumor | children | clinical trials | CNS tumor | network

ABSTRACT

Background: The HIT network was established in 2000 to create a population-based structure aiming to improve survival rates and reduce late effects for children with central nervous system (CNS) tumors by conducting comprehensive clinical trials.

Methods: The HIT network currently consists of 10 coordinating trial centers mandated by the German Society for Pediatric Oncology and Hematology (GPOH) to conduct clinical trials and research projects, and to provide counseling to local centers for individual patients. The network is complemented by 11 reference centers (neuropathology, tumor biology, neuroradiology, pediatric neurosurgery, cerebrospinal fluid [CSF], assessments, radiotherapy, genetics), biostatistical support, and currently 72 local treatment sites.

Results: Numbers of children and adolescents with newly diagnosed CNS tumors registered to trials and registries increased from approximately 500 to more than 600 per year, corresponding to >95% of affected HIT-eligible children and adolescents in Germany.

Abbreviations: AGPHO, Austrian Working Group for Paediatric Haematology-Oncology; AT/RT, atypical teratoid rhabdoid tumor; cfDNA, cell-free tumor DNA; CNS, central nervous system; CNV, copy number variation; CPS, cancer predisposition syndromes; CSF, cerebrospinal fluid; DKKR (GCCR), Deutsches Kinderkrebsregister—German abbreviation for German Childhood Cancer Registry; EFS, event free survival; ERN-PaedCAN, European Reference Network for Paediatric Cancers; G-BA, Federal Joint Committee; GPOH, German Society for Pediatric Oncology and Hematology; HIT, *Hirntumor*—German abbreviation for brain-tumor; INFORM, individualized therapy for relapsed malignancies in childhood; MDPE, medical data and picture exchange; MNP, molecular neuropathology; MTB, multidisciplinary tumor board; NGS, next-generation sequencing; QoS, quality of survival; RT, radiotherapy; SIOP, Société Internationale D'Oncologie Pédiatrique (International Society of Paediatric Oncology); SIOPE, European branch of the International Society for Paediatric Oncology; SIOPE-BTG, SIOPE brain tumor group; SPOG, Swiss Pediatric Oncology Group; WHO, World Health Organization.

Clinical counseling and upfront reference assessments ensure homogeneous clinical standards and avoid inadequate treatment of individual patients. Since 2007, the established reference services have been partially re-funded by German health insurances.
Discussion: The HIT network provides a unique structure for population-based state-of-the-art diagnostic assessments, treatment recommendations and counseling. It increases the "a priori" accuracy of stratification parameters, and the timely inclusion into clinical trials and tumor-specific registries. Favorable outcomes are achieved within the trials and registry landscape, for example, through consistent reference assessments, reducing the gap to real world data. Resulting data facilitate representative, unbiased high-quality research projects across all CNS tumor entities. Interdisciplinary cooperation and competitive scientific output are enhanced.

1 | Background

Each year approximately 600 patients below 18 years of age are diagnosed with central nervous system (CNS) tumors in Germany. The standardized incidence of CNS tumors in Germany is 39.6 per million per year, and the median age 7.0 years [1]. Recent biological research improved classification of pediatric CNS tumors and led to description of new subgroups. Biologically defined subtypes with characteristic biological features have been included for medulloblastomas, low- and high-grade astrocytomas, ependymomas in the current WHO classification CNS5 [2–4]. Their association with distinct clinical, epidemiological, molecular, and prognostic characteristics support therapeutic decisions [5].

Although tumors of the CNS constitute the most common solid malignancy of childhood, distinct diagnoses remain rare, especially when considering the ever-growing number of molecularly defined subtypes [6]. Thus, progress for therapy and outcome may only be achieved by collaborative efforts within a densely nit consortium of treating institutions as realized early by Kühl [7]. The first trials of the HIT network (HIT: *Hirntumor*, German abbreviation for brain-tumor), HIT SKK '87/'88, the pilot protocol HIT '88/'89, and HIT 91 provided evidence for the feasibility of multimodal management for all malignant pediatric CNS tumors [8–10]. Recent and current HIT-initiated protocols such as the SIOP PNET5 trial for medulloblastoma (NCT02066220), HIT-HGG-2013 (NCT03243461) for high-grade glioma, SIOPE ATRT01, KRANIOPHARYNGEOM Registry 2019 pay tribute to the heterogeneity and complexity of biological specifics.

Contemporary HIT-initiated national (GPOH, the German Society of Pediatric Oncology and Hematology) or international (commonly SIOPE, the European Society for Paediatric Oncology) clinical trials have evolved to answer relevant research questions ideally using multi-institutional randomized designs. An overview of past and current tumor-specific trials of the HIT network, and an outlook for HIT-initiated clinical trials is provided in the Appendix. The small size of potential patient cohorts necessitates extreme diligence in protocol adherence and close network collaboration.

The major mission of the HIT network is to improve the care of children and adolescents affected by CNS tumors by the establishment of tumor-specific multi-institutional treatment protocols in a continuously diversifying fashion. Despite an overall low frequency of pediatric CNS tumors, their high heterogeneity requires extensive expertise by the diagnostic and treatment teams, which is often difficult to acquire and maintain in small or medium-sized pediatric oncology units. However, small inaccuracies in diagnostic assessment may have significant impact on therapeutic decisions.

We describe the German/Austrian/Swiss concept to establish centralized, highly specialized centers of reference for all children with CNS tumors, while leaving final therapeutic decisions to the treating institutions.

2 | Patients and Methods

The HIT network was established in the Year 2000 under the leadership of Joachim Kühl, Würzburg, aiming to create a clinical trial infrastructure for all German children with CNS tumors. Specific aims remain to (1) improve the quality of the most relevant diagnostic assessments, (2) to offer qualified, multimodal therapy in the framework of clinical trials in a population-based approach, (3) to provide advice by experts from involved disciplines to local centers, (4) to facilitate associated research projects, and (5) to establish resource-efficient structures.

The HIT network of German-speaking countries (Germany, Austria, Switzerland) consists of (a) coordinating trial centers mandated by the GPOH to conduct trials, facilitate ancillary research and provide counseling for individual patients (currently 10 coordinating trial centers), (b) interdisciplinary reference centers specialized in neuropathology, neuroradiology, pediatric neurosurgery, CSF-assessments, radiotherapy (RT), and tumor biology (currently 11 reference centers), and (c) participating local institutions providing specialized care for children with cancer (currently 72 centers). Partners receive qualified support for quality of survival (QoS) assessments, statistical trial design, and biostatistics. The structure of the treatment network HIT is depicted in Figure 1, a map and a list of clinical trial and reference centers is provided in Figure 2.

Close cooperations have been established between the national clinical trial groups in Germany, Austria, and Switzerland, and the national German Childhood Cancer Registry (GCCR) regarding trial eligibility, reference assessments, and clinical counseling [11, 12]. Upon written consent of their legal representatives, patients are registered to clinical trials or registries of the treatment network HIT. In addition, consent for GCCR registration is requested. Though not mandatory, consent is provided for the large majority of patients. If not, the incident case is registered anonymously, and as such is included in quantitative comparisons provided here.

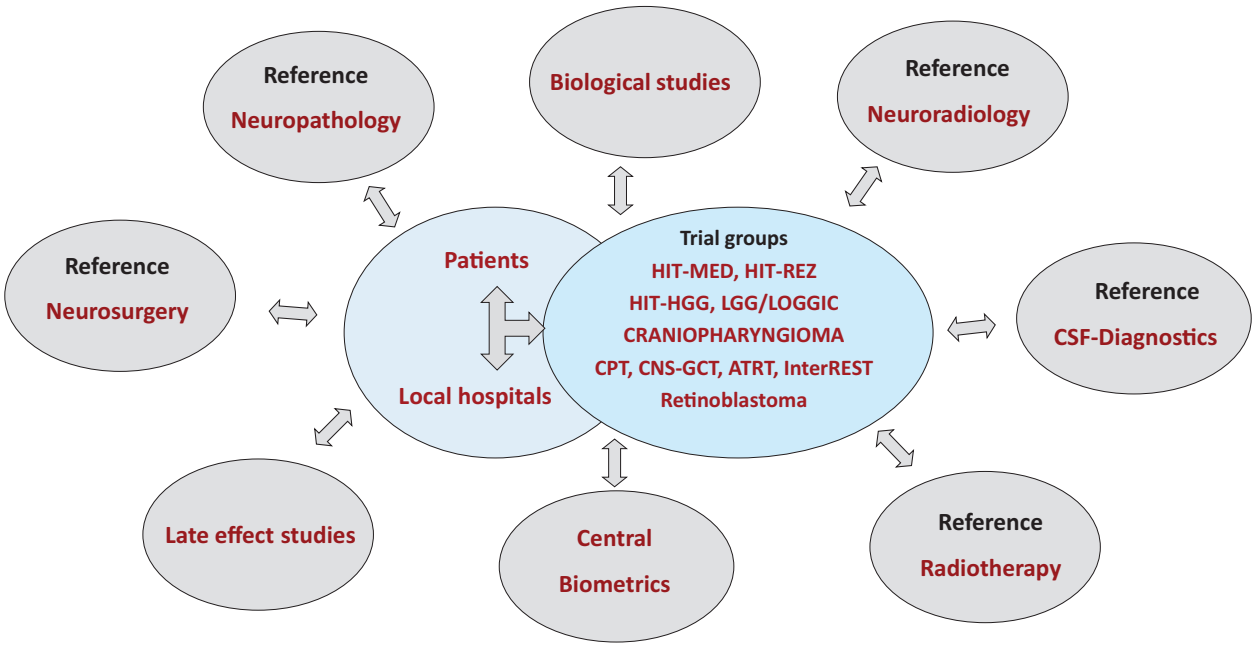

FIGURE 1 | Current structure of the HIT network.

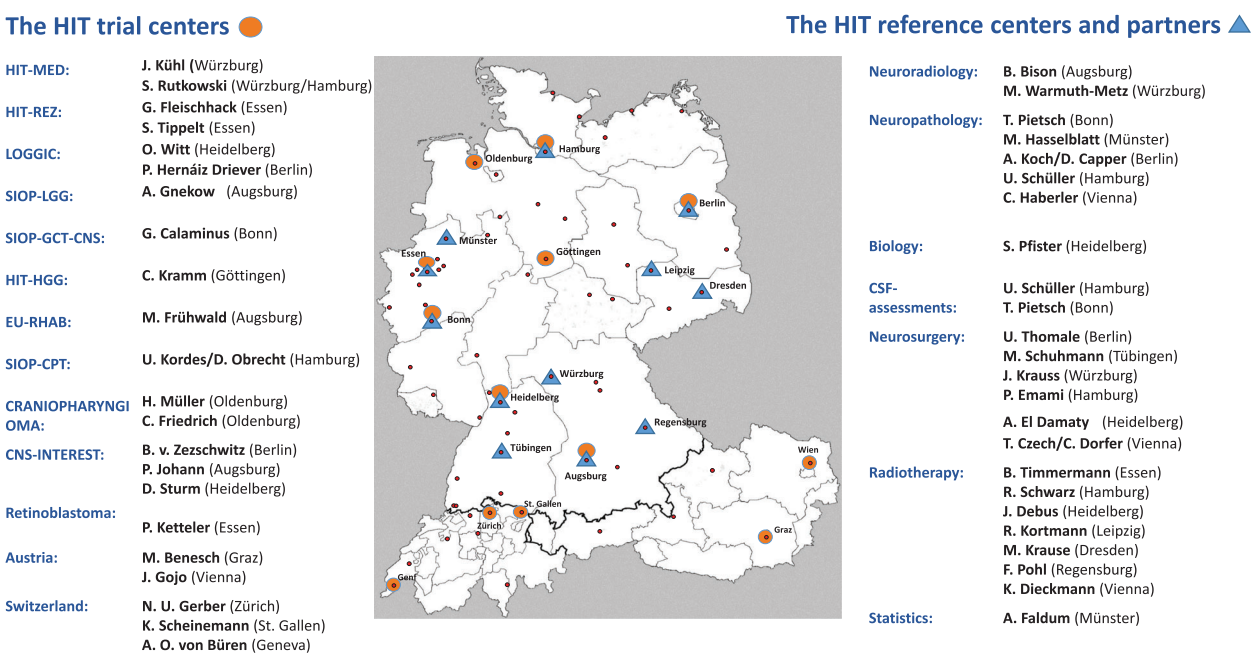

Figure 2

FIGURE 2 | Map and list of clinical trial centers and reference centers of the HIT network.

Recently, a series of consensus documents on standard of care procedures has been developed by the SIOPE brain tumor group (SIOPE-BTG) to support their implementation in other countries [13].

3 | Results

Since 2001, numbers of children with newly diagnosed CNS tumors registered to trials and registries of the HIT network increased by 20% from approximately 500 to 600 per year ($p = 0.32$; Table 1). In the five exemplarily chosen years between 2001 and 2022, the cumulative number of German patients with new diagnoses of a CNS tumor registered to the HIT network was 2951, while the number of newly diagnosed children registered to the German Children's Cancer Registry in the same years was 2879. The numbers of patients who received reference assessments or counseling by the respective institutions are listed in Table 2.

TABLE 1 | Numbers of patients registered to clinical trials or registries of the HIT network and to the German Childhood Cancer Registry.

Study group	Entities	HIT Study Groups					GCCR				
		2001	2010	2019	2021	2022	2001[§]	2010	2019	2021	2022
HIT-MED	Ependymoma	27	49	40	32	40	22	41	33	29	36
	Medulloblastoma	110	83	96	77	86	65	57	81	67	80
	Pineoblastoma and others	26	23	26	13	13	6	3	4	8	5
CPT	Choroid plexus tumors	8	24	10	12	9	4	9	5	9	6
LGG/LOGGIC	Pilocytic astrocytoma	95	132	52	104	145	118	137	138	153	142
	Other low-grade glioma	64	128	164	288	204	120	166	200	191	212
HGG	DIPG	12	18	13	14	18					
	High grade glioma	52	71	19	23	30					
GCT	Germ cell tumors	80	34	26	37	41	17	25	19	27	27
Kraniopharyngioma/HIT-Endo	Craniopharyngioma	24	23	18	19	22	22	26	18	20	22
EURHAB	AT/RT	1	28	28	20	31	8	21	20	15	21
Kraniopharyngioma/HIT-Endo	Pituitary adenomas and carcinomas	2	7	9	15	6	28	28	20	31	10
Kraniopharyngioma/HIT-Endo	Meningiomas	6	3	8	5	8	15	10	7	6	2
GCCR	Medulloepithelioma	Due to different codes used, It is unknown, to which HIT study group these cases have been registered					2	10	11	10	6
GCCR	CNS-PNET (brain plus spinal)						22	38	65	63	54
GCCR	Neuronal and mixed neuronal-glial tumors						6	3	16	6	9
GCCR	Unspecified intracranial and intraspinal tumors						3	5	7	23	4
Total/year		507	623	509	659	653	430	552	626	635	636
Total/5 years				2951					2879		
HIT-REZ[a]	Ependymoma	4	8	10	7	18	[#] The GCCR includes only newly diagnosed primary tumors				
	Medulloblastoma	17	21	14	15	13					
	Pineoblastoma and others	13	4	1	0	4					

Note: Numbers are listed for German patients with newly diagnosed CNS tumors for five exemplary years between 2001 and 2022.

[a]The GCCR registers all newly diagnosed primary tumors. For the purpose of the paper, specific inclusion criteria were applied to match inclusion criteria of HIT study groups (more details provided in the Appendix). The numbers of patients treated for recurrences (e.g., HIT-REZ) are listed separately.

TABLE 2 | Central reference assessments, clinical counseling, and tumor boards provided in 2021 and 2022.

		Neuropathology				Neuroradiology				CSF diagnostics				Radiotherapy				Neurosurgery		Clinical counseling and tumor boards			
Year		**2021**		**2022**		**2021**		**2022**		**2021**		**2022**		**2021**		**2022**		**2021**	**2022**	**2021**	**2022**	**2021**	**2022**
Study group	Entities	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of assessments	# of patients	# of patients	# of patients	# of clinical counselings	# of clinical counselings	# of tumor boards	# of tumor boards
HIT/HIT REZ	Ependymoma	46	44	48	45	1000	354	928	333	52	36	52	41	108	58	115	66	15	13	263/84	136/79	121/61	132/42
	Medulloblastoma	84	84	91	91					171	98	150	105	79/29	77/24	72/20	72/18						
	Pineoblastoma and others	17	17	6	6					21	10	7	5	8/1	5/1	6/2	3/2						
CPT	Choroid plexus tumors	13	13	12	12	42	15	30	13	1	1	0	0	4	4	3	3	2	1	12	9	4	2
LGG/LOGGIC	Pilocytic astrocytoma	184	182	152	151	1243	547	1151	580	n.a.	n.a.	n.a.	n.a.	56	56	43	43	53	40	319	608	29	76
	Other low-grade glioma	123	121	110	108																		
HGG	DIPG	23	23	38	38	333	105	310	113	9	8	8	8	15	15	22	22	7	0	197	137	55	74
	High grade glioma	18	17	20	17					5	5	5	5	12	12	14	14						
GCT	Germ cell tumors	9	7	12	10	60	21	5	25	10	7	7	7	21	21	18	18	0	0	234	237	7	5
Kraniopharyngeom/ HIT-Endo	Craniopharyngioma	18	18	22	22	222	73	120	69	1	1	0	0	16	16	17	16	3	3	15	21	1	2
EURHAB	AT/RT	16	16	29	28	119	37	151	46	32	20	47	24	16	10	16	10	0	1	16	2	56	9
Total		551	662	540	528	3019	1152	2695	1179	302	186	276	195	364	299	351	291	80	58	1140	1229	334	342

Note: Numbers are listed for 2021 and 2022 for patients with newly diagnosed CNS tumors and with relapse. Clinical counseling: Individual recommendations given upon request by the respective study center. Tumor boards: Individual recommendations provided after interdisciplinary case discussion.

3.1 | The Neuroradiology Reference Center

This center provides reference reports concerning tumor site, radiological characteristics of the primary tumor and regarding dissemination, as well as tumor size at predefined time-points by homogeneous entity-specific evaluation criteria, aiming to avoid discrepant assessments and artifact misinterpretation from local centers [14].

The MRI should be performed in accordance with national and international guidelines. The quality of imaging in terms of diagnostic reliability is checked and, if necessary, repeat MRIs are requested. Due to technological advances and personnel changes at the local clinic, there remains a steady number of inadequate MRIs. At initial diagnosis, this affects up to 25% of spinal MRIs, which must be repeated. This remains relatively stable over time. The neuroradiological review improves diagnostic reliability, particularly with regard to the assessment of dissemination.

Reference center staff are involved in the preparation of guidelines and consensus recommendations [15–17].

Importantly, timely central neuroradiological review (e.g., before stratification of patients to clinical trial, risk groups etc.) improved survival rates: In the HIT/SIOP-PNET4 trial, children with standard risk medulloblastomas and incomplete central staging review tended to have lower event-free survival rates than children with complete review (EFS 69% vs. 82%, $p = 0.13$) [18]. Other trials have reported similar findings [19, 20].

In suspected diffuse intrinsic pontine glioma, bifocal germinoma or NF1-associated optic pathway glioma, neuroradiological reference confirmation of diagnosis may allow inclusion into clinical trials without biopsy and histological confirmation. In uncertain cases or in those with discrepancies between local and review assessments, timely central review allows assigning individual patients to the appropriate clinical trial or treatment recommendation. An imaging server, medical data and picture exchange (MDPE), is the basis for an efficient exchange of MRIs and clinical information between local centers, reference institutions, and clinical trial centers.

3.2 | The Neurosurgical Reference Panel

Surgical therapy for brain tumors and adequate fresh tissue sampling and processing are an essential component of treatment for the majority of pediatric CNS tumors [13, 21, 22]. The benefits of surgical options (complete resection, debulking, biopsy) must be weighed against potential risks and nonsurgical therapeutic approaches: Complete resection must be aimed for ependymoma [23], while safe tumor debulking may be the goal in selected optic pathway glioma [24], and biopsy may be required in diffuse intrinsic pontine glioma [25] as a precondition to trial inclusion.

As expertise in pediatric neurosurgery may not always be available especially in smaller centers, a neurosurgical reference panel was established within the HIT network to evaluate complex cases. This system was tested in the context of the SIOP ependymoma II trial in which both the local team and the study's neurosurgical reference panel provided an independent presurgical assessment to achieve R0 resection [26]. This offer was expanded to include complex cases with other tumor types. Local centers may request neurosurgical consultation of two to four experienced pediatric neurosurgeons. Their suggestions aim to support the local neurosurgical team. In addition, the pediatric neurosurgical panel has investigated neurosurgical factors for improved implementation into treatment protocols of the HIT network [5, 27–29, 30].

3.3 | Neuropathological Reference Diagnostics and Biology

Since the 1980s, more than 17,000 CNS tumors in pediatric patients have been diagnosed in accordance with the WHO classification guidelines for CNS tumors. These diagnoses have been carried out using appropriate techniques, including immunohistochemistry and molecular genetic methods such as next-generation sequencing (NGS), copy number variation (CNV) assessment, and methylation-based analysis. Neuropathological reference diagnostics, performed by a panel of experts at various institutions, allows a rapid and precise reference diagnosis for pediatric brain tumor patients secures routing for the inclusion into appropriate therapeutic studies and registries of the HIT network. The final diagnosis may change in up to 15% of cases by reference assessment. Discrepancies are most prominent in glial and rare tumor types. Numbers of neuropathological reference assessments are given in Table 2.

Access to centralized material allows reference neuropathologists and collaborating researchers to correlate neuropathological features to outcomes of clinical trial cohorts [29, 31, 32].

DNA methylation signatures, and targeted gene panel sequencing as part of the molecular tumor classification, were pioneered since 2015 in the molecular neuropathology (MNP) registry to improve diagnostic accuracy at the time of diagnosis. After analyzing > 2000 CNS tumors to date, results demonstrated an increased diagnostic accuracy in a substantial proportion of patients [5].

The pediatric precision oncology registry INFORM (INdividualized therapy FOr Relapsed Malignancies in childhood) was also initiated in 2015 and offers comprehensive molecular profiling to identify molecular targets for added therapeutic options for children/adolescents with very high-risk primary or relapsed/refractory tumors [33]. The molecular targets were shown to be predictive for matched treatment response [33]. Meanwhile, the diagnostic pipeline is expanded, aiming to develop innovative phase I/II studies such as the INFORM2 basket trial series. Both the MNP and INFORM registries facilitate the identification of cancer predisposition syndromes (CPS), indicating development of ~10% of CNS tumors based on an underlying CPS, often in children without clinical signs or a family history suspicious of CPS [5, 33, 34].

3.4 | CSF Assessments

Central assessment of cerebrospinal fluid (CSF) cytology is as crucial as reference neuropathology of tumor tissue. Some centers

rarely treat childhood CNS tumors with dissemination of tumor cells into the CSF, and therefore lack diagnostic experience. Moreover, biomaterial is limited, and immunocytochemistry may be challenging. The HIT CSF reference centers receive > 500 samples/year from children with CNS tumors. Protocols and recommendations regarding the prognostic value of cytology findings have been established, for example, cytological tumor dissemination alone (M1 stage only) was identified in medulloblastoma as a high-risk factor with an outcome comparable to M2/M3 stage [35, 36]. The reference centers are in an excellent position to perform liquid biopsy assays to sensitively detect cell-free tumor DNA (cfDNA). Respective results may be used to classify tumor DNA in a presurgery situation, and to detect relapse early [37].

3.5 | RT Reference

RT plays a crucial role in the treatment of CNS tumors [38–41]. Since the 1990s, standardized guidelines were implemented in brain tumor protocols of GPOH studies, aiming to ensure a comprehensive high quality of RT across all brain tumor protocols with standards for RT to permit a reproducible treatment within prospective trials. Individual radiooncological recommendations to treating institutions are now offered for patients to assure a correct radiotherapeutic treatment (target volumes and dose prescriptions) including the benefits of advanced modalities such as proton beam therapy, and to discuss potential side effects along with their management strategies [42, 43].

Several international studies have demonstrated a correlation between the quality of RT and clinical outcome [44–49]. Prospective or retrospective review of RT treatment plans for optimization represents a key component of RT quality assurance and was first implemented in Germany already as retrospective quality assessment within the HIT91 trial, and was extended in 2015 into prospectively within the SIOP PNET5 trials for medulloblastoma, and into the SIOP Ependymoma II and SIOPE AT/RT01 trials [42]. Findings from these programs demonstrate the necessity of such quality assurance programs for pediatric brain tumors [50–52]. Experience derived from clinical trials and interdisciplinary collaboration have led to guidelines and recommendations aiming to standardize RT and improve care [53, 54].

3.6 | QoS and Neuropsychological Outcome

The consistent assessment of QoS and neuropsychological outcomes at harmonized predefined time-points informs individual care and research, as well as counseling in terms of school and vocational training decisions. Therefore, uniform QoS and neuropsychological assessments have been introduced into several HIT trials and registries of the German HIT network since the 1990s. Direct QoS measures include both medical parameters and neuropsychological assessments. A harmonized approach, using the Neuropsychological Basic Diagnostic tool has been implemented in various HIT trials [41, 55–60]. Indirect QoS measures include standardized paper–pencil or online-based assessments for domains like executive function, behavioral difficulties and quality of life. Those assessments are performed in different trials of the HIT network (currently SIOP PNET5, SIOP Ependymoma II, SIOP-HRMB, CNS GCT, and SIOPE ATRT01) according to the recommendations of the Brain Tumor working group of the European Society of Paediatric Oncology [46, 61–63]. About 60% of patients, who have consented to participate in QoS outcome testing have been compliant throughout the whole study period in a stable fashion for the assessments. Regarding neuropsychological testing, between 44% and 73% receive at least one assessment, while the longitudinal assessment rates vary between 11% and 25%. If patients are not registered on a trial or registry, neuropsychological testing with the standard age adjusted battery is offered 2 and 5 years after diagnosis by the local psychologist of the treating hospital as required by the respective families. QoL outcome measures are used regularly in some but not in all hospitals. As these measures are optional and not systematically ascertained, there are no exact data on overall compliance.

HIT-LIFE, a HIT network project aiming to systematically analyze important brain tumor-specific late effects across the German HIT-studies, relies on the well-established research infrastructure of the HIT network, a cohort of over 5000 long-term pediatric CNS tumor survivors with well-documented diagnostic and therapeutic information [64]. This illustrates how the HIT network benefits broadly from previously collected trial-based data. In the German VIVE project, self-reported QoS information has been collected in 270 children and adolescents with a median follow-up of 21.2 years after their CNS tumor diagnosis [65].

3.7 | Clinical Counseling

Evidence-based clinical decision making in pediatric brain tumors can be challenging and requires specialized expertise, not available at all participating sites. Therefore, all coordinating trial centers offer clinical counseling to participating centers. This is usually done by an integrated interpretation of the central reference opinions during a multidisciplinary tumor board (MTB), which are mostly conducted as regular (e.g., weekly) tumor boards, and written reports to participating sites. Moreover, participating centers can approach the coordinating centers with specific questions at any time. With this infrastructure, the HIT network offers state-of-the-art clinical advice according to the most recent clinical and scientific standards, especially to pediatric oncology departments without dedicated pediatric neuro-oncology programs. Furthermore, the coordinating centers collect data on rare complications and provide evidence-based recommendations. Moreover, cases can be presented to an interdisciplinary pediatric CNS-tumor board through the European Reference Network for Paediatric Cancers (ERN-PaedCAN), which benefits from the broad expertise of the neuroradiological HIT reference center [14].

3.8 | Cooperation With Austria and Switzerland

Austrian children and adolescents with hemato-oncological diseases are treated in five centers with well-established expertise in pediatric CNS tumor treatment, and most patients are included into clinical trials and registries of the HIT network. Complex

cases are discussed within specific ERN-PaedCan boards or the national tumor boards. Study updates are regularly presented at the meetings of the Austrian Working Group for Paediatric Haemato-Oncology (AGPHO). Members are involved in scientific projects of both, HIT and SIOPE networks.

In Switzerland, eight of the nine accredited pediatric oncology centers have a dedicated oncologist responsible for patients with a CNS tumor. All clinical trials and registries of the HIT network are chaired by an elected national study coordinator via the Swiss Pediatric Oncology Group (SPOG). At a monthly occurring SPOG pediatric neuro-oncology working group meeting of SSPHO (Swiss Society of Pediatric Hematology and Oncology), cases and scientific projects are discussed, and information about newly opened trials, registries, upcoming meetings, is provided.

3.9 | Financial Support

Ever since its establishment in 2000, the institutions of the HIT network received major funding support by the German Children's Cancer Foundation (Deutsche Kinderkrebsstiftung, Bonn). Moreover, certain services provided by the trial and reference centers of the HIT network have been partly re-funded since 2007 by the German health insurances, based on an agreement of the GPOH with the Federal Joint Committee (G-BA) [61] in 2006, the chief decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. The Austrian HIT trials center is funded by the Styrian Children's Cancer Aid (Steierische Kinderkrebshilfe). In Switzerland, the SPOG, which serves as the national sponsor for the HIT trials, is funded through both public and private sources. The SPOG also financially contributes to the data management by the treating centers. The involved experts in the trial and reference centers provide their services in full- or part time in addition to their daily duties, with support by staff members funded by the sources mentioned.

4 | Discussion

The HIT network provides a unique and comprehensive structure for population-based access to qualified diagnostic assessments, evidence-based treatment recommendations and counseling for all pediatric CNS tumors, serving children and adolescents in a population of more than 100 million people in the three countries.

The corresponding numbers of the population-based GCCR for children 0–14 years, and from 2009 onwards children and adolescents 0–17 years, with HIT-eligible CNS tumors fluctuate for several reasons (see footnotes Table 1). For the most representative calendar years, 2021 and 2022, HIT-eligible new tumor diagnoses have increased to 600 per year and represent a very close coverage of > 95% vs the GCCR.

The coverage was traditionally high for children with malignant CNS tumors, and has improved for the large group of children with low-grade gliomas, which due to the less aggressive behavior and need for postoperative treatment have traditionally been cared for not always by pediatric oncologists but sometimes exclusively by pediatric neurosurgeons or and neurologists, who have been less familiar with the HIT network structure. [66, 67]

The HIT network facilitates the timely inclusion into clinical trials and registries, as building similar structures for each tumor-specific trial would duplicate work and costs for all partners. Furthermore, the HIT network provides population-based access to qualified diagnostic assessments, treatment recommendations and counseling. The availability of representative, reliable data from "real-world" cohorts of clinical trials and registries according to high diagnostic standards and homogeneously defined criteria facilitates the generation of unbiased high-quality research projects across all CNS-tumor entities.

Each individual patient benefits directly from advice by highly specialized experts, independent from the availability of local expertise of the respective disciplines, and independent from participation in a clinical trial. This refers to advantages due to (a) central reference assessments (staging, molecular pathology including subtypes and prognostically relevant biomarkers), (b) therapy planning (risk stratification and overarching multimodal strategy, neurosurgery, RT, medical treatment) and QoS assessments, and (c) counseling in specific situations, for example, in case of unusual adverse events [68]. As an example from the perspective of a typical patient, flow of data and samples through the institutions of the HIT network, the resulting feedback, and counseling steps are illustrated in Figure 3. For individual patients, it is of paramount importance that all relevant parameters are verified before risk-adapted stratification is defined. The HIT network structure allows the confirmation or correction of all relevant parameters, and subsequently, in case of discrepancies, timely assignment of the patient to the appropriate treatment regimen. This increases the "a priori" accuracy of stratification parameters used for inclusion of each individual patient into clinical trials or registries, and the applied treatments. As such, potential inadequate treatment of patients is avoided. Occasionally, colleagues in the local centers did not want to lose influence to the reference centers, especially when the network was launched. However, discussions on discrepant assessments were offered and are perceived positively in the vast majority of cases, especially in smaller centers where local experience with rare constellations is limited. Interestingly, the rates of relevant discrepancies between local and central reference assessments (approximately 5%–25% according to the respective discipline and topic, see Section 3) have remained stable over the years [69]. This might be partially explained by the fact that interpretations in the local centers are frequently made by less-experienced, rotating staff, and lack of time to focus on very rare diseases. The HIT network structure compensates these deficits efficiently. High discrepancy rates, which otherwise are often only identified by "post hoc" central assessments in clinical trials, and the importance of "a priori" reference assessments have been reported in the setting of the clinical trial ACNS1422 [70]. Early reference imaging has recently been proposed for use in clinical practice and in clinical trials by the Children's Oncology group [71]. However, children with CNS tumors benefit from upfront quality assurance not only for imaging, but also for molecular pathology, CSF assessments, RT, and so forth.

In Canada, national standards of practice have been established for the most prevalent pediatric brain tumors, and allow children

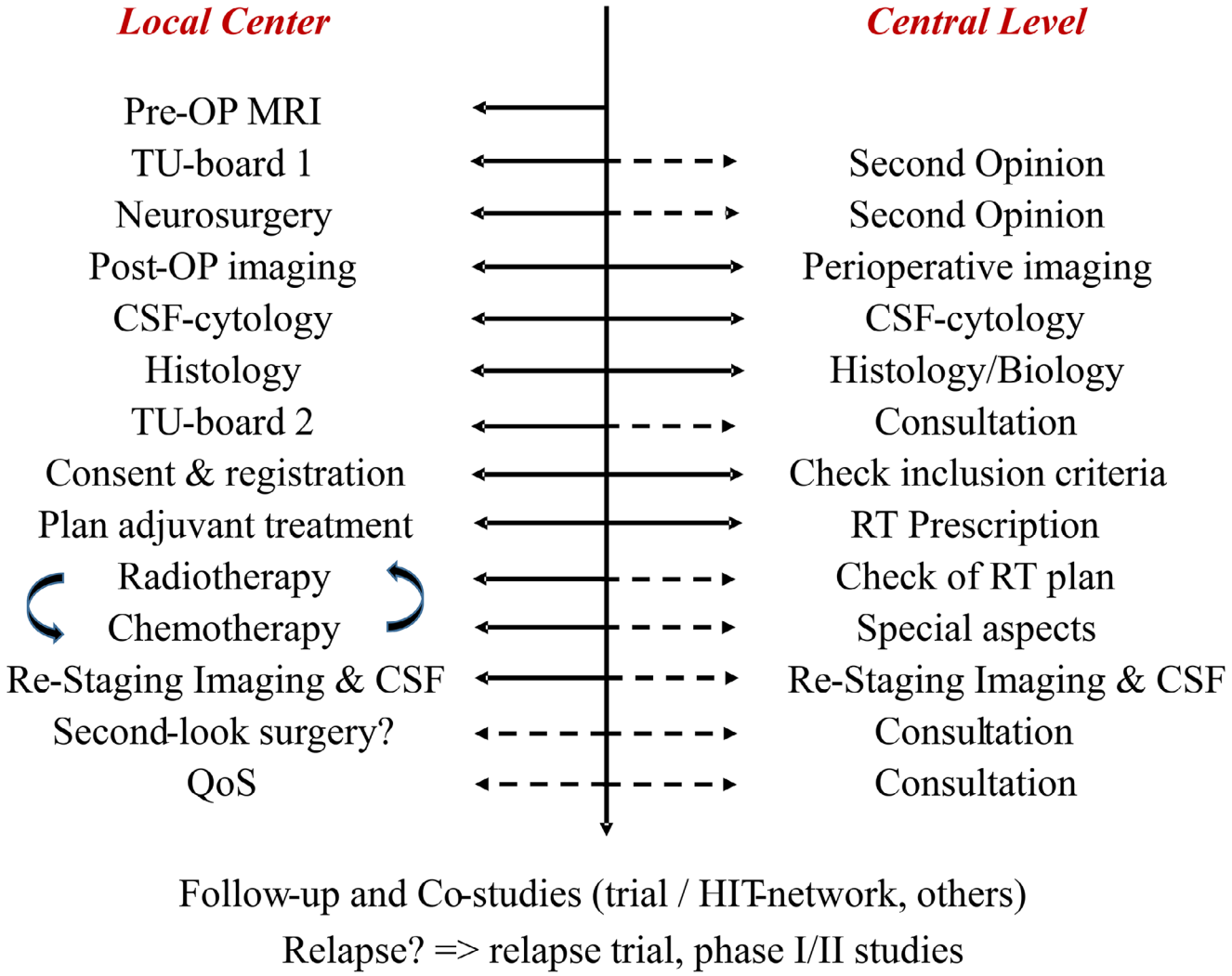

FIGURE 3 | Flow of counseling, data and samples through the HIT network from the patient's perspective.

to receive equivalent care regardless of location [72]. In our experience, the individual counseling provided by the treatment-network HIT to the local institutions in specific, rare constellations (Figure 3) is unique and favorable for survival outcome and the avoidance of complications. There is some evidence that survival rates of children included in registries may be comparable to rates obtained within prospective clinical trials, if the relevant parameters for treatment stratification are controlled "a priori," as done in the HIT network. For example, this has been shown for children with non-metastatic medulloblastoma and for children with AT/RT [51, 73]. Ultimately, the benefits of the treatment network HIT contribute to closing the gap between selected clinical cohorts and "real-world" outcomes [74]. This can be used as a model for low- and middle-income countries, where the components of the network which are most relevant in their respective setting may be established and adapted. To our experience, reference institutions installed permanently and independently from the availability of open clinical trials are more sustainable and potentially more cost-efficient than services established transiently in the context of selected trials.

The high quality of data facilitates the discovery and validation of biomarkers, the improvement of risk-adapted stratification of patients, the development of novel multimodal treatment concepts, and internationally accepted QoS assessment batteries. Our network structure also facilitates the implementation of complementary research projects across specific CNS-tumor types and clinical trials, for example, the molecular MNP registry and more clinically focused projects [5, 60, 75]. The key benefits of the HIT network, covering the entire spectrum from preclinical research, diagnostic and treatment related topics to late-effect aspects are summarized in Table 3. The high-quality research generated by the HIT network is documented by more than 1000 articles published in peer-reviewed journals since the year 2000 (pubmed search: (Rutkowski, S[Author]) OR (Kramm, CM[Author]) OR (Fruehwald, MC[Author]) OR (Gnekow, A[Author]) OR (Hernaiz Driever, P[Author]) OR (Muller, HL[Author]) OR (Fleischhack, G[Author]) OR (Temming, P[Author]) OR (Ketteler P, [Author]) OR (Calaminus, G[Author])).

Since its foundation, the treatment network HIT has been continuously funded by the German Children's Cancer Foundation as one of their major areas of support with more than 48 Mio Euro. While these funds are primarily dedicated to the conduct of clinical trials, registries, and related research, the costs for quality assurance of relevant diagnostic and therapeutic

TABLE 3 | Key benefits of the HIT network.

	Advantages for individual current patients	Advantages for research and for future patients
Central reference for diagnostic assessments (neuroradiology, histopathology, CSF)	Avoidance of misdiagnoses Allocation to correct treatment regimens prior to their application	Reliable data available, according to high diagnostic standards and homogeneously defined criteria
Multimodal treatment (neurosurgery, radiotherapy, medical treatment)	Access to modern, risk-adapted standard treatments Quality control, for example, of individual radiotherapy plans before start of radiotherapy, and adaptation if required Timely allocation to innovative treatments in available clinical trials Individual counseling by experts for local institutions	Documentation of multimodal treatment details in high quality Detection of treatment deviations and evaluation of their clinical impact
Toxicities/late effects, QoL, neuropsychology	Systematic assessment of side effects and access to counseling, for example, in unusual toxicities Less frequent/severe occurrence due to modern risk-adapted stratification algorithms	Systematic detection of toxicities and potential for future systematic assessment and recording of llate effects/QoL, neuropsychology allows comprehensive analyses on causative factors (treatment details, host factors, etc.) and related research across entities (e.g. HIT-life)
Population-based patient care	State of the art diagnostics and treatments are available irrespective of the place of residence	Generation of representative, less-biased results, based on "real-world" cohorts from clinical trials and registries
Overall benefits	Improved survival rates and quality of survival even outside of clinical trials ("real-world" data) Enhanced interdisciplinary cooperations and competitive scientific output, also for designing future clinical trials Improved, cost-effective conduct and feasibility	

assessments are refunded by the German health insurances. The German Children's Cancer Foundation also supports the annual nationwide HIT network meetings for all partners and staff from the local pediatric oncology centers. Every second year, this rotating meeting between centers participating in the HIT network is open to patients and their families with specific lectures, workshops, and individual meeting opportunities for the 400–500 attendees. By bringing together many involved stakeholders, the HIT network also serves as an ideal platform for initiatives conferring political impact.

The achievements of the HIT network are matching the recommendations of the SIOP-Europe Brain Tumor Group for the availability of quality control measures for diagnostic assessments, treatment, and aftercare, to which the institutions of the treatment-network HIT have contributed significantly as well as to the development of clinical trials within the SIOPE Brain Tumor Group and other consortia [13]. The fact that the services provided by the trial and reference centers of the HIT network have been re-funded since 2007 by the German statutory health insurances [2] underlines that its quality assurance programs are independently recognized to be clinically relevant for population-based improvement [5]. Envisaged next steps are the implementation of a common HIT network registry collecting the relevant basic data, and a tumor-banking platform with clear logistics [29] at local and central levels.

In conclusion, we demonstrate that population-based quality control measures for upfront diagnostic assessments, treatment, and related research are provided efficiently in our network structure. In addition, individual counseling contributes to improved outcome for individual patients even in less specialized centers and outside of clinical trials and facilitates representative research of high quality for children with CNS tumors. This may serve as an example for other communities or consortia, aiming to benefit from similar synergies.

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Acknowledgments

All partners of the HIT network thank the German Children's Cancer Foundation, Bonn (Deutsche Kinderkrebsstiftung, Bonn) (www.kinderkrebsstiftung.de) for the outstanding continuous financial and logistical support of the study centers, reference institutions, and the annual HIT network meetings.

Open access funding enabled and organized by Projekt DEAL.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix: Overview of past and current tumor-specific trials of the HIT-network.