Canada's Drug and
Health Technology Agency

Multi-Stakeholder Dialogue: Optimizing the Use of Real-World Evidence for Decision-Making for Pediatric Low-Grade Glioma in Canada

What We Learned

Canada's Drug and
Health Technology Agency

CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Contact **requests@cadth.ca** with inquiries about this notice or legal matters relating to CADTH services.

CADTH's Real-World Evidence Learning Period for Rare Diseases

With the support of Health Canada, CADTH launched a learning period in November 2021 (Real-World Data and Real-World Evidence at CADTH) to better understand how to optimize the use of real-world evidence (RWE) to inform decision-making for drugs for rare diseases. As part of this learning period, CADTH is coordinating collaborative "learning by doing" projects that will inform the development of 4 key pillars related to the optimal use of RWE (outlined in Figure 1), one of which involves multi-stakeholder engagement and dialogue.

Figure 1: Strategic Pillars for CADTH Rare Disease Learning Projects

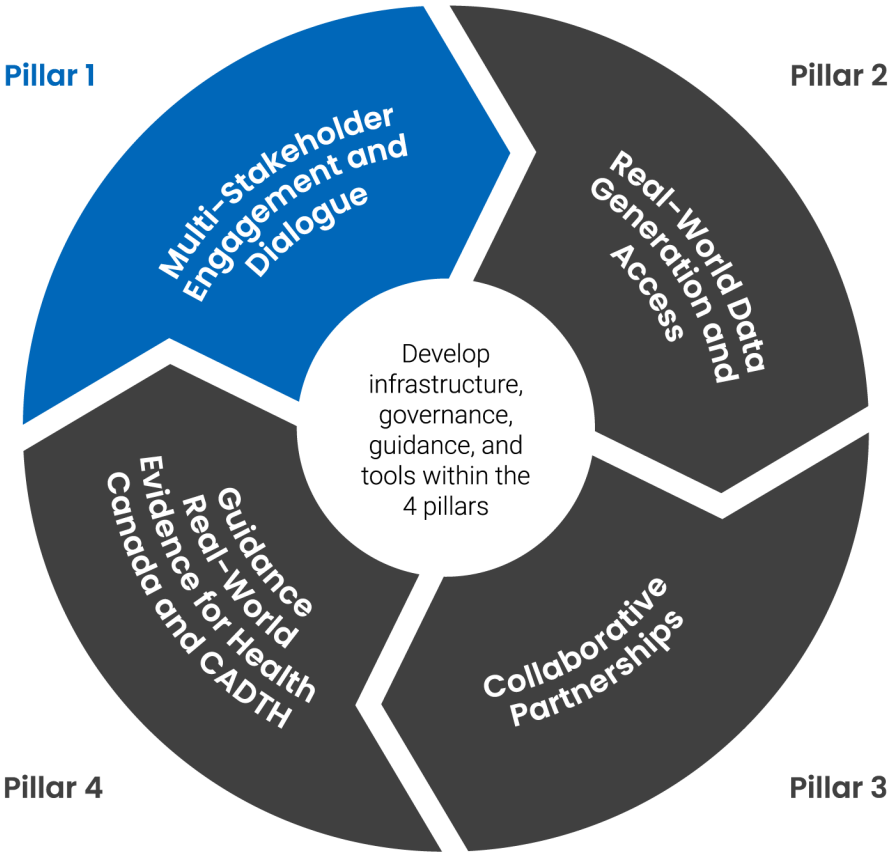
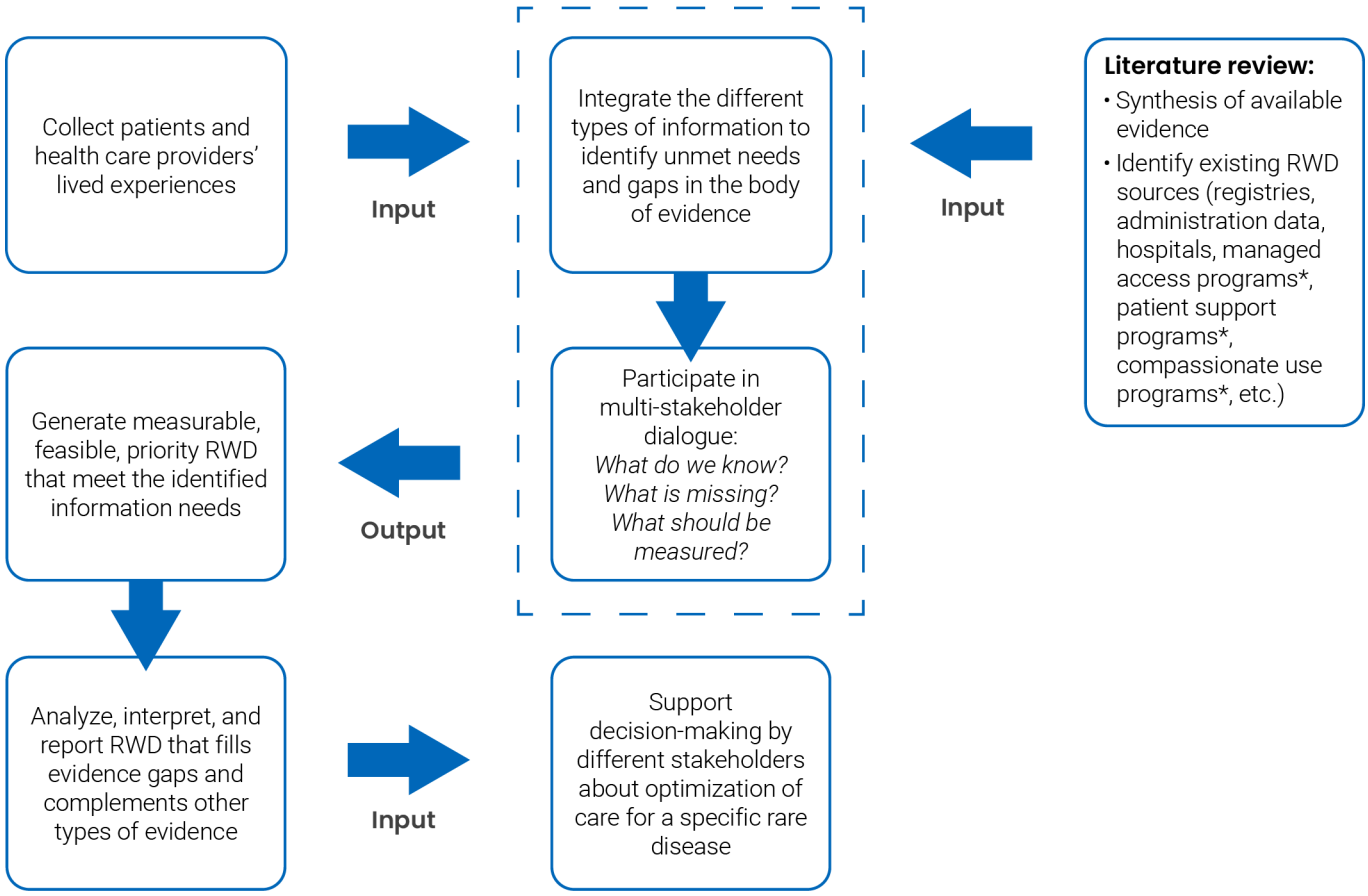


Figure 2: Different Types of RWD Integrated Through Multi-Stakeholder Dialogue to Better Inform the Decision-Making Process for Drugs for Rare Diseases

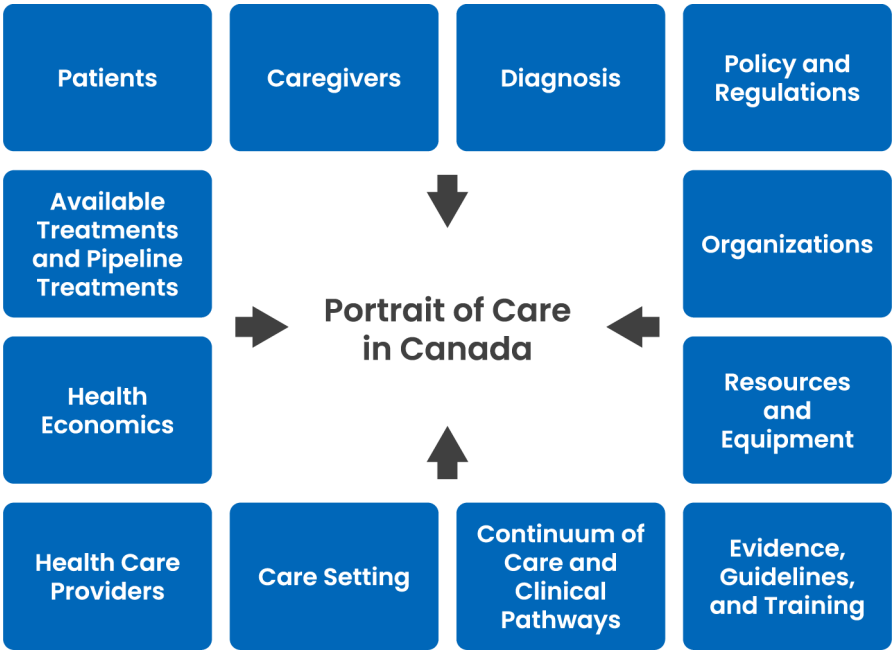


*The definitions of these programs may vary.

Integrating existing information from the literature and real-world data (RWD) sources, as well as understanding the perspectives of different stakeholders and their unmet needs related to their current care, may both enhance and streamline decision-making processes for rare diseases (Figure 2). Early dialogue between stakeholders is particularly important for rare diseases to identify and understand uncertainties that may occur about the care pathway, natural history, clinical outcomes of treatments in the longer term, added value to patients, and value for money to society.[1] This can then serve to inform RWE generation plans. CADTH recently posted a narrative review on multi-stakeholder engagement in a Health Technology Assessment for public feedback, which is now under revision. The key learnings from this narrative review will help develop guidance for multi-stakeholder engagement and dialogue.

During this learning period, CADTH is developing a framework to understand and analyze a more complete portrait of care for different rare diseases (Figure 3). This proposed framework has been inspired by the Guide to Systematic Systems Analysis,[2] the Constellation map,[3] and the Donabedian conceptual framework.[4] It encompasses the wide variety of components of the health care system and is currently being used to help structure multi-stakeholder dialogue meetings and identify questions, knowledge gaps, and issues that need to be discussed. To generate fit-for-purpose RWE, multi-stakeholder dialogue can also serve to determine what should be measured in relation to these components in order to meet identified information needs. The Donabedian conceptual framework[4] can be used to classify these indicators into patient characteristics, structures of care, processes of care, and outcomes. For the project described in this report, the Portrait of Care framework was tested as a way to structure the multi-stakeholder meeting, and the Donabedian framework was used to classify the examples of indicators presented to the stakeholders during the meeting as well as the list of indicators that came out of the discussions presented in Table 3.

Figure 3: Framework to Assess Outstanding Information Needs for a Specific Disease in the Components of the System of Care (Inspired by the Guide to Systematic Systems Analysis,[2] the Constellation Map,[3] and the Donabedian Conceptual Framework[4])



Pediatric Low-Grade Glioma Multi-Stakeholder Meeting Context and Objective

CADTH brought together different types of stakeholders from various areas of expertise. The objective of the multi-stakeholder meeting was to learn about potential measurable indicators and outcomes that different stakeholders deemed important for their specific decision-making needs related to the care of pediatric low-grade glioma (pLGG) patients in Canada.

Multi-Stakeholder Meeting Approach

Meeting Design

In preparation for the multi-stakeholder meeting, CADTH conducted:

- a narrative literature review on multi-stakeholder engagement and identified key learnings
- a review of existing evidence and identified gaps related to pLGG care
- several pre-meetings — 2 with participants from the patient community (i.e., families, caregivers, patient advocacy and support groups) and 1 with health care providers (i.e., doctors, nurses, pharmacists). During these meetings, stakeholders discussed the unmet needs, challenges, and gaps in care for pLGG. Transcripts of the meetings were reviewed and summarized by the project team.

Learnings from the literature and pre-meetings helped frame the content and discussion questions for the multi-stakeholder meeting. A week before the meeting, all participants received preparation material, which included a glossary and a slide deck summarizing key elements from the literature overview, pre-meetings, existing data from a registry, and examples of indicators and outcomes (refer to the Supporting Documents section).

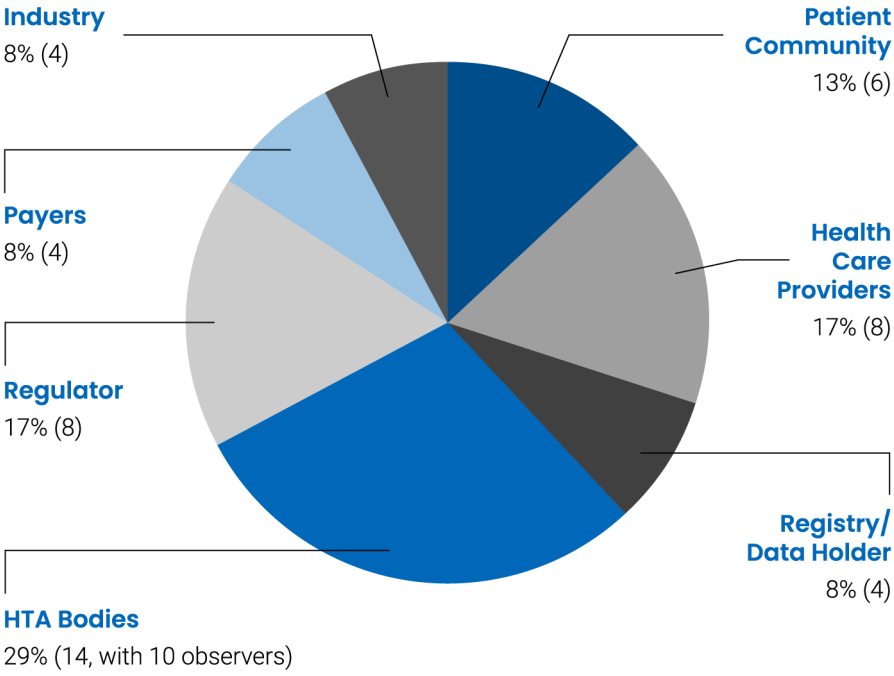
The multi-stakeholder meeting was held virtually, in a single meeting room, over a period of 3 hours. The meeting was mediated by a professional facilitator. An emotional support professional (i.e., a registered nurse specializing in pediatric oncology and hematology) was made available to all participants, if required, during the meeting.

The key messages from the literature overview and the pre-meetings were presented by CADTH staff, and representatives from the Pediatric Oncology Group of Ontario (POGO) presented on sources of RWD for pLGG. These sources include the POGO Networked Information System (POGONIS) Registry and its national counterpart, Cancer in Young People in Canada (CYP-C).

Participants

The multi-stakeholder meeting featured a total of 48 attendees from 7 different stakeholder groups. The perspectives represented at the meeting included those from the patient community (i.e., patients, families, caregivers, patient advocacy and support groups), health care providers, payers, industry representatives, data holders, regulators, and health technology assessment bodies. A distribution of stakeholders is provided in Figure 4. For a full overview of the stakeholder engagement process for the pre-meetings and the multi-stakeholder meeting, please refer to "Pediatric Low-Grade Glioma Multi-Stakeholder Dialogue Methods and Practices" (in the Supporting Documents section).

Figure 4: Types of Stakeholders Present at the Multi-Stakeholder Meeting



Total Participants: 48

Analysis of the Meeting Output

An audio recording of the multi-stakeholder meeting was transcribed and analyzed using qualitative data analysis software to identify key topics and themes from the discussion. For a full overview of analysis methods, please refer to "Pediatric Low-Grade Glioma Multi-Stakeholder Dialogue Methods and Practices" (in the Supporting Documents section).

Key Findings About pLGG

Key findings from the evidence overview that were presented at the meeting are described in the sections that follow.

Patient Characteristics

- From 2001 to 2015, the Canadian incidence of pLGGs in children aged 0 to 14 was 1.41 cases per 100,000 person years.[5]
- pLGGs are the most frequent solid primary tumours of the central nervous system (CNS) in pediatrics. pLGGs are a diverse group of tumours that differ greatly in terms of location in the CNS, histology, and molecular profile.[6]
- Two hereditary conditions are associated with an increased risk of developing pLGG: tuberous sclerosis complex (TSC) and neurofibromatosis type 1 (NF-1).
- The median age at diagnosis is 6 to 8 years.[7]
- Recent research suggests that the majority (90%) of pLGG tumours have alterations to the MAPK/ERK pathway, which is involved in cell growth, proliferation, and survival.[8]

Process of Care

A Canadian national standard of practice for CNS tumours was established in 2020 through a survey of pediatric neuro-oncologists across the country.[9] The survey was followed by a discussion among experts during Canadian National Rounds and a manuscript review to ensure agreement. The consensus treatment recommendations for pLGGs are summarized as follows.

The preferred first-line treatment is complete surgical removal (resection) of the tumour. If this is not possible due to the location of the tumour, then the following treatments are recommended, as summarized in the following table.

Table 1: Treatment Guidelines for pLGG in Canada

Canadian treatment guidelines	Drug name	Route of administration	State of access in Canada
First line *If surgical removal not possible,* **chemo monotherapy**	Vinblastine (Velban®)	Intravenous	Off-label
Second line *If BRAF V600E mutation alteration identified,* **targeted inhibitor**	Vemurafenib (Zelboraf®)	Oral	Off-label
	Dabrafenib (Tafinlar®)	Oral	Off-label
Second line *If BRAF fusion identified or NF1 patient with optic/ suprasellar tumour,* **targeted inhibitor**	Trametinib (Mekinist®)	Oral	Off-label Ongoing clinical trial
	Selumetinib (Koselugo®)	Oral	Ongoing clinical trial(s)
Second line *If no MAPK alteration identified,* **2 chemo agents**	Vincristine (VCR; multiple brands available) AND	Intravenous	Off-label
	Carboplatin	Intravenous	Off-label

Avoidance of radiation for patients of all ages, especially NF-1 patients, was recommended, but use in older patients and in cases where other therapy options have been exhausted is possible.

Ongoing Clinical Trials for pLGG (Canada)

Key characteristics of identified ongoing clinical trials in Canada were highlighted to show that:

- the study populations being included in ongoing trials vary
- the outcomes being measured and how they are measured also vary across studies
- estimated study completion dates are all at least a year away. There may be gaps in knowledge about optimal care of pLGG even when these study results are reported
- patients and their families may have to travel long distances to be a part of ongoing trials, depending on where they live in Canada.

Key Findings: Pre-Meetings on Unmet Needs, Challenges, and Gaps for pLGG Care

The following findings from the pre-meetings conducted with participants from the patient community (i.e., families, caregivers, patient advocacy and support groups) and with health care providers include unmet needs, challenges, and gaps related to the current portrait of care for pLGG in Canada, as well as some suggested indicators and outcomes. These findings were also included in the multi-stakeholder pre-meeting material (refer to the Supporting Documents section).

Patient Community Perspective

Key messages from 9 people from the patient community were grouped into the following themes.

Access to Treatment

- Accessing treatment is time-intensive for parents and their children, and adds to the already heavy burden of caring for a sick child.
- There is a perception of a lack of novel and potentially effective treatments in Canada.
- There is a reliance on communication with other families with lived experience, through virtual platforms, to guide them in their search for treatment options and what to expect from the care process.
- At completion of clinical trials or treatment courses, families wait for the next steps in the care pathway.

Variation in Care

- Provinces and territories may have differing approaches to treatment plans.
- Clinicians operating in the same institution may have differing approaches to providing care.
- Access to specialist physicians and resources can vary based on geographical location.
- There is a perception of a lack of coordination between hospitals across Canada and with care providers in the US and elsewhere.
- The care pathway can make it difficult for children to maintain their personhood.
    - Seeing a consistent set of specialists familiar with the child as an individual and integrated access to psychosocial care were perceived as beneficial.

Financial Burden of Care

- Drugs for pediatric oncology and other rare diseases can often be associated with high costs and problems with access, especially when they are not listed on the public formulary and prescribed "off-label" (e.g., out-of-pocket treatment costs, access issues).
- Out-of-pocket costs can include:
  - medical tests and procedures
  - medical supply and equipment costs for at-home care
  - complementary alternative medicines (e.g., vitamins, supplements)
  - psychosocial support, childcare, and other non-medical supports
  - cost of travelling within or outside of Canada to receive care (e.g., lodging, other accommodations, and/or transportation costs such as gas, parking fees, and public transit).
- Some have experienced misalignment in the language and requirements communicated between physicians and insurance companies, and this disconnect often falls on the family to manage.

Other Challenges

- Orally administered versus IV therapies may be preferred because they can be administered outside of treatment centres, which:
  - allows children to miss fewer days at school and with friends
  - reduces the burden on caregivers in terms of travel time
  - reduces expenses and potential missed days at work.
- There are barriers associated with the transition from care in pediatric centres to adolescent/adult centres.

Indicators and Outcomes

- To access certain targeted treatments, confirming a patient's **molecular tumour status** is frequently required, and there are also uncertainties surrounding the complex classification of pLGG and associated cancers, which can add further complexity to accessing treatments indicated for **specific tumour types** and patient populations.
- There should be an increased focus on **outcomes and indicators related to the mental health of patients and their families, as well as children's social development while living with the disease.**
- Indicators such as **days a child misses from school, emotional burden, academic performance, and the ability to develop and maintain personal relationships** should be considered.
- Given the relatively recent availability of targeted therapies and their use in pediatric populations, a more thorough, comprehensive, and **long-term follow-up** of patients should be considered, including acknowledgement of the following:

- There are unknown effects of targeted treatments in terms of safety, and effects on other factors, such as a child's perception of self, their body image, fertility, and the ability to engage in social relationships.
- Patients can age out of pediatric indications and may no longer have access to the same treatment options, support services, or care providers as they grow with their disease.

- Financial burdens are experienced by caregivers and families, including loss of income and missed time from work; travel and accommodation for accessing treatment options; the cost of accessing high-cost therapies, home care and other supports; and the need for resources for emotional and psychosocial support.

Clinical Perspective

Key messages came from 14 health care providers.

Off-Label and Special Access Program Medications

- A lot of time and effort on the part of health care workers, especially pharmacy staff, is needed to complete the required paperwork to provide medications to patients; there is typically no remuneration for these efforts.
- Approval processes:
  - Intravenous therapies are provided at clinics or institutions; they have an easier approval process.
  - Oral therapies require more effort to acquire the necessary approvals.
  - Special access approval is required for compounded liquid preparations of a medicine.
- Programs where the manufacturer provides the medication to patients can be discontinued at any time.
- There may be burden/costs associated with:
  - diagnostics
  - filling prescriptions for oral therapies at pharmacies.

Ongoing Clinical Trials

- There is harm in waiting for these trials to be completed before making decisions in practice.
- There is concern that these studies do not have the right follow-up periods to fully capture the necessary end points of interest.
- There is concern that these studies do not include young adult patients.
  - It is very difficult to access treatments for these individuals.

Indicators and Outcomes

- The short-term mortality risk is low for pLGG; the morbidities, however, can be devastating (e.g., blindness) and need to be captured.

- **Radiation-free survival and delaying or avoiding the use of increasingly toxic chemotherapy agents** are important outcomes to consider; pLGG patients have a long survival, so deferring (or avoiding) these interventions can help decrease or prevent long-term sequalae.
- **Secondary neoplasms**: If a patient receives a chemotherapy agent or radiation therapy, there is the potential to develop cancer in a different location.
- Collecting data on the **number of times treatment regimens** have been provided or changed is important. Any change in treatment plan (e.g., going back under observation) is an important data point for pLGG.
- **Different types of therapies** present with different side effects that can impact a person's quality of life and these should be captured.

Information Shared by Canadian Registries During the Meeting

Pediatric Oncology Group of Ontario Networked Information System (POGONIS)

A representative from the POGONIS childhood cancer registry (POGONIS — Childhood Cancer Database — POGO) provided an overview of the registry and details on the types of RWD available for pLGG. Key information highlighted during the multi-stakeholder meeting is listed below.

- The registry has active data collection via funded data managers working in each of the 5 specialized childhood cancer programs in Ontario. The data managers work with the care teams to review patient charts, collect information from electronic patient records, and attend patient tumour boards and rounds to collect information on each new childhood cancer case in patients being treated in a specialized childhood cancer program in Ontario.
- Data in POGONIS is collected under a waiver of consent, which means patient consent is not required to collect information. This is because POGONIS is recognized as a prescribed entity under the provincial personal health information protection act, allowing the registry to collect information to monitor and evaluate the system to support system planning.
- More than 20,000 childhood cancer cases have been collected in the registry since 1985.
- POGONIS has nearly complete (estimated as 98%) population-based capture of children with cancer aged 0-14 years old. Previous research found 95% agreement in CNS/brain tumour diagnoses between POGONIS and the Ontario Cancer Registry.
- POGONIS captures approximately 60% of adolescents between ages 15-17 years old, with the remainder being treated primarily in adult cancer programs.

Data on pLGG Available via POGONIS

- Approximately 1,600 low-grade glioma cases have been captured in the registry since 1985, an average of about 50 to 65 cases per year.
- Available data include:
  - number of children diagnosed (i.e., crude number or adjusted to population size and age-standardized rates)
  - demographics (e.g., sex, age at diagnosis)
  - postal code of residence at time of diagnosis
  - predisposing conditions (including NF-1, TSC)
  - tumour biology characteristics (e.g., BRAF mutations)
  - treatment summaries (e.g., modality received, treatment start dates, dosing)
  - enrolment in clinical trials
  - overall survival
  - time to progression or death
  - subsequent malignant neoplasms.
- Some data are collected as free text and require additional analysis and validation.
- POGONIS data are routinely linked to the Ontario Death Record and Ontario Cancer Registry, enabling long-term follow-up of cases and capture of subsequent cancers and death information.
- Additional linkages to other administrative data holdings could enable measurements of health service utilization, hospitalizations, ambulatory or outpatient visits, OHIP billing, and drug benefits.

Cancer in Young People in Canada (CYP-C)

A representative of the national data holding on childhood cancer, CYP-C, briefly spoke about some features of this data holding and how it differs from POGONIS. They mentioned that an advantage of a national data holding like CYP-C is broader capture of children with cancer treated in childhood cancer programs in Canada, which means a higher number of pLGG cases are included in the registry. However, the data are currently only collected 5 years from diagnosis, which is a concern for pLGG, which is often a chronic disease. Furthermore, there are challenges associated with linking a registry to administrative data (including the provincial cancer registries and death record). However, there are ongoing efforts to improve linkage capacity to fill this gap.

Examples of Potential Indicators and Outcomes to Support Decision-Making

Examples of measurable indicators and outcomes, as identified from the literature overview on pLGG, ongoing clinical trials (identified via ClinicalTrials.gov listings), the registry overview, and the pre-meetings content, were included in the preparation material and presented to the multi-stakeholder meeting participants to stimulate discussion. Table 2 presents a sample of indicators presented at the meeting. A complete list of indicators can be found in the slides (refer to the Supporting Documents section).

Table 2: Examples of Indicators/Outcomes for pLGG

Indicator/outcome	Examples
Patient characteristics (descriptive statistics)	Sex, age at diagnosis, tumour site, incidence, geographical location (i.e., where patients live)
Structure of care	Availability of child life specialists, number/type of specialist, pediatric centre volume, and location
Process of care	Time from symptom onset to diagnosis, diagnostic procedures, frequency, sequencing, and duration of treatments
Outcomes	
Burden of care	Out-of-pocket costs (e.g., treatment, gas, parking, overnight stays), time out of school, psychosocial burden
Clinical outcomes	Progression-free/event-free survival, response rate, change in function (e.g., vision, motor function, cognitive), drug safety and tolerability, quality of life

Learnings from Multi-Stakeholder Dialogue: Indicators and Outcomes

Overview

The following themes and topics were identified from the multi-stakeholder discussion about potential indicators and outcomes that are important to measure and report to support decision-making about care for pLGG. Several stakeholders voiced direct agreement with the examples of indicators and outcomes in the slide deck and no objections to the listed examples were made during the meeting.

The indicators and outcomes identified in the discussions were grouped into 3 overarching categories: **Patient Characteristics, Process of Care, and Outcomes**.

Patient Characteristics	Process of Care	Outcomes
• Equity, diversity, and inclusion • Genetic conditions • Molecular tumour characteristics	• Treatment history • Nursing workload • Health care provider administrative burden • Prescribing data	• Financial burden for families and caregivers • Long-term outcomes • Patient-reported outcomes • Quality of life • Response to treatment

Patient Characteristics

Equity, Diversity, and Inclusion

- Stakeholders noted that it is important to capture equity, diversity, and inclusion data in relation to access to care for pLGG, such as:
  - **socioeconomic status** of patients' families
  - **ethnicity and race** that patients and their families identify as belonging to
  - **geographical location** of patients' residence (e.g., rural versus urban)
  - data on **underserved groups**; stakeholders identified the need for data on Indigenous peoples in particular.

Genetic Conditions

- Stakeholders identified the genetic condition of **NF-1** as an important factor to consider in the context of care for pLGG. Specifically, they noted that NF-1 is a factor that may impact access to care and treatment response.
  - Stakeholders reported that parents of children with NF-1 often have learning disabilities that may make accessing clinical trials and navigating continued access to treatments more onerous once trials finish.
  - Stakeholders identified NF-1 as a "huge factor to consider" for potential drug approval, and distinguished data on treatment response for patients with NF-1 from other pLGGs during the discussion.

Molecular Tumour Characteristics

- Stakeholders indicated that capturing data related to molecular tumour characteristics may add insights into treatment and outcomes.
  - In particular, stakeholders considered molecular tumour characteristics to be a key factor in current clinical practice when choosing frontline treatment for low-grade gliomas. For example, they noted that recent clinical trial data indicates that targeted therapy is favoured for BRAF mutations, including fusions and V600E substitutions.
- Stakeholders highlighted that compared to younger pediatric patients, young adults experience greater issues accessing molecular biology analysis.
- They also indicated that several Canadian RWD sources capture data on "clinically actionable" biomarkers, but do not capture entire sequencing data on tumours.

Process of Care

Treatment History

- Stakeholders highlighted the advantages of capturing **sequential therapy steps** during the meeting. They suggested that changes in treatment plan may mark clinically important events, lending an advantage to databases that include treatment history.

Nursing Workload

- Stakeholders indicated that from a nursing perspective, it would be important to capture data on:
  - the **number of nursing hours** required to provide treatment and care
  - the **number of hospital admissions needed for different treatment options** (i.e., admissions for actual administration and/or to treat side effects).

Health Care Provider Administrative Burden

- Stakeholders noted that health care providers experience substantial administrative burden (i.e., paperwork) when attempting to provide their patients with treatment options requiring compassionate or special access.

Prescribing Data

- Stakeholders noted that capturing the **rate of prescribing for targeted agents** in pLGG would be important, as this would demonstrate that clinicians are advocating for these types of drugs in this population.
- They also noted that when looking at extending usage of a product to a pediatric population, **safe dosage data (i.e., pharmacokinetic-pharmacodynamic modelling)** would be important information, but would be incumbent on the manufacturer and would likely not come from a registry.

Outcomes

Financial Burden for Families and Caregivers

- Stakeholders spoke to a lack of evidence in the following areas of financial caregiver burden.
  - **Out-of-pocket costs** related to treatment access:
    - Stakeholders noted that families may have issues affording continued access to clinical trial drugs when the trials finish.
    - They also reported nervousness about expensive drugs being provided via industry without insurance company or hospital involvement, as they saw potential for this payment model to fall through and leave families paying out-of-pocket or unable to afford treatment.
  - Cost of taking **time off work**
  - How the burden of **cost** to families and caregivers may be modified or influenced by:
    - **geographical location**
    - **marital status** (e.g., single parent versus 2-parent family)
    - **number of other children in the family.**

Long-Term Outcomes

- Stakeholders indicated that having **long-term follow-up (preferably more than 5 years)** for patients is important, given the chronic nature of the disease for many patients.
- Stakeholders mentioned the burden of **late effects** on patients and their families.

Patient-Reported Outcomes

- Stakeholders discussed the potential inclusion of patient-reported outcomes in regulatory decisions, perceiving a need for validation and statistical analysis of data measuring these outcomes to determine whether they are meaningful.

Quality of Life

- Stakeholders noted the need to assess quality of life along the treatment path, including between treatments, as quality of life may decrease because of tumour growth during observation or toxic treatment avoidance.
- Quality of life was also mentioned as an important factor from a health economics perspective.
- Stakeholders brought up several measurable variables that they felt may impact quality of life, including:
  - **number of clinic visits** (this may impact patients' and family members' quality of life)
  - **number of hospital/emergency room visits** (these may occur as a result of treatment side effects and may impact patients and family members)
  - **number of hours spent in hospital**
  - **number of needles/pokes.**

- Stakeholders emphasized the need to measure the qualitative aspect of clinic and hospital visits (i.e., the impact on families in their own words), as this experience may not line up exactly with quantitative metrics like the number of visits over a certain time period. For example, visiting the hospital regularly for IV treatment might be a different experience than going to the hospital regularly to treat side effects, or being admitted to the hospital to treat side effects.
- The importance of collecting self-reported measures to speak to experiences of impacted quality of life while receiving treatment at home was mentioned (e.g., taking medication at home orally or even by injection). Specifically, stakeholders brought up the following potential self-reported metrics of quality of life during the discussion:
  - number of days of school missed
  - ability to do regular daily activities (e.g., ability to play with friends or do hobbies)
  - degree to which patients are impacted by side effects of medications.

Response to Treatment

- Stakeholders identified several outcomes as universal, standard, and/or hard end points for pLGG:
  - survival (overall, progression-free, event-free)
  - tumour control/volume
    - The importance of measuring remaining tumour volume was emphasized, as there can be a large volume left even if treatment has decreased it
  - vision.
- Stakeholders identified the need to carefully define progression for pLGG as there is difficulty defining its progression relative to other tumours. A change in therapy plan was proposed by stakeholders as a data point reflecting progression (i.e., a change in radiology [increased tumour size] or change in symptoms).
- They suggested that patients experiencing relapse might be an important subgroup for drug approval.
- Stakeholders discussed the risk of toxicity. They noted that there is a desire to avoid therapies with known toxicities; however, there is also a risk that comes with avoiding a toxic treatment like radiotherapy for too long and ending up with unintended negative outcomes like blindness or decreased quality of life.
- Stakeholders noted that capturing direct data on secondary neoplasms via registry data is preferred to relying on indirect measures from administrative data.
- They also identified the importance of using guidelines for response assessment like the response assessment in neuro-oncology criteria (RANO) and response assessment in pediatric neuro-oncology (RAPNO).

Learnings from Multi-Stakeholder Dialogue: Remaining Unmet Needs, Challenges, and Gaps for pLGG Care

While the objective of the meeting was to identify indicators and outcomes, stakeholders provided additional insights into remaining challenges and unmet needs pertaining to decision-making about care for pLGG. The themes and topics of these additional insights, which expand upon or reinforce those identified in the pre-meeting engagement sessions, are highlighted below, and will help inform future CADTH work.

Access to Treatment

- Stakeholders noted delays in the treatment process related to navigating administrative burdens.
- They also suggested that more patients could access clinical trials if these trials integrated aspects of virtual care. It was mentioned that this may ease the burden on both patients and caregivers.
- They noted that some patients should be able to benefit from therapies based on the literature, but cannot access them because of administrative barriers.
    - Stakeholders brought up the case of a patient with a hypermutated tumour who could not access immunotherapy in time in the adult health care system. During this story, they highlighted the lack of available funding and resources required to navigate the application to special access and compassionate access in the adult care system, particularly when compared to that available in the pediatric care system.
- Stakeholders proposed that adolescents and young adults could be granted access to molecular testing via pediatric clinics to reduce gaps in access for this population.
- They also suggested that a national adolescent and young adult CNS tumour board could be developed to get better consensus for therapy and reduce barriers to access treatment.

Funding Barriers

- Stakeholders noted that differences in the access to and funding for drug therapies between pediatric and adult patients can contribute to different treatment experiences and outcomes.
- They also highlighted that while clinical care is often considered distinct from research, and consequently funded separately in Canada, this is a false dichotomy. They emphasized that people should realize that trials and clinical care are linked.

Guidance for Real-World Evidence

- There was a consensus amongst stakeholders that RWD and RWE can play a role in decision-making by providing additional, complementary evidence.
- Stakeholders mentioned that there is a continuum between clinical trials and clinical care on the one hand and registries on the other that are often considered in silos. They emphasized that the system needs to start to think about the modification of registries prospectively to collect meaningful data, rather than relying on retrospective data only.
- Stakeholders emphasized that to be considered for use in decision-making, sources of RWD and the resulting RWE must be assessed for utility, validity, and rigour.
- Stakeholders indicated that they would likely rely on the expertise of organizations such as CADTH to determine what pieces of RWD are valid, useful, and worth considering in decision-making processes.
- They generally agreed that current Canadian registries such as POGONIS and CYP-C are valuable sources of RWD in Canada, and specifically:
  - registries could be modified in a prospective way to collect data identified as potentially meaningful in trials, rather than relying on retrospective data only
  - registries could be used as data sources for regulatory and HTA decision-making, as this potential is currently untapped.
- They also noted a desire for increased international collaboration regarding guidance, outcome selection for decision-making, and potential sources of RWD.

Key Feedback from Stakeholders on Their Multi-Stakeholder Dialogue Experience

The participants of the multi-stakeholder meeting were asked to give their feedback via a survey after the meeting. The key elements related to their multi-stakeholder dialogue experience were summarized and will be used to develop guidance for multi-stakeholder engagement and inform future CADTH work involving multi-stakeholder dialogue for rare diseases. Feedback on operational aspects, such as length and time of the meeting, is not reported here but was noted and will be used to plan future meetings.

Key Feedback on What the Participants Liked Most About Multi-Stakeholder Dialogue

- The opportunity to hear different perspectives from a variety of stakeholder groups
- The mix of people from different areas working with pediatric brain tumours
- The fact that it was a national and multidisciplinary meeting
- The ability to brainstorm together
- The excellent opportunity to discuss issues with CADTH and to bring back learnings to their own organization
- The equal opportunity for voices to be heard
- The focus groups (pre-meetings) done ahead of time was a good initiative
- The dialogue was valuable and enriching to perspective, and its openness and the learning obtained from it were great
- Hearing the thoughts and view from people in the different organizations and hospital positions was found to be very educational
- The level of engagement of clinicians, patients, and parent representatives was excellent
- The fantastic opportunity to meet the stakeholders and learn more about the landscape of pLGG in Canada
- The last presentation (POGONIS registry overview)
- The emphasis on the RWD that is to be collected and the challenges in accessing pLGG therapy.

Key Feedback to Improve Development and Planning of Future Meetings

- In the future, only include participants who will be engaged. Some participants felt uncomfortable having people silent without video and highlighted that full participation in these meetings is critical for open dialogue
- Include more specific financial information, for example comparison of conventional chemotherapy versus targeted therapy, including hospital visits and quality of life
- More networking time would have been nice
- Make goals and end results clearer
- Separate the discussion from clinical perspectives versus government/structural perspectives for challenges in drug access.

Summary and Next Steps

In summary, stakeholders discussed many indicators during the pre-meetings and multi-stakeholder meeting, some of which are already being collected and reported on in the literature, and others that are novel. At many points during the multi-stakeholder dialogue process, stakeholders made comments that added important context about how to measure indicators and/or the value they hold to different stakeholder groups. Table 3 below provides a summary of key indicators and outcomes for pLGG and their sources.

Some topics raised in this meeting or in written feedback by stakeholders were out of scope. However, they will inform future CADTH initiatives to optimize the use of RWE to support decision-making about the care for rare diseases.

The learnings from the multi-stakeholder dialogue process (including pre-meeting content) will be used to inform the development of a protocol for a retrospective analysis of available POGONIS registry data to describe the patient population, structure and process of care, and outcomes for pLGG in a Canadian health system context. The findings of these analyses will be summarized as a portrait of care published on CADTH's website.

The learnings from the multi-stakeholder dialogue process for pediatric low-grade glioma will also be used by CADTH to inform the development of guidance on multi-stakeholder dialogue.

Supporting Documents

- Multi-Stakeholder Dialogue Methods and Practices
- Multi-Stakeholder Pre-Meeting Material

Table 3: Summary of Key Indicators and Outcomes for pLGG and Their Source

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
1. Patient characteristics (descriptive statistics)					
1.1 General characteristics					
Comorbidities (other health conditions)	YES	—	—	—	—
In a clinical trial, special access program, managed access program, or receiving off-label treatment	YES	—	YES	YES	—
1.2 Diversity, equity, and inclusion					
Ethnicity / race / underserved groups	—	YES	—	—	YES Registry/data holder Patient community
Geographical location (where do patients live, rural vs. urban)	—	YES	YES	—	YES Registry/data holder Regulator Payers
Socioeconomic status	—	YES	YES	—	YES Registry/data holder Patient community Regulator
Age	YES	YES	YES	YES	—
Sex	YES	YES	—	—	—
1.3 Genetic conditions					
Type of tumour according to predisposing condition	YES	YES	YES	—	YES Health care providers Patient community

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
1.4 General tumour characteristics					
Molecular profile	YES	—	YES	—	YES Health care providers Registry/data holder Patient community
Biological marker	—	YES	—	—	—
Tumour site/size	YES	—	—	—	—
2. Structure of care					
Geographical location of care	—	—	YES	—	—
Number and type of specialists	—	—	YES	—	—
Pediatric vs. adult centre	—	—	YES	—	—
Number of doctors per speciality caring for individual patient (consistency of care)	—	—	YES	—	—
Child life specialist: yes/no	—	—	YES	—	—
3. Process of care					
3.1 Diagnosis					
Cost of diagnostic tests	—	—	—	YES	—
Diagnostic procedure	—	—	—	YES	—
3.2 Treatment					
Health care provider administrative burden:					
Paperwork time associated with off-label, special access program medications and accessing oral therapies	—	—	—	YES	YES Health care providers

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
Nursing workload: • Number of nursing hours required to provide treatment and care • Number of admissions needed for different treatment options (i.e., due to administration or side effects)	–	–	–	–	YES Health care providers
Wait times for treatment related to:					
Off-label medication usage	–	–	–	YES	YES Health care providers
Adult vs. pediatric systems	–	–	–	YES	YES Health care providers
Treatment history (frequency, sequencing and duration of treatments/time between treatments)	YES	YES	–	YES	YES Health care Providers Registry/Data Holder
Prescribing data:					
Rate of prescription of targeted agents	–	–	–	–	YES Health care Providers Regulators
Safe dosage	–	YES	–	–	
Routes of administration of current treatments	YES	–	–	–	–

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
4. Outcomes					
4.1 Long-term outcomes (preferably more than 5 years)					
General measurement considerations • Stakeholders emphasized the need for long-term follow-up of patients with pLGG due to: • the chronicity of the disease course for many children • the importance of having the right follow-up periods to fully capture the necessary end points of interest.	—	YES	YES	YES	YES Health care providers Registry/data holder Patient community
Self-image/body image	—	—	YES	—	—
Fertility	—	—	YES	—	—
Relationships	—	—	YES	—	—
4.2 Response to treatment					
Progression	YES	YES	—	—	YES Registry/data holder
Relapse	—	—	—	—	YES Health care providers
Survival:					
Radiation-free survival	—	—	—	YES	—
Toxic chemotherapy agents' free survival	—	—	—	YES	—

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
Overall survival	YES	YES	—	—	YES HTA bodies Health care providers Registry/data holder Industry Regulator
Progression-free/ event-free survival	YES	—	—	—	
Response rate (stable, minor response, partial response, or complete response)	YES	—	—	—	—
% of tumour resection	YES	—	—	—	—
Tumour control/ tumour volume	YES	—	—	—	YES Health care providers Patient community
Toxicity/adverse effects or events (e.g., secondary tumours, cognitive impairments)	YES	—	—	YES	YES Health care providers Registry/data holder Industry
Tolerability	YES	—	—	—	—
Vision/sight	YES	—	—	YES	YES Health care providers
Motor function	YES	—	—	—	—
Standardized Response Assessment Criteria (use RAPNO for the pediatric population and the RANO for adults)	—	—	—	—	YES Health care providers

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
4.3 Quality of life					
General measurement considerations Stakeholders noted the need to assess quality of life along the treatment path, including between treatments. Quality of life was mentioned as an important factor from a health economics perspective.	–	–	–	–	YES HTA bodies Health care Providers
Indicators that may be important for measuring the impact of pLGG on Quality of Life as reported by stakeholders:					
Time out of school	–	–	YES	–	YES Patient community
Time out of regular daily activities (e.g., playing with friends, hobbies)	–	–	–	–	YES Patient community
Side effects from medications	–	–	–	YES	YES Patient community
Number of clinic visits (regular visits vs side effects visits or admissions)	–	–	–	–	YES Patient community Health care providers Registry/data holder
Number of hospital/ emergency room visits	–	–	–	–	YES Patient community Health care providers
Number of hours spent in hospital	–	–	–	–	YES Health care providers
Number of needles/ pokes	–	–	–	–	YES Patient community

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
4.4 Psychosocial burden					
Mental health/ emotional burdens	–	–	YES	–	–
Social skills and social Development	–	–	YES	–	–
Academic performance (e.g., scholarship)/work status	–	–	YES	–	–
4.5 Caregiver burden					
Mental health/ emotional burden	–	–	YES	–	–
Travel time	–	–	YES	–	–
Out-of-pocket costs:					
Diagnosis	–	–	–	YES	–
Dispensing and preparation fees	–	–	–	YES	–
Non-approved or non-reimbursed treatments	–	–	YES	–	YES Health care providers
Travel expenses (e.g., gas, parking, public transit, overnight stays)	–	–	YES	–	–
Medical tests and procedures	–	–	YES	–	–
Medical supply and equipment costs for at-home care	–	–	YES	–	–
Complementary alternative medicines (e.g., vitamins, supplements)	–	–	YES	–	–
Resources/services to support changes in sight, speech, and mobility	–	–	YES	–	–
Psychosocial support	–	–	YES	–	–
Childcare	–	–	YES	–	–
Other non-medical supports	–	–	YES	–	–

Indicators / outcomes	Source of reported indicators/outcomes				
	Key findings from the evidence overview	Registry/data holder overview[a]	Patient community perspective from pre-meetings	Health care provider perspective from pre-meeting	Multi-stakeholder meeting[b]
Costs for drugs post-trial	—	—	—	—	YES Patient community
Time out of work/loss of income	—	—	YES	—	YES Regulator
Influence of the following indicators on cost to families/ caregivers: • Geographical location • Marital status (e.g., single parent vs. 2-parent family) • Number of other children in the family	—	—	—	—	YES Regulator

[a] This column represents the indicators/outcomes that were identified as measurable and relevant to the pLGG population by the data holders. It is not a comprehensive summary of all the indicators that could be measured from the registry.

[b] The types of stakeholders that mentioned the indicator/outcome are listed in each cell.

References

1. Annemans, L. & Makady, A. TRUST4RD: tool for reducing uncertainties in the evidence generation for specialised treatments for rare diseases. *Orphanet J Rare* Dis 15, 127, doi:10.1186/s13023-020-01370-3 (2020).
2. Duchscherer, C. & Davies, J. (ed Health Quality Council of Alberta) (Calgary, 2012).
3. Incident Analysis Collaborating Parties. Canadian Incident Analysis Framework, Section H: Creating a Constellation Diagram. Edmonton, AB: Canadian Patient Safety Institute; 2012.
4. Donabedian, A. The Quality of Care: How Can It Be Assessed? *Journal of the American Medical Association*, 1743-1748 (1988).
5. Larouche, V. et al. Incidence trends in pediatric central nervous system tumors in Canada: a 15 years report from Cancer and Young People in Canada (CYP-C) registry. *Neurooncol Adv* 2, vdaa012, doi:10.1093/noajnl/vdaa012 (2020).
6. Goebel, A. M. et al. Natural History of Pediatric Low-Grade Glioma Disease - First Multi-State Model Analysis. J Cancer 10, 6314-6326, doi:10.7150/jca.33463 (2019).
7. Fangusaro, J. et al. Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet Oncology* 21, e305-e316, doi:10.1016/s1470-2045(20)30064-4 (2020).
8. Ryall, S., Tabori, U. & Hawkins, C. Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun* 8, 30, doi:10.1186/s40478-020-00902-z (2020).
9. Bennett, J. et al. Canadian Pediatric Neuro-Oncology Standards of Practice. *Front Oncol* 10, 593192, doi:10.3389/fonc.2020.593192 (2020).