PEDIATRIC LOW-GRADE GLIOMAS (PLGG)

Voice of the Patient Report

Externally Led Patient-Focused
Drug Development Meeting (EL-PFDD)

Public meeting: February 23, 2024
Report submitted: August 5, 2024

Hosted by:

Pediatric Brain Tumor
FOUNDATION

This report is dedicated to the brave children and young adults facing life with a brain tumor and the devoted families by their side.

Voice of the Patient: PEDIATRIC LOW-GRADE GLIOMAS

AUTHORS: This report was submitted and prepared on behalf of the Pediatric Brain Tumor Foundation. Input was provided by Courtney Davies (President and CEO), Ian Joyce (Chief Marketing and Mission Experience Officer), Dr. Ryne DeBo (VP of Research), and Dr. Michael Kennedy. The Pediatric Brain Tumor Foundation contracted with consultant Trista Dawson Rutledge for assistance in writing this report.

CONSULTING ADVISORS: Larry Bauer, RN, MA, and James Valentine, JD, MHS, offered crucial guidance and support for the meeting as well as for the review of the Voice of the Patient Report. Hyman, Phelps & McNamara, P.C. is a law firm that represents sponsors who are developing drugs for rare diseases and patient advocacy organizations.

ACKNOWLEDGMENT: Thank you to all the parents who participated in the meeting and shared stories of their children's journey with pLGGs and the profound impact on the entire family.

We are also grateful for our supporting organizations: American Brain Tumor Association, Brain Tumor Network, Making Headway Foundation and Children's Brain Tumor Foundation.

Special thanks to Dr. Elizabeth Duke (FDA) for discussing the importance of EL-PFDD meetings, as well as Dr. Jason Fangusaro (Children's Healthcare of Atlanta) and Dr. Rob Lober (Dayton Children's Hospital) for providing in-depth medical overviews of pLGGs.

Thank you also to Dudley Digital Works for providing technical support around the meeting.

DISCLOSURES: This meeting was organized by the Pediatric Brain Tumor Foundation with financial support by Day One Biopharmaceuticals and The Sontag Foundation.

Important note: Although financial support was provided, no pharmaceutical company was involved in the planning, content or coordination of the meeting.

PUBLIC MEETING: February 23, 2024

PUBLICATION DATE: July 17, 2024

SUBMITTED TO: Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)

VERSIONS AND MODIFICATIONS: This document has not been revised and/or modified in any way after the report date. The submitters have all necessary permissions to submit this external resource to the FDA and linking to this resource from the FDA website does not violate the proprietary rights of others.

POINT OF CONTACT: Ian Joyce, Chief Marketing and Mission Experience Officer, ianjoyce@curethekids.org

Table of Contents

EXECUTIVE SUMMARY

Pediatric low-grade gliomas (pLGGs) are a diverse group of brain tumors affecting children and adolescents. These tumors exhibit a wide array of molecular subtypes, each with distinct genetic and biological characteristics.

For some patients, if the tumor is in an accessible location and can be fully removed without damaging essential brain functions, surgery can be curative. For most though, surgical resection is often incomplete and does not fully eradicate the tumors. And for some, the location of the brain tumor does not permit any type of resection or debulking of the tumor and other approaches must be considered.

Despite being characterized as "benign" tumors with high survival rates, children with pLGGs face a wide spectrum of serious physical and mental health conditions that they will have to live with for the rest of their lives. In some cases, the tumor causes complications leading to premature death. In addition, there are many unknowns, surrounding if, how, and when the tumor will progress and what that means for their future.

Advances in molecular biology have paved the way for the development of targeted therapies, offering hope for more effective treatments. However, there remains a dire need for more options and further innovation in this area, particularly for treatments with less toxic side effects and those that will help preserve functional abilities for these children to lead healthy and productive lives.

On February 23, 2024, the Pediatric Brain Tumor Foundation convened an Externally led Patient-Focused Drug Development (EL-PFDD) meeting on pLGGs. The goal of this meeting was to enable the FDA and other important drug development stakeholders to hear from those directly impacted by pLGGs. Participants shared their experiences with symptoms and the daily impacts of these tumors, as well as the tremendous need for new treatment options.

The meeting presentations, video stories, panelist discussions, caller remarks, meeting polling data and comments submitted online provided the content for this "Voice of the Patient" report.

KEY MEETING THEMES

Several themes emerged from the meeting which are summarized below and explored throughout the report.

- **Pediatric low-grade gliomas (pLGGs) are the most common type of brain tumor in children and despite being classified as "benign" or "low grade," pLGGs have profound and far-reaching impacts on the health and long-term well-being of the child and entire family.**
  - Affected children face life with a brain tumor that can grow and change over time, which can potentially lead to more severe symptoms, potential disabilities and unknown capabilities for the future.
  - Parents bear an immense burden, from worrying about tumor and symptom progression to agonizing over critical medical and treatment decisions, all while deeply concerned about the care of their children and what the future holds.

- **Many affected children suffer extensive physical and mental health effects, not only from the tumor itself but also from multiple surgeries, extensive chemotherapy and severe side effects.**
  - Children can become physically disabled, suffer from incapacitating headaches and seizures, lose their vision, struggle with frequent vomiting and deal with a range of other debilitating symptoms from pLGGs and side effects from treatments.
  - Emotional and mental impacts seen in children are often severe, ranging from behavioral problems and cognitive delays to medical trauma and anxiety.

- **pLGGs drastically diminish quality of life by negatively impacting normal childhood development and essential activities such as school, sports and social interactions, with lasting impacts both now and for the future.**
  - Academic and extracurricular activities suffer as children face a range of challenges including behavioral issues, learning difficulties and extensive absences.
  - Socially, children diagnosed with a pLGG can face exclusion from their peers and bullying for being different, leading to feelings of isolation and loneliness that can damage mental health and self-esteem.

- **Molecular insights have led to targeted treatments which offer hope for some, but there remains a critical need for effective and tolerable treatment options for these children.**
  - Surgical resection is often incomplete and does not fully eradicate the tumors.
  - While some targeted treatments have emerged for specific pLGG mutation types, there are limited options.
  - There is an urgent need for treatments that minimize off-target side effects, ensuring that children can preserve their quality of life during and after treatment.

- **Treatment success needs to go beyond tumor response and survival rates to focus on the capacity for these children to lead fulfilling, healthy and productive lives into adulthood.**
  - Given that pLGGs are often a chronic condition, focus needs to be placed on how to help children not simply survive, but to truly thrive as they move into adulthood.
  - Treatment efficacy should include long-term functional outcomes related to cognitive function, emotional well-being, physical functioning, and the ability to achieve educational/career goals as well as being able to live independently.

INTRODUCTION

The Externally-led Patient-Focused Drug Development (EL PFDD) meeting on pediatric low-grade gliomas (pLGGs) was held on February 23, 2024. The PFDD initiative by the FDA grew out of the realization that patients and families, who navigate a disease daily, hold unique insights crucial for guiding drug development, risk/benefit evaluations, and drug review.

The information gathered at the meeting and summarized in this report may impact decisions regarding drug development and FDA evaluation of potential therapies, and ultimately, may improve the overall quality of life for children with pLGGs and their families.

The EL-PFDD meeting was organized by the Pediatric Brain Tumor Foundation, a group dedicated to assisting families as they navigate the journey following a child's brain tumor diagnosis, by providing educational, emotional and financial support. The organization is committed to leading the way to a future without brain tumors, with a mission to accelerate the development of treatments, fund novel research and amplify the voices of patients and families.

Disease Overview: Pediatric low-grade gliomas (pLGGs)

Pediatric low-grade gliomas (pLGGs) are the most common central nervous system (CNS) tumor in children, accounting for 30-35% of all pediatric CNS tumors. Unlike their counterparts in adults, these tumors are characterized by slow growth rate and rare progression to higher-grade lesions. Occurring anywhere in the brain or spinal cord, pLGGs present a wide range of histopathological, demographic, radiographic and clinical characteristics.

Symptoms of pLGGs vary widely, depending on both the size and location of the tumor in the brain, rather than being defined by a single characteristic symptom. Most common symptoms include headaches, nausea and vomiting, vision problems (double vision, blurry vision, loss of vision), seizures, endocrine symptoms (changes in weight, premature puberty), difficulty walking or balancing/clumsiness, localized weakness, confusion, sleepiness or changes in behavior.

Recent advances have expanded the understanding of the molecular landscape of pLGGs, allowing the identification of specific mutations and pathways driving the tumor's growth. Key among these are changes in the MAP kinase pathway (MAPK, the most common abnormality in pLGGs) and P13K-AKT-mTOR pathway (mTOR, less common), both of which play crucial roles in the onset and progression of pLGGs. The most common mechanisms of MAPK pathway of pLGG are BRAF fusions (the most frequent BRAF-KIAA1549), alterations in NF1 and mutations in the BRAF gene (BRAFV600E). Less common drivers of pLGG include mutations/fusions of FGFR1, MYB/MYBL1, and NTRK2. Understanding these molecular characteristics can guide the development of targeted therapies, such as inhibitors of MEK, BRAF and pan-RAF (within the MAPK pathway) as well as mTOR. Additionally, newer inhibitors targeting further along these pathways are in the earlier stages of development.

Treatment approaches for pLGGs include:

- **Surgery (resection):** The preferred option, if feasible, is to completely remove the pLGGs through surgery, which can potentially cure the condition. However, complete surgical removal may not be possible, depending on the tumor's location or if the disease has spread (metastasized).

- **Chemotherapy:** When surgery isn't an option or if the tumor cannot be fully removed, chemotherapy is often the next course of action.

- **Targeted therapies:** Thanks to advances in understanding pLGG's molecular basis, including the roles of the MAPK and mTOR pathways, new targeted treatments are being developed. These include inhibitors targeting specific molecules involved in tumor growth, such as MAPK, MEK, BRAF, pan-RAF, and mTOR. It is important to note that the long-term effects of these therapies in children are not well characterized.

- **Watchful waiting (no treatment):** Depending on the size and growth of the tumor, in some cases, ongoing monitoring of the tumor is a suggested path forward, with no treatment considered unless the tumor grows or symptoms change. Tumor tissue can sometimes lose the ability to grow by the time the child is in their late teens/early adulthood.

- **Radiation:** Although radiation therapy can be effective, it's generally avoided in treating pLGGs due to potential risks such as the development of secondary cancers and cognitive decline.

Long-term follow-up studies reveal that most individuals with pLGGs survive well into adulthood, leading to its recognition as a chronic condition of childhood. This shift in classification underscores the importance of looking beyond tumor response and survival rates. It necessitates a broader focus on various outcomes, including motor function, vision and neurological health, and the importance of enhancing long-term quality of life. As these children are likely to reach adulthood, it's crucial to optimize their functional capabilities for their future well-being.

A look at the pLGG journey

- **Symptoms:** Most children will arrive at a clinic or emergency room presenting new symptoms, such as headaches or vomiting.
- **Imaging** Typically a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is conducted on the brain to investigate further.
- **Identification:** When a mass is identified in the brain, the next step usually involves a neurosurgical procedure which could be a biopsy or, ideally, a resection (removal) of the mass.
- **Diagnosis:** The extracted tissue is examined under the microscope for molecular changes to establish a definitive diagnosis of pLGG.
- **Treatment:** In some cases, pLGGs may be managed with surgical resection alone, while others might necessitate chemotherapy or targeted therapy. In some cases, tumors are observed without immediate treatment intervention.

Meeting Overview

This meeting was designed to highlight the experiences and daily impact of pLGGs as well as available treatment approaches and hopes for future treatments (agenda and discussion questions are included in Appendix 1).

The meeting began with opening remarks by co-moderator Courtney Davies, President and CEO of the Pediatric Brain Tumor Foundation, who welcomed participants and shared her hopes that this meeting will encourage future research and successful new product development for pLGGs where new treatments are urgently needed. She noted the profound and far-reaching impact of pLGGs on the health and long-term well-being of the children affected, as well as the severe emotional, mental, spiritual, and financial toll on each family member.

Dr. Elizabeth Duke, Clinical Reviewer in the Division of Oncology 2, Center for Drug Evaluation and Research (CDER), FDA, reinforced the importance of the meeting, noting that patient input can help support the FDA in conducting benefit-risk assessments for products under review and advising drug sponsors on development programs.

Dr. Jason Fangusaro, Director of Developmental Therapeutics at Children's Healthcare of Atlanta, provided an in-depth medical overview of pLGGs, illustrating the complexities of the disease and wide-ranging symptoms faced by affected children. Later in the day, Dr. Robert Lober, Director at the Living Biobank at Dayton Children's Hospital, discussed current and investigational treatment strategies, including considerations for parents and patients.

James Valentine, JD, MHS, from Hyman, Phelps, & McNamara, P.C., who helped launch the PFDD program during his time at the FDA, served as co-moderator and outlined the meeting format and guidelines.

Both the morning and the afternoon sessions included pre-recorded video submissions from parents followed by panel discussions. There were panelists for each session that attended live via zoom and responded to questions from the moderator. Viewers were encouraged to provide their perspectives via phone and or by submitting written comments online. Participants were also periodically invited to respond to online polling questions (by using phone, computer or tablet) to provide a sense of demographics and experiences. Caregivers were instructed to respond for patients currently under their care or for those who may have passed away from pLGG complications.

The meeting concluded with a summary provided by Larry Bauer, RN, MA, a former member of the FDA Rare Diseases Program, and closing remarks from Courtney Davies and James Valentine.

Members of the pLGG community were invited to submit written comments both during the meeting and in the 30 days following, which were incorporated throughout this report and included in Appendix 2.

A recording of the pLGG EL-PFDD meeting in its entirety can be found here:
https://www.youtube.com/watch?v=8FGLg0MboD8

Meeting participants: By the numbers

- 30+ parents of children with pLGG
- Age of those with pLGG represented: 30% were under the age of 5, 37% were between 6 and 12 years old and 33% were between 12 and 18 years old
- Age of diagnosis of pLGG represented: birth to 1 year (5%), 1-3 years old (38%), 6-10 years old (41%), 11-18 years old (16%)
- Almost an equal split of female/male representation
- Majority of participants reside in the US Eastern region, with some representation from the Pacific and Central time zones in the US, as well as Europe

Report Overview

This Voice of the Patient report intends to support the FDA's understanding of the pLGG burdens and unmet medical needs of children and their families, and their personal perspectives on current and future treatments. This input may also be of value to the drug development process more broadly as well as informing clinical trial design.

This report aims to summarize the input provided by parents during the EL-PFDD meeting and is not meant to represent in any way the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments or other aspects of pLGGs that are not included in the report.

LIFE WITH PLGGS: SYMPTOMS AND IMPACT

Parents described a challenging spectrum of pLGG symptoms, including motor functioning issues and loss of balance, speech and vision difficulties, nausea/vomiting, fatigue, as well as profound mental health impacts and other health concerns. A meeting poll highlighted the most distressing symptoms as motor function/balance issues, vision problems, and anxiety/depression (see Appendix 3 for polling results). What became clear during the discussions was the far-reaching impact on daily life for affected children and their families.

Top worries for parents are that pLGG symptoms will get worse and their child will die prematurely

Cynthia, mother to her 2-year-old son with pLGG, said: **"I fear what Greyson's future will be and how long it will be. I fear what his quality of life will be if the tumor invades other critical areas of the brain."**

Children experience a wide array of severe symptoms that can evolve over time

Children with pLGGs experience a diverse range of symptoms, influenced by the tumor's size and location. Families often find themselves in an endless battle to manage evolving symptoms, reflecting the complexity and unpredictability of this condition.

"It's been one thing after another. I feel like we're chasing control of these symptoms and it's a never-ending cycle," said Caitlyn, mother to 10-year-old Adelaide with pLGG.

Alice wrote about her daughter who has been living with pLGG for more than two decades, highlighting just how quickly things can change: "After a period of stability, nine years, her tumor exploded at age 19, and she had a major surgery followed by a brain hemorrhage and subsequent emergency major brain surgery."

Loss of movement and mobility

Parents noted the physical disabilities experienced by affected children with pLGGs, either due to the tumor itself or as a result of surgery. They recounted a range of challenges from balance issues to the loss of function on one side of the body to losing the ability to walk.

Christine spoke about her son Peter who was diagnosed with pLGG around age 3. She talked about him having weakness on his right side, not being able to hold things in his right hand. "He was dropping his school bag a lot, dropping his jacket a lot, and then ultimately when we were doing potty training, he wasn't able to push down and pull up his pants. He was only using his left hand."

Cynthia noted that her son Greyson "is showing signs of left-sided weakness and asymmetry in his gait."

"As birthdays pass, Inayah throws coins into wishing wells, hoping that she'll soon walk again," said Khadijah, whose daughter with pLGG remains unable to walk on her own.

Visual impairment

For some children with pLGG, visual impairment is a profound challenge, in some cases leading to legal blindness which can severely restrict daily activities and create challenges to becoming independent.

Heather wrote that "vision has been the most significant impact of pLGG for my daughter. She is well adjusted but is legally blind and it has been a challenge for her as well as the rest of the family. There are many activities we no longer participate in due to her vision. It affects her everyday of her life."

While Amy shared that within six weeks of starting chemotherapy, her daughter (age 10 at the time) "lost all but near, blurry, peripheral vision in her eye" which was the start of many years of trying different treatments to retain what vision she had left.

Medical anxiety and trauma

In the grip of ongoing medical care, children and their families frequently endure the emotional turmoil of medical anxiety and post-traumatic stress disorder (PTSD). Routine medical encounters can become battles, stirring deep fear in the child, and casting a long shadow of distress and heartache over the entire family. This cycle of fear and trauma is magnified by each hospital visit, surgery or treatment, creating ongoing emotional turmoil and stress.

Joseph, father to his son Joseph who was diagnosed at age one, talked about the prevalence of medical anxiety and PTSD. He spoke about trying to take his son for a routine dental cleaning and that the mere sight of medical personnel is so traumatizing that his son "screamed and fought and begged for us to stop" with the parents trying to hold him down. Joseph said: "It's not only traumatizing for him, it's re-traumatizing for us because it reminds us of some of those initial hospitalizations." They ended up not being able to get the teeth cleaning done and now have to schedule it six months in advance to arrange for sedation.

Stephanie, an oncology nurse and mother to a young son with pLGG said: "The challenges of getting him into a doctor's office or a hospital are exhausting. We know that he's going to struggle. We've watched him be restrained with a sheet to get an IV in his arm, and it's heartbreaking. We're very anxious before any appointment, whether it be our fear for Declan or our fear for what we're going to be told at that appointment. Declan's been diagnosed with anxiety, PTSD from medical trauma and ADHD."

Frequent nausea and vomiting

Nausea and vomiting can profoundly disrupt the lives of children. Parents recounted the harrowing frequency and intensity of these episodes, with affected children experiencing everything from daily bouts of vomiting to distressing throat sensations.

Joseph said that his young son's most severe symptom has been vomiting "almost every day, often multiple times a day." He described the experience as being "very traumatic waking up and throwing up at two or three years old and being covered in your own vomit and not knowing really what's going on" adding that once his son begins vomiting, he has a difficult time stopping.

Chetasi, mother to three-year-old Aashvi with pLGG, described a similar experience: "The nausea and vomiting were constant despite titrating the anti-nausea medications" and noting that her daughter "woke up with projectile vomiting on many occasions."

Shelley discussed her 9-year-old son Max's experience who, while he doesn't vomit, described a sensation he refers to as "spiderwebs" in his throat. He describes this feeling as a gagging sensation similar to what it might feel like if there were actual spiderwebs obstructing his throat.

Debilitating dizziness and vertigo

Dizziness and vertigo present unique challenges in children, with parents describing how these conditions restrict their children's participation in normal activities, leading to both physical and emotional distress.

Shelley talked about her son's experience with low-grade dizziness, saying that "backwards motion instantly starts that vertigo," such as when laying down for an MRI or sleep. She goes on to say that "he'll have days where he wakes up and says, 'I don't feel good.' That's his reality. It's a combination of dizzy and nauseous. I feel like he's a little old man."

Caitlyn talked about the debilitating nature of dizziness for her daughter with pLGG: "On Adelaide's best days, she seems much like a normal ten-year-old little girl, but on her bad days, she can't walk, doesn't want to eat because she is so dizzy. On a bad day, Adelaide is pretty much couch or bed-bound until we get the dizziness under control." She goes on to say that the dizziness has impeded her in school and has stopped her from horseback riding.

Constant monitoring and management of seizures

Seizures frequently serve as a primary symptom of pLGGs, indicating the tumor's impact on brain function. These seizures can vary in severity and frequency, with many parents describing the constant shadow of uncertainty, bracing for when the next seizure might strike.

Cynthia, mother to a 2-year-old with pLGG, said: "I hope that Greyson doesn't have to feel the fear of another seizure. He is aware of them and comes to me crying before it happens with eyes wide, terror on his face. He stops breathing and gags all the while looking at me with fear. It crushes me I can't take his pain away."

Stephanie, an adult oncology nurse, shared her experience: "My son, Declan, started having freezing spells when he was three, where he would grab his chest and kind of wince in pain. And originally, the pediatrician thought that he might be having some type of constipation. It wasn't until our third visit when I was begging for answers in the Boston Children's Emergency Room where we learned that those freezing spells were seizures and he was having up to 15 of them a day."

Severe headaches and migraines

Headaches are a common presenting symptom of pLGGs, often signaling the presence of brain tumors. Their frequency and intensity can vary, potentially affecting the child's daily activities and overall quality of life.

Sam talked about his daughter Maddie who started having headaches at three years old and now in kindergarten when talking to her teachers, "the headaches are the biggest question that come up."

Katie talked about her son Alexander, now 22 years old who was diagnosed after 12 months of "terrible migraines" along with a number of other debilitating symptoms. While Geralynn shared that her 24-year-old daughter Anna has "chronic nausea, migraines that last two to three days."

Speech impairment

Parents described the impacts of pLGGs on their children's communication abilities, highlighting issues such as excessive drooling, speech difficulties and delays. These challenges not only affect daily interactions but also raise concerns about social difficulties.

Shelley talked about her 9-year-old son Max who experiences drooling and speech issues due to where is tumor is located. "Sometimes he'll be talking and the drool will literally... There will be a big blob that will just fall out while he's talking." She worries about potential bullying as well as his speech being impacted further and not being able to be understood.

Christine talked about her young son Peter: "The main problem that we're having is with his communication. The right-side weakness impacts his face and his tongue. He can be quite difficult to understand and he still has drooling. He gets frustrated when he's not understood." Alice also noted that her 26-year-old daughter has "severe difficulty with speech."

Cognitive challenges

Cognitive challenges in children with pLGGs can vary widely but often include difficulties with attention, memory, processing speed and executive functioning. These challenges can result from the tumor itself due to its location in the brain or side effects of treatment.

Janet, mother to Kelsey who lives with pLGG said: "Before Kelsey's first really aggressive resection, she was four and she hadn't even been in kindergarten, and she could already tie her shoes. And after that surgery, she said to me, 'Mommy, I used to be smart, but now I'm like not.'

Cathy talked about her daughter Erin, sharing that at 25 years old, she has issues with executive function and many traits of autism.

Mandy wrote that "the most significant impact of our daughter's brain tumor is her memory impairment. Her short- and long-term memory are severely impacted, with the same conversations multiple times a day and a limited ability to retain what she has learned. She now has specific learning disorders with impairment in reading, written expression, and mathematics, as well as severe neurocognitive deficits with diminished verbal learning and memory skills."

Other symptoms:

Parents shared a diverse array of symptoms, beyond those commonly identified. The range of symptoms, which undoubtedly extend beyond what is covered in this report, underscores the multifaceted impact of pLGGs on patients' health and quality of life.

- **Hiccups for days:** Shelley talked about her son who has "hiccups that sometimes last literally for days. He'll hiccup all day long, all through the night, all day long, all through the night and big deep ones." She went on to say that his muscles and rib cage "gets really sore" with the hiccups also reducing his appetite.
- **Sinus pressure:** Joseph noted that his son "constantly has sinus infections," while Sam shared that his daughter deals with "really bad sinus pressure."
- **Scoliosis:** Bonnie wrote about her son diagnosed at the age of three, noting that "treating scoliosis along with the tumor is a delicate balance. Scoliosis hardware can get in the way of the imaging for the tumor monitoring."
- **Hallucinations:** Janet shared that her daughter's symptom of audio hallucinations "were terrifying to her". She went on to say the hallucinations "sounded like lions growling. She was three. She couldn't explain it to us."

pLGGs profoundly impact the daily lives of affected children and their families, with lasting implications for the future

Parents shared that because of pLGG, their loved ones were not able to attend school, play sports, work, attend social events and more (see meeting poll in Appendix 3). In addition, many noted how the personality and abilities of their children completely changed throughout the journey due to the tumor itself as well as various surgical and treatment interventions. A recurring theme in the discussions was the paradox of how a "benign" tumor could drastically affect every facet of life for the children involved and their families as a whole.

Cathy said about her 25-year-old daughter Erin, living with pLGG. "She will never drive. She will never be able to have a family of her own. She'll never live independently. She's not accepted by her peers. She went from a child that was ahead of the curve at four years old to a person that will never live a normal or independent life due to this benign low-grade tumor."

Geralynn spoke about her daughter, diagnosed at 14 and now 24: "The impact the disease has had on Anna's daily life, no one prepared us for. No one prepared us for this." She goes on to say that "the color for brain tumor [awareness] is gray, and Anna's forever altered life is in a constant state of gray."

"My daughter's life has been nothing short of a tragedy," said Cathy, whose daughter Erin lives with pLGG.

Education challenges

Navigating the educational landscape presents significant challenges for families affected by pLGG. The impact of the condition on children's academic performance and attendance is profound, with challenges ranging from fatigue to frequent absences, significantly hindering their ability to function effectively in school. Parents face the additional struggle of ensuring that educators understand their child's unique needs and create a balance between acknowledging the child's differences and challenging them.

Janet, whose daughter Kelsey lives with pLGG, talked about the impact on schooling and ongoing challenges with the school: "She experienced so many years of exhaustion, she wasn't able to function academically" and that "there were a lot

of battles with the school systems trying to figure it out, knowing most teachers have never had a child with cancer, let alone a brain tumor. So that was really, really challenging."

Maria talked about the struggles her 14-year-old son Gavin is having in school: "A once honor student in advanced classes is now receiving 40s on exams." And goes onto say that "Gavin was in the hospital for 24 days with his most recent surgeries. So besides the effects of surgery, he missed the whole first quarter of his high school year."

Stephanie wrote: "It amazes me how hard it is to get educators to understand the need for an IEP. These children have the equivalent effect as a traumatic brain injury. We were turned down for an IEP for 2 years before we finally convinced them he needed one."

Christine talked about navigating challenges in the classroom: "We need to know that the caregiver in the classroom is aware of that and understands what a concerning symptom is and what to do. And when there's a pool of substitutes circulating through the classroom, that's a major concern because there was no protocol at the school for how to pass on that information." She also noted challenges around wanting his differences to be acknowledged while wanting him to be challenged and "we haven't quite found what that balance should be."

Restricted participation in sports/activities

Some children experience physical limitations that prevent them from participating in sports, which affects not just their physical activity but also their social interactions and team experiences. Others may become risk-averse, fearful of physical interactions that could lead to injury, leading them to withdraw from active play and observe rather than participate.

Lesli wrote that "prior to my daughter's diagnosis she was very active and played soccer competitively on a travel soccer team. Following her surgery, she was left with weakness on her left side and balance issues and has never been able to return to soccer and she misses playing not only for the sport but social impact as well."

Shelley noted that because of her son's physical limitations, it impacts how he plays at recess with his friends: "They're all running around playing soccer and he just doesn't have that ability to join in. He often feels isolated because of that."

Jennifer talked about her son Sam who is now eight years old, diagnosed at 20 months: "He's pretty risk averse," often sitting and watching other kids. She said: "I think he fears being in a situation where he doesn't have full control of the physical environment, so he fears being pushed or kids run fast past you. He can't run as fast. I think he's scared of getting run over a bit or not getting out of the way in time."

Leads to significant trauma and mental health consequences

The profound mental health impacts faced by individuals, especially during critical developmental stages, manifest as feelings of isolation along with intense fears about the future. These struggles not only affect the individuals but also bring significant emotional distress to their families.

"The mental health impact is tremendous. The unknown about the future of this disease is difficult for children to live with. My son worries that in a year he won't be able to walk again or breathe on his own, or that he won't live another year. This tumor continues to take away from our kids," said CJ.

Janet, whose daughter lives with pLGG, said that "for all of these kids, whether it's wanting to play a sport or just have friends, that's a trauma in and of itself. And it's a trauma to the whole family because we grieve for our kids."

"These kids are in their developmental time of their lives, they're identifying who they are as people and understanding who they are and how they relate to people," said Shelley, who went on to share that her son feels different, alone and isolated.

Heavy burdens for caregivers: Navigating constant worries about today and the future

Navigating pLGG plunges parents and caregivers in a state of constant vigilance, from deciphering everyday health concerns to making life-or-death decisions for their child to concerns about the future. The unrelenting worry and enormity of this responsibility reflects the intense challenges faced when caring for a child with pLGG.

Fears around everyday health concerns: Sam talked about his daughter Maddie and the constant worry: "When she has a headache or feels under the weather, we always wonder if it's a cold or a medical emergency related to her tumor."

Overwhelmed with life-or-death decisions: Christine, mother to her young son Peter with pLGG, talked about the enormous decisions parents face: "Should we be more aggressive with surgery? Should we wait it out and hope for a better treatment to come so we can avoid that? This is all on me. I am the accountable person. It's not the doctor. It's not the surgeon. It's me because I'm the one who's pushing him through this medical system. I feel that weight. I feel that burden. I feel that responsibility."

Worries about symptoms progressing and the potential of their child dying: Chris, who lost his son David to pLGG, wrote: "Though death from these tumors is uncommon. It does happen and it should not be ignored as rare. We lost a really good kid with a lot of potential, just like all of these kids."

Grief for their child missing out on their dreams: Stephanie said of her young son Declan who dreams of being a police officer but with pLGG that will never be a reality. "His brain tumor, a tumor considered benign, has taken away the ability for him to live a life that he dreams of." Geralynn spoke about her daughter, diagnosed at 14 and now 24, saying, "She has her high school sweetheart and they will get married in a couple years and I worry about her being able to have children someday."

Fears of chronic dependence: Khadijah talked about her daughter with pLGG: "Today, Inayah is 12 years old and still unable to walk on her own…She's dependent on me for bathing, transporting, and many other things as she still has problems with balance and coordination." Lesli wrote: "My biggest fear as my daughter gets older is that she won't be able to live independently."

Concerns for what the future holds: Shelley, talked about her son Max with pLGG saying: "Will he be able to drive? Will he be able to have a job? Will he be able to be in a relationship? Will somebody want to take on a relationship with somebody who has a brain tumor? I mean, that might cause somebody to pause. So yeah, I have a lot of concerns, and its that constant unknown, I guess, is not knowing where the tumor is going to go, what's going to happen in the future with that. It's hard."

"Really there are no accomplishments that have meaning when you see daily that you may or may not lose your child. It's an acute clarity," wrote Amanda, whose daughter lives with pLGG.

CURRENT TREATMENTS AND HOPES FOR THE FUTURE

Many current treatment approaches for pLGGs are associated with potentially acute as well as life-long adverse effects. Parents shared heart-breaking journeys of navigating numerous surgeries, issues with shunts, rounds of chemotherapy, endless scans and more. The pleas for more treatment options with manageable side effects were clear, as parents fear for how the tumor will impact their children's lives and the threat it poses to a "normal" future.

Children face extensive surgeries, harsh side effects and endless interventions

Children with pLGGs endure an overwhelming journey marked by invasive surgeries, prolonged chemotherapy sessions, and an array of side effects. Their lives are often characterized by a relentless cycle of medical interventions aimed at controlling the disease, which imposes a continuous state of crisis and adaptation for both the children and their families. A meeting poll showed that 50% of participants see their current treatment regimen as treating the most significant symptoms only "somewhat," with the biggest drawbacks to current approaches noted as not being very effective at treating the target symptom, side effects, only treating some symptoms, high cost/co-pay and limited availability/accessibility (Appendix 3).

Sam talked about this experience with daughter Maddie who had "several surprise surgeries to deal with shunt malfunctions and the related headaches and pain that go along with those." More recently, she finished the first course of a year-long chemotherapy followed by another surgery which ended up being nearly 20 hours long.

Lisa wrote about her daughter who was diagnosed with pLGG 24 years ago. "She's had six brain surgeries, had radiation at the age of two, and is currently on her tenth drug therapy. Her pLGG is a chronic condition where treatment has caused many disabilities."

Janet noted that her daughter with pLGG has undergone 24 surgeries.

"Crisis mode is our norm," said Stephanie, an oncology nurse whose young son lives with pLGG. **"Declan's had 18 months of chemotherapy, seven surgeries, 21 sedated MRIs, thousands of seizures and numerous side effects."**

Surgery: Often the initial treatment, yet with potential for severe consequences

The ability to successfully resect the tumor depends on the location and size of tumor. Although removal of the entire tumor equates to a cure, for many children, that is not possible as the tumor is either throughout the brain or in an area where it cannot be safely resected. Surgery also brings considerable risks and unknowns, with several parents recounting how they said goodbye to their child entering surgery, only for them to return a different child.

Several parents talked about the devastating impact of the surgery

Khadijah, mother to Inayah who lives with pLGG, talked about her daughter's initial surgery: "We were relieved when she awoke and began to talk and answer questions. Unfortunately, our relief only lasted a short time, as she became mute and lost her ability to walk and move. My youngest child who was always singing, chatting and running around was now like a newborn child, unable to speak or hold her head up, stand."

Cathy shared a devastating account about her daughter Erin's experience: "My daughter entered the surgical suite a happy neurotypical four-year-old and came out a completely different person." She goes on to say that everything changed when she came out of surgery, being unresponsive for 12 months: "She was mute, unable to swallow her own secretions, unable to voluntarily move her limbs. She was incontinent. She was unable to hold her own head up, she was unable to move her eyes, her fingers, or any other part of her body. She was fed by a tube for over eight months."

CJ wrote, **"We are certainly not back to the child we said goodbye to on the day of his first surgery."**

For some, surgery is used until other options become available

Cynthia, mother to 2-year-old Greyson said: "I hope this surgery buys us time as we wait for an FGFR inhibitor to become available for his FGFR3 mutation."

For others, surgery is not an option at all

As one parent recounted: "the first best case scenario is not having a tumor and the second-best case scenario is a gross total resection. And neither of those were our options."

"We were told that surgery is not possible. It's like trying to separate coffee and milk from a cappuccino, this metaphor used by the oncologist will stay with me forever," said Paola whose daughter Monica was diagnosed at nine months old.

Chemotherapy: Decades old with toxic side effects

The reliance on decades-old chemotherapy protocols for treating pLGGs brings with it a host of severe side effects for children to endure, from invasive IVs and ports, frequent lab work and diagnostic tests, compromised immune systems, repeated hospitalizations, and cognitive and physical impairments.

Janet, whose daughter lives with pLGG, talked about the lack of innovation in chemotherapy that "when we started in 1994, it was already a 25-year-old protocol and it was the only protocol."

Stephanie, an oncology nurse and mother to young son Declan with pLGG said: "Chemo led to a low immune system, platelet transfusions, increased seizures, nausea, vomiting, and multiple hospital stays."

Lacie shared about her son who was diagnosed with pLGG at four months old and is now 13: "The symptoms that have most significant impacted Jimmy are the side effects from the chemotherapies currently offered to treat pLGG. From cognitive delays to physical and OT delays, as well as pain in the body. Whether from a stomachache, diarrhea, nausea and just an overall lower quality of life. He has had to fight every inch to have some semblance of a normal life."

Targeted inhibitors: Some success but limited options

While there are some targeted treatments that offer hope by stabilizing tumors in some pediatric cases, there are limited options and many unknowns regarding their long-term impact.

Katie spoke about her 22-year-old son trying different targeted treatments: "Alex says he feels like a lab rat, but that he is certain that he is still alive because of the targeted treatments that he has taken."

Heather talked about her daughter being on oral inhibitors. "Her treatment continues to keep her tumor stable, which is great, but there are many unknowns. We do not know the long-term side effects. At times, the side effects of the medication are difficult. She fatigues easily and struggles to keep up with peers. She develops skin reactions and fevers associated with the medication. These side effects cause her to miss school and other fun activities which is heartbreaking. No child should have to miss out on the fun things in life, she has had to grow up way too fast."

Rebecca shared her daughter's experience with a BRAF/MEK inhibitor: "Our daughter's most significant symptom is not addressed by her current treatment, unfortunately. She has a very rare symptom that causes her eyes to roll in the back of her head every 15-45 seconds in varying degrees of intensity. We were hoping that the inhibitors would shrink her tumor to reduce the severity of the symptoms, but unfortunately it has not shrunk it at all - just kept it stable. We are in a circumstance where we have a successful treatment by definition (i.e. the tumor is stable), however we are not seeing improvement of symptoms. So at this point, we are struggling with when to consider a more aggressive treatment that may have more significant side effects in order to see quality of life improvement with potential shrinkage."

Additional therapies

A wide range of supportive therapies were noted by parents beyond the primary medical treatments for children with pLGGs. A meeting poll showed that physical/occupational therapy as most often used, followed by speech therapy and counseling/psychotherapy, among others (Appendix 3).

Future treatments

The heartbreaking pleas from parents was a common theme throughout the meeting, as many talked about the lack of urgency and focus on pLGG due to its status as a "benign" tumor. Patients with pLGG are in critical need of new, innovative options that help to preserve the lives of these children.

Parents ideal pLGG treatment (short of a cure) would stop disease progression and improve daily functioning, along with providing relief from companion emotional symptoms

Raising the bar for success

Frustrated parents are advocating for a broader definition of success in treating pLGG, emphasizing that treatment goals need to extend beyond mere survival. They urge a shift in perspective that recognizes the serious long-term impacts of the disease, despite its non-malignant status, and calls for more ambitious treatment standards.

Maria, mother to son Gavin with pLGG said: "I'm frustrated that many doctors and companies do not treat it as seriously because this is not considered a malignant tumor. But it does not matter because in the end, the damage is the same, it just happens over a longer amount of time, loss of function and potentially death."

CJ wrote: " I think our experience with the tumors feel like we're always lowering the bar for what we can expect of our child's life."

"Success [for pLGG] is determined as not dying," said Christine, whose young son Peter lives with pLGG.

An outcry for new treatments

Parents watch in desperation, knowing the tumor will continue to grow, with treatment options running out for their child.

Stephanie said: "The reality is that Declan's living with a tumor the size of a lemon in his child-sized brain, and there's no meds to shrink it, there's no surgery that's going to remove it, and this monster will continue to grow."

Joan shared her experience caring for her son, who was diagnosed in 1998 and passed away in 2006. She said it was "eye-opening" that the treatments he went through are the same being offered today. "I just can't believe after all these years that there hasn't been anything really new."

Keith wrote about his 8-year-old daughter: "Our biggest concern is that we don't have many treatment options left and are desperate that more treatments options become available. Her tumors always start growing again after treatments or during. We need more options, more treatments, our little girl need this."

Ideal future treatments are targeted with limited side effects

Parents painted a clear picture of what is needed for the future of pLGG – more precise treatments with fewer side effects. After enduring countless surgeries and rounds chemotherapy, there was a resounding call for more effective and safe treatment options for these young patients.

"We need more targeted therapies, because if she fails this combo, there are not any other good or effective choices to keep her alive," wrote Alice, whose 26-year-old daughter lives with pLGG.

Lisa wrote, "We need treatments that will stop the tumor but have little side effects because a pLGG is a chronic condition and current treatments still have too many possible side effects that increase over time."

Monica shared a similar sentiment that "an ideal treatment will be a targeted approach that gives stability with more manageable side effects."

Lesli wrote: **"We need less invasive procedures that don't damage the brain and leave our children with brain injuries that change their entire life. There are so many devastating and life-changing side effects to the current treatments they receive."**

INCORPORATING PATIENT INPUT INTO A BENEFIT-RISK FRAMEWORK

The assessment of benefits versus risks forms the foundation of the FDA's evaluation process for human drugs and biological products. The Benefit-Risk Framework plays a crucial role in the regulatory decision-making process for drugs, offering essential insights for balancing the advantages and drawbacks of a new treatment being considered.

The following chart was compiled using contributions from the pLGG EL-PFDD meeting that took place on February 23, 2024. It incorporates insights from discussions, polling data, and comments received after the meeting. This example framework aims to assist the FDA in conducting Benefit-Risk Assessments for emerging pLGG treatments.

SAMPLE BENEFIT-RISK DIMENSIONS FOR PEDIATRIC LOW-GRADE GLIOMAS (pLGGs)

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	**Pediatric low-grade gliomas (pLGGs) are the most common type of brain tumor in children and despite being classified as "benign," pLGGs have profound and far-reaching impacts on the health and long-term well-being of the child and entire family.** pLGGs can grow and change over time, which can potentially lead to more severe symptoms, disabilities and unknown capabilities for the future.	**Given that pLGGs are often a chronic condition, focus needs to be placed on how to help children not simply survive, but to truly thrive as they move into adulthood.** Children with pLGGs face a wide spectrum of serious physical and mental health challenges that they will have to live with for the rest of their lives.
Current treatment options	**For some patients, if the tumor is in an accessible location and can be fully removed without damaging essential brain functions, surgery can be curative. For most though, surgical resection is often incomplete and does not fully eradicate the tumors.** Many affected children suffer extensive physical and mental health effects, not only from the tumor itself but also from multiple surgeries, extensive chemotherapy and severe side effects. Children can also suffer from medical anxiety and trauma.	**There is an urgent need for treatments that minimize off-target side effects, ensuring that children can preserve their quality of life during and after treatment.** Treatment efficacy should include long-term functional outcomes related to cognitive function, emotional well-being, physical functioning, and the ability to achieve educational/career goals as well as being able to live independently. **Molecular insights have led to targeted treatments which offer hope for some, but there remains a critical need for effective and tolerable treatment options for these children**. While some targeted treatments have emerged for specific pLGG mutation types, there is a crucial need for a broader spectrum of options.

CONCLUSION

The EL-PFDD meeting on February 23, 2024, provided a critical platform for the pLGG community to voice the profound and often overlooked challenges of a condition misleadingly labeled as “benign.” Participants detailed the extensive effects of brain tumors on their children’s lives, including the relentless cycle of surgeries, chemotherapy and more. They spoke of the painful reality of watching their children miss out on typical childhood experiences compounded by worries for the future.

There is a critical need for more treatments for these children who face a life forever altered by pLGGs. This community urgently needs a broader spectrum of targeted treatments with manageable side effects to ensure these young patients can lead fulfilling and functional lives.

The Pediatric Brain Tumor Foundation is grateful for the chance to offer a glimpse into the daily realities faced by those living with pLGGs. By raising awareness about what these children and their families endure, we aim to inspire further innovation and foster developments that can pave the way for a more hopeful future.

APPENDIX 1 – MEETING AGENDA AND DISCUSSION QUESTIONS

TIME	TOPIC	PRESENTER
10:00 – 10:05 AM	Opening Remarks/Welcome	Courtney Davies, President and CEO, PBTF
10:05 – 10:15 AM	FDA Opening Remarks	Dr. Elizabeth Duke, FDA
10:15 – 10:30 AM	Clinical Overview	Dr. Jason Fangusaro, Children's Healthcare of Atlanta
10:30 – 10:35 AM	Introduction and Meeting Overview	James Valentine, JD, MHS, Meeting Moderator
10:35 – 10:45 AM	Demographic Polling	James Valentine, JD, MHS, Meeting Moderator
10:45 – 11:10 AM	Patient/Caregiver Panel	Pre-recorded Statements
11:10 – 12:30 PM	Audience Polling and Moderated Discussion	Co-moderators
12:30 – 1:00 PM	Break	
1:00 – 1:10 PM	Treatment Overview	Dr. Rob Lober, Dayton Children's Hospital
1:10 – 1:35 PM	Patient/Caregiver Panel	Pre-recorded Statements
1:35 – 2:45 PM	Audience Polling and Moderated Discussion	Co-moderators
2:45 – 2:55 PM	Meeting Summary	Larry Bauer, RN, MA, Hyman, Phelps, & McNamara, P.C.
2:55 – 3:00 PM	Closing Remarks	Courtney Davies, President and CEO, PBTF

TOPIC 1 – LIVING WITH pLGG: SYMPTOMS AND DAILY IMPACT

1. Of all the symptoms and health effects of pLGG, which 1-3 symptoms have the most significant impact on you or your loved one's life?

a) Which symptoms most affect you or your loved one now?

b) Which symptoms were the most significant at other times in you or your loved one's life?

c) What were the first symptoms that you detected (where you suspected something was not right, or when looking back after diagnosis you now believe to be related to pLGG)

2. How does pLGG affect you or your loved one on best and on worst days? Describe your best days and your worst days.

3. How have your or your loved one's symptoms changed over time? How has the ability to cope with the symptoms changed over time?

4. Are there specific activities that are important to you or your loved one that you/they cannot do at all or as fully because of pLGG?

a) How does pLGG affect you or your loved one? What are the challenges you face?

b) How does pLGG affect life activities (school/work, learning abilities, self-sufficiency, living situation, activities, etc.)?

c) If you or your loved one could do one activity that you are currently unable to, what would it be?

5. What do you fear the most as you or your loved one gets older? What worries you most about your or your loved one's condition?

a) What capabilities are you most concerned about you or your loved one potentially losing while growing older?

b) What frustrates you or your loved one most about this condition?

TOPIC 2 – PERSPECTIVE ON CURRENT AND FUTURE APPROACHES TO TREATMENT

1. What are you currently doing to manage your or your loved one's pLGG symptoms?

a) Which specific pLGG symptoms do the treatments address?

b) How has this treatment regimen changed over time and why?

2. How well do these treatments treat the most significant symptoms and health effects of pLGG?

a) How well do these treatments improve the ability to do specific activities that are important in daily life?

3. What are the most significant downsides to your or your loved one's current treatments and how do they affect daily life? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, etc.)

4. Short of a complete cure, what specific things would you look for in an ideal treatment for pLGG? What factors would be important in deciding whether to participate in a new research trial?

APPENDIX 2 – SUBMITTED COMMENTS ONLINE

Organized alphabetically by first name

Name, country	Comment
Alice, USA	My daughter is now 26. She was diagnosed with a PLGG at age 3 and 1/2 months. She has had several major craniotomies, the first ant 4 months, and did carb/vinc and later TPCV. After a period of stability, 9 years, her tumor exploded at age 19, and she had a major surgery followed by a brain hemorrhage and subsequent emergency major brain surgery. The pathology came back grade 3, but V600e, so she had full brain radiation and is now on daily dabrafenib and trametinib. She has had severe ventriculitis, shunt failures and a shunt infection. We need more targeted therapies, as if she fails this combo, there are not any other good or effective choices to keep her alive. She has a ton of endocrine issues, no peripheral vision, no short term memory, severe difficulty with speech, can't live independently, etc.
Amanda, USA	My child nearly lost her sight last October when she then received a shunt. Her masses are disrupting cerebral spinal fluid flow/pressure. Liberty experiences disruption of help about three times a year in her PT OT and now to see her medicine be paid for, without it her masses will grow. As her mom, I long to do something other than hustle for her medicines/ treatments by interfacing with our insurance and now the Medicaid that we are somehow over income for. I do fear she will get skin cancer as this is historically occurs in about 5-10 of the users of Trametineb/ Mekinist users? I don't care if I can't go back to work so long as we can see her live to get married and have a family of her own. Really there are no accomplishments that have meaning when you daily see that you may or may not lose your child. It's an acute clarity. Thank you for listening.
Amy, USA	My daughter began treatment for Optic Pathway Glioma with Carbo/Vincristine in 2018, (age 10) which caused her to get very sick and lose all but near, blurry, peripheral vision in her eye within 6 weeks of beginning treatment. (She began treatment with 20/80 vision in her eye). She switched to Vinblastine and had a good response-tumor shrank and stabilized, and she ended treatment in April of 2019 after 56 treatments. The tumor remained stable until a visual field exam showed more vision loss on 2/22/21. She began treatment again with Irinotecan and Avastin in early February 2022. The Irinotecan made her extremely sick for days at a time, so she stopped that drug and stayed on the Avastin. Her vision improved a bit after a year of Avastin treatments, but her kidneys weren't tolerating it well. (We had reduced dosage and frequency of treatments over the year). Last May of 2023, just three months after ending her year of Avastin, her visual field test again showed decreased vision (what very little she still has). She again started Irinotecan at a lower dose and Avastin. After a couple of months of treatment, she had to discontinue Irinotecan again, and as much as we wanted her to stay on Avastin, she could

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Amy, USA *continued*	only tolerate one treatment every 3-6 weeks. She began Trametinib on Dec. 22, 2023, and is tolerating it well so far. But we are desperately waiting for Day 101!!!!! The surgeons won't perform a biopsy because they want to preserve her eye/vision, so we're hoping and praying that we can even get access to new targeted treatments. But right now we and our team are holding out hope for Day 101. She's a beautiful 16-year-old, and I don't want her to have to fear for her future and worry about her vision and memory loss.
Angelica, USA	My son was diagnosed in 2019 with a pLGG in his cerebellum, he was 13 years old at the time. He had partial resection and has been since taking Debrafenib to manage growth. I keep hearing that there is no data available for the long-term side effects of these inhibitors. This is what they told me 5 years ago and it is still the response every year I ask. What I would like to know is if there is an established research plan to gather information of the pediatric patients taking this drug? This drug has been given to kids for approximately 5-10 years and I would like to understand if there is research platform to monitor these kids and their side effects and start documenting all this information and start building possible theories and patterns of the possible long term side effects. And also who is responsible for this? Are the pharmaceutical companies talking to doctors and research institutions, are they even requesting this information? I would really appreciate some insights about this. My son will be 18 years old next month and I worry about side effects such as infertility and related cancers in adulthood. Thank you so much. Angelica Kirsten
Bonnie, USA	My son was diagnosed with the LGG spinal cord tumor at the age of 3. He has serious complications with scoliosis - treating the scoliosis with the tumor is a delicate balance. Scoliosis hardware can get in the way of the imaging for the tumor monitoring. It can feel that spinal cord tumors, while so similar to brain tumors, are in their own category and receive less attention.
Bonnie, USA	My daughter's low grade glioma is on her brainstem and the dizziness she experiences impacts her life significantly. She has major vestibular issues that cause her to miss school and activities often. All we can do is treat with an anti vertigo medication like meclizine which sometimes doesn't work and we have to resort to lorazepam.
Caitlyn, USA	On Adelaide's best days, she seems much like a normal ten year old little girl, but on her bad days, she can't walk, doesn't want to eat because she is so dizzy. On a bad day, Adelaide is pretty much couch or bed bound until we get the dizziness under control.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Caitlyn, USA *continued*	My worry for her future is that she will start having more and more complications from the tumor as she gets older. I worry kids will be mean to her because of her different appearance and head movement she makes because of the tumor. I worry that she won't get the accommodations that she needs in school. I also worry that the world is just going to be harder for her and it breaks my heart.
Chelsi, USA	I will forever be indebted to the Pediatric Brain Tumor Foundation!!! My daughter had 3 brain surgeries between a 6-year time span and the support we received is priceless! I am in complete support of whatever treatments you all are willing to pursue because based on the treatments we received, I KNOW any new technological treatments will be even better!! My daughter now is in college majoring in Accounting and I owe that all to your organization! Thank you so much for your love and support!
Chris, USA	Though death from these tumors is uncommon, it does happen and should not be ignored as rare. Our son David, diagnosed with a pLGG in his optic chiasm when he was in fourth grade, had various forms of chemo over the years, experiencing many of the symptoms mentioned here already at various times. When he was 17, David started experiencing severe hydrocephalus due to a blocked third ventricle. He ultimately died of this condition, the result of multiple failed (clogged) shunts and resulting hydrocephalus and brain damage. We lost a really good kid with a lot of potential, just like all these kids.
CJ, unknown	I am the proud mom of a 12-year-old boy who has a Juvenile Pilocytic Astrocytoma in his cerebellum and pons in his brainstem. He had a partial resection followed by 13 months of weekly standard chemo (Carboplatin/Vincristine followed by Vinblastine) and we are in watch and wait now. Treatment and tumor left him with right-side weakness, deafness, and facial numbness, but through tremendous effort he learned how to walk again play the piano again. One of the most difficult things for us is knowing when to intervene again. He has had slow progressive growth of a cyst associated with his tumor, but there is a difference of opinion about when to intervene. One neurosurgeon has told us they could do another neurosurgery but that our son could wake up not able to walk, talk, swallow or use the right side of his body ever again. Another neurosurgeon has said that if we don't intervene, this cyst could lead to those same outcomes. There is currently no medicine to treat the cystic portion of JPAs, so our options are both bad, and as parents we feel unqualified to be choosing between two such different opinions. I think our experience with this tumor feel like we are always lowering the bar for what we can expect for our child's life. At diagnosis, we thought we would do surgery and then resume life as normal. Now we are 4 years in and we realize how everything can change in an instant.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
CJ, unknown *continued*	The mental health impact is tremendous. The unknown about the future of this disease is difficult for children to live with. My son worries that in a year he won't be able to walk again or breathe on his own, or that he won't live another year. This tumor continues to take away from our kids.
	Because there is not consistent approach for PLGG, doctors across the country and at different centers do not agree on the best approach for these tumors. The weight of choosing between significantly different approaches in treatment is significant, especially with so little data on long term outcomes with each choice of treatment.
	For the question about how well therapies help manage symptoms, I would say that the therapies do help to recover some of the hearing loss, loss of balance, and right-side weakness that is a result of the surgery to save his life from the brain tumor, but we are certainly not back to the child we said goodbye to on the day of his 1st surgery.
	One of the difficult things to hear on this call is the huge variability in treatment options and likelihood of maintaining Quality of Life for these children depending on where you live. There are great options in major centers but so many fewer options in other areas. I wish there would be a way to guarantee access to information and treatment options for children no matter where they live.
	I am hopeful for a drug that treats the cystic component of these tumors.
	I would like to echo one of the callers to say that we keep taking the kids to the drugs, but I would love to an improvement in bringing the drugs to the kids.
	The other comment is hearing loss due to tumor location on the cranial nerve as well as a result of neurosurgery.
	Thank you for an incredible day. I appreciate all the work that went into this as well as the way that you handled every parent and story. Thank you!
Derek, USA	I am so thankful for the work that has been done in constantly furthering treatment options for pLGG. My son was a part of a clinical trial for two years that eventually led to him gaining access to Koselugo, his current treatment. Despite minor skin irritation this medication has proven to keep his tumor stable over the last couple years and has been a great blessing to our family. Thank you for your work and continue to push forward to finding ways of bringing relief to families like us who have a child fighting cancer.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Geralynn, unknown	Pediatric brain tumor survivors often have damage to their optic disc/nerves *sadly this damage is not treatable - I am hoping this will change in the future ***
	My daughter's pituitary gland was affected. I am deeply concerned that she will have problems with reproduction. She is on a hormone pill at this time, has attempted to go off of it and became extremely symptomatic.
Heather, USA	Vision has been the most significant impact of pLGG for my daughter. She is well adjusted but is legally blind and it has been a challenge for her as well as the rest of the family. There are many activities we no longer participate in due to her vision. It effects her everyday of her life. I am proud of how strong she is, but its hard having this challenge.
	My daughter is on oral inhibitors. Her treatment continues to keep her tumor stable, which is great, but there are many unknowns. We do not know the long-term side effects. She has been on the medication and will be on the medication for the foreseeable future. At times the side effects of the medication are difficult and not ideal. She fatigues easily and struggles to keep up with peers. At times, she develops skin reactions and fevers associated with the medication. These side effects cause her to miss school and other fun activities which is heartbreaking. No child should have to miss out on the fun things in life, she has had to grow up way to fast. I do not like to see her struggle.
	Short of a cure, I would like to see more education, access, and availability in treatment options. We have come a long way towards better treatment options, but it's years behind other types of cancers.
Joan, USA	My son was diagnosed with a disseminated Pilomyxoid tumor in 1998. He endured 9 years of various chemotherapies ending with full brain and spine radiation. He was on Vincristine and Carboplatin which we were told was the gold standard at that time, the drug having been developed in the 50's. I see where it is still being used today for our low-grade kids. He developed drop foot from that protocol. He then went on Temador, followed by Cilengitide and neither drug stopped the growth. He then went on TCPV which was a very challenging protocol for him and once again did not stop the growth. He then at the advice of Dr. Bouffet at Sick Children's in Toronto went on Vinblastin which did help somewhat. His tumor then caused compression on his spinal cord and we reluctantly did radiation in hopes of stopping it. In the end he became paralyzed anyway and the radiation morphed the low grade to a high grade and he passed away in 2006. My hope is that new drugs with better results and better quality of life can be found for these kids. Many kids that I know were good after treatment for a number of years and then in their 20's many of them developed various problems. I pray that a treatment can be found that keeps these kids alive and at the same time gives them a somewhat normal life.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Keith, USA	My daughter has a diffuse pylocitic astrocytoma since she was five months old she is now 8. Our biggest concern is that we don't have many treatment options left and are desperate that more treatments options become available. Her tumors always start growing again after treatments or during. We need more options more treatments our little girl need this. Thank u for taking time to hear our voice.
Lacie, USA	Our son Jimmy was diagnosed with an Optic Pathway Glioma at 4 months old. He is now 13. He has lived his entire life on and off treatments. We're still hoping for a cure one day that won't cost him his quality of life. The symptoms that have most significant impacted Jimmy are the side effects from the chemotherapies currently offered to treat PLGG. From cognitive delays, to physical and OT delays, as well as pain in the body. Whether from a stomach ache, diarrhea,, nausea and just an overall lower quality of life. He has had to fight every inch to have some semblance of a normal life. Jimmys best days are when he forgets he has to take pills to treat a tumor he doesn't understand why he has it. When he gets to be a kid. His worse days are when he wonders why he has to do all of this and other kids don't. Jimmy loves hanging out with his friends, playing sports, keeping up with everyone and feeling like he is part of it all. Sometimes he is behind when it comes to the physical abilities his peers have, the cognitive abilities are also behind and sometimes it's difficult for him to relate and fit in. He does his best though and he is truly loved by his friends and family. Jimmy has had nystagmus and borderline hydrocephalus as an infant. The only way as a teenage we know what is happening is if a scan reveals it. Jimmy is currently asymptomatic from the tumor itself. Honestly, we just want to find a way to cure him so he can live a full life and not worry about it. If he has to take medicine to treat it we wish it to give him the highest quality of life possible. Even with the Mek inhibitor what frustrates us most is that treatment options over the last 13 years haven't expanded as much as we would like. The Mek still can affect the heart, which is literally disheartening. We'd love for him to regain some of his cognitive losses and processes. We're hoping for some advances in the Neuro-plasticity field and the treatment field. We have to help repair what the chemo has damaged. Currently Jimmy is on a Mek inhibitor or treat one of the spots mid brain, it's called Selumetinib. It's been helpful but we have to watch its effect on his heart closely.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Lacie, USA *continued*	The current treatment over the last 9 months has shrunk the tumor by 50%. Percent to are pleased with that part. The most significant downsides of Selumetinib is eating restriction times, the damage it does to his skin and the diarrhea it causes along with stomach aches. He also has to take it daily, so he has a daily reminder that he has a brain tumor and has to treat it. That is daunting to a kid. They affect his emotional health the most because of those factors. A once-a-month treatment would be much more beneficial because he could live his life the 29 days not thinking about it or being restricted by it. Take it less often, once a month if possible. Very little side effects, especially to major organs, or skin (fingertip cuts can be very painful). Have little restrictions as far as eating and of course not to make him sick. We'd love to see something that could make his immune system smarter to locate the tumor and of course we would want the treatment to not be invasive at all. The ideal treatment would treat the tumor to have it go dormant and give the child the highest quality of life possible, so they can just be a kid and grow up. Thank you for trying to make our kids lives better, we know collectively we can make a difference and eventually find a cure. We have faith.
Lesli, USA	Symptoms with biggest impact - my daughter's short-term memory has been affected by surgery and I believe that is her biggest struggle with daily life. Activities - prior to my daughter's diagnosis she was very active and played soccer competitively on a travel soccer team. Following her surgery she was left with weakness on her left side and balance issues and has never been able to return to soccer and she misses playing not only for the sport but social impact as well. She also used to play piano and was amazing. Now it is very challenging since she has issues with her left hand and can't play at the same level. She continues to try to play songs that she learned prior to her diagnosis. but hasn't been successful in learning new songs. My biggest fear as my daughter gets older is that she won't be able to live independently and I also worry about her long term health. She has a history of seizures and lots of endocrine issues that she will have to manage for the rest of her life and I don't think she is capable of managing all of the doctors appointments and meds independently. She will always need someone to manage and oversee that for her.

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Lesli, USA *continued*	An ideal treatment would be less toxic and damaging to the brain. My daughter never had chemo only surgery and proton radiation but we need less invasive procedures that don't damage the brain and leave our children with brain injuries that change their entire life. There are so many devastating and life changing side effects to the current treatments they receive.
Lisa, USA	My daughter was diagnosed with a pLGG 24 years ago. She has had 6 brain surgeries, had radiation at the age of 2, and is currently on her 10th drug therapy. Her pLGG is a chronic condition where treatment has caused many disabilities. A surgery has left her with hemi-paresis; radiation has stopped her from producing necessary hormones, left her with airway and swallowing issues so she has a tracheostomy and feeding tube, and scarred her eardrums so she requires hearing aids; drugs have left her with extreme fatigue, skin issues, learning disabilities, and nausea. One of the most significant impacts is that every drug protocol she has been on has caused extreme fatigue which has affected her ability to learn and understand, but has also impacted her social life. She does not have the stamina to do school work at the level of her peers and doesn't have the stamina to engage in social activities. The drugs have also affected her temperature regulation so she is either too cold or too hot depending on the temperature. This not only affects her but also her sibling who has to lose out on fun activities because his sister cannot tolerate the activity. Vacations or doing fun activities are hard to plan because they are dependent on how she is feeling. Her symptoms have increased with age. It has affected her emotional well being because she isn't able to do things with peers so she is very isolated and has few friends that understand. My biggest fear is that the radiation she received will cause a radiation induced tumor that will not be able to be stopped. I also fear that her body is getting tired from all the treatment which may lead to her body systems failing. My last fear is that she will out live me and have no caretaker. We need treatments that will stop the tumor but have little side effects because a pLGG is a chronic condition and current treatments still have too many possible side effects that increase over time. Thank you.
Liza, USA	My Son was dx with low grade glioma. He has had so many issues since his brain tumor recession along with a spinal fusion laminectomy in the c-4 he now has plates and screws. His surgery was 10 hrs and along the way while in the hospital he got mengitis when they failed to see he was leaking CSF when they removed his evd. Hearing these stories helps me understand alot more.
Mandy, USA	The most significant impact of our daughter's brain tumor is her memory impairment. She has no fornix on the right side of her brain (no one is certain if it was due to the tumor/cyst or the surgeries that saved her life). Her short and long-term memory are severely impacted, with the same conversations multiple times a day and a limited ability to retain what she has learned. She now has specific learning

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Mandy, USA *continued*	disorders with impairment in reading, written expression, and mathematics, as well as severe neurocognitive deficits with diminished verbal learning and memory skills. Her social skills remain at about an 11-year-old (she is now 17). Despite this, she has 20/15 vision and loves going to school more than anything. Her kindness and compassion know no limits.
Maria, USA	Can patients have direct access to the FDA and sign waivers to be able to take medicines as the risk of tumor outweighs risk of medicines. We need direct access as patients get lost in the very formal clinical trial approval processes.
	This speaker forgot name. Wearing white glasses is minimizing the disease and impact of the disease! Living into adult adulthood is not the point. These patients have great deficits and do die if tumor keeps growing.
	Can we make it clear that there are meds to give our kids but they are not truly options for the FGFR mutation. Physicians are just trying something.
	Great emotional day. I hope it has impact. Thank you for organizing and executing!
Rebecca, USA	How well do your/your child's current treatments address the most significant symptoms of your/your child's pLGG? Our daughter's most significant symptom is not addressed by her current treatment, unfortunately. Our current treatment for our toddler's glioneuronal brain stem tumor is with dabrafenib/trametinib (BRAF/MEK Inhibitors). Unfortunately, she has a very rare symptom that causes her eyes to roll in the back of her head every 15-45 seconds in varying degrees of intensity. We were hoping that the inhibitors would shrink her tumor to reduce the severity of the symptoms, but unfortunately it has not shrunk it at all - just kept it stable. We are in a circumstance where we have a successful treatment by definition (ie the tumor is stable), however we are not seeing improvement of symptoms. So at this point, we are struggling with when to consider a more aggressive treatment that may have more significant side effects in order to see quality of life improvement with potential shrinkage. This has been made more difficult by the fact that she is only 2.5 years old and her doctors are very cautious about switching treatments given her age and tumor location. Pertinent medical history if helpful - Cerebellopontine angle glioneuronal tumor underwent partial resection at 11 months old, has been on Dabrafenib/Trametinib for over a year without shrinkage, but no growth since starting. Initial post op MRI at 3 months did show growth at which time she was put on "the combo."

APPENDIX 2 – SUBMITTED COMMENTS ONLINE continued

Organized alphabetically by first name

Name, country	Comment
Sara, USA	Having had a brain tumor myself when I was a child. I think that the government needs to provide much more funding to this effort.
Shibani, USA	We need more non-invasive treatments.
	I would like to spread awareness about various facebook groups that are a safe haven for parents to share their experience and gain access to a lot of information.
	I am so grateful for all the parents for sharing their experiences. I resonate with everyone here. My 9-year-old daughter who was diagnosed at age 2, asks me when will she ever get rid of the tumor? or when will her shunt come out? In our case it is likely she was born with a tumor. There is not a day that goes by when I don't feel the burden of not doing anything when I was pregnant with her. I am disappointed that our medical system did not have the means of catching it sooner. My daughter has a rare tumor which technically is being treated as low grade however has high grade features in it. Doctors across the country think it is low grade however, due to the initial report we don't qualify for latest clinical trials as a document from 2017 stated the words "high grade". Due to low tumor burden, there is no specific medicine that will work, so all we continue to do is experiment with highly toxic chemotherapy protocols hoping they work.
Stephanie, USA	It amazes me how hard it is to get educators to understand the need for an IEP. These children have the equivalent effect as a traumatic brain injury. We were turned down for an IEP for 2 years before we finally convinced them he needed an IEP. Thanks to Dana Farber's Jimmy Fund Clinic they provide a school liaison advocate. They come to all of our meetings, present medical side effects of brain tumors and speak for the physicians. Why are they so ignored????

APPENDIX 3 – POLLING RESULTS

The response percentages are a percentage of the total number of responses received and not a percentage of people responding.

DEMOGRAPHIC POLLING QUESTIONS

1: Are You:

Response options	Count	Percentage
A. Someone living with pLGG	0	0%
B. A caregiver of someone with pLGG	**23**	**100%**

Response options	Count	Percentage
A. US Pacific time zone	3	9%
B. US Mountain time zone	0	0%
C. US Central time zone	6	18%
D. US Eastern time zone	**23**	**70%**
E. US Alaska time zone	0	0%
F. US Hawaii time zone	0	0%
G. Europe	1	3%
H. Middle East	0	0%
I. Asia	0	0%
J. Canada	0	0%
K. Mexico	0	0%
L. Other	0	0%

2: Where do you currently reside?

3: Are you or your loved one with pLGG:

Response options	Count	Percentage
A. Female	15	47%
B. Male	**17**	**53%**
C. Other	0	0%

4: How old are you or your loved one with pLGG?

Response options	Count	Percentage
A. 0-2 years of age	6	20%
B. 3-5 years of age	3	10%
C. 6-12 years of age	**11**	**37%**
D. 13-18 years of age	6	20%
E. 19-35 years of age	4	13%
F. 36-50 years of age	0	0%
G. 51-60 years of age	0	0%
H. 61 years of age or older	0	0%

5: At what age were you or your loved one diagnosed with pLGG?

Response options	Count	Percentage
A. Prenataly	0	0%
B. Birth to 12 months	2	6%
C. 1-3 years	12	38%
D. 4-5 years	0	0%
E. 6-10 years	**13**	**41%**
F. 11-18 years	5	16%

TOPIC 1 POLLING QUESTIONS: LIVING WITH pLGG: SYMPTOMS AND DAILY IMPACT

1: Which of the following pLGG-related health concerns have you or your loved one ever had?

Select ALL that apply.

Response options	Count	Percentage
A. Loss of balance, motor function problems	**19**	**13%**
B. Headaches	17	11%
C. Speech problems	15	10%
D. Vision problems	15	10%
E. Nausea/vomiting	18	12%
F. Seizures	8	5%
G. Fatigue or sleepiness	**19**	**13%**
H. Weight loss or gain	12	8%
I. Anxiety/depression	18	12%
J. Other	10	7%

2: Select the most troublesome pLGG-related health concerns that you or your loved one has ever had.

Response options	Count	Percentage
A. Loss of balance, motor function problems	**16**	**21%**
B. Headaches	6	8%
C. Speech problems	7	9%
D. Vision problems	9	12%
E. Nausea/vomiting	7	9%
F. Seizures	7	9%
G. Fatigue or sleepiness	3	4%
H. Weight loss or gain	2	3%
I. Anxiety/depression	11	14%
J. Other	8	11%

Select top 3.

3: What specific daily life activities that are important to you or your loved one are you/they NOT able to do or struggle with due to pLGG? Select TOP 3.

Response options	Count	Percentage
A. Attending school	7	12%
B. Ability to walk	3	5%
C. Biking or playing sports	11	19%
D. Self-care	5	9%
E. Sleeping	7	12%
F. Working or having a career	6	11%
G. Attending social events with family/friends	6	11%
H. Other	**12**	**21%**

Response options	Count	Percentage
A. Worsening ability to walk	2	3%
B. Worsening seizures	4	5%
C. Impacts on social life	11	14%
D. That symptoms will get worse	**20**	**26%**
E. Inability to live alone	12	16%
F. Falling	1	1%
G. Dying prematurely	17	22%
H. Ability to start my/their own family	5	6%
I. Other	5	6%

4: What worries you most about your or your loved one's condition in the future? Select TOP 3.

TOPIC 2 POLLING QUESTIONS: PERSPECTIVE ON CURRENT AND FUTURE APPROACHES TO TREATMENT

1: What medications or medical treatments have you or your loved one used (currently or previously) to treat symptoms associated with pLGG? Select ALL that apply.

Response options	Count	Percentage
A. Surgery	**22**	**23%**
B. Radiation therapy	0	0%
C. Chemotherapy	14	15%
D. Seizure medication	10	11%
E. Targeted therapy (dabrafenib, trametinib, tovorafenib)	15	16%
F. Pain medication	11	12%
G. Antidepressants or anti-anxiety medications	5	5%
H. Other medications or supplements	18	19%
I. We have not used medications or medical treatments	0	0%

2: Besides medications and treatments (currently or previously), what has your loved one used to help manage

Response options	Count	Percentage
A. Physical/occupational therapy	**22**	**26%**
B. Speech/language therapy	15	18%
C. Assistive devices	9	11%
D. Acupuncture	3	4%
E. Aqua therapy	3	4%
F. CBD	8	10%
G. Counseling or psychotherapy	14	17%
H. Other	10	12%
I. We are not doing anything to help manage symptoms	0	0%

the symptoms of pLGG? Select ALL that apply.

3: How well does your current regimen treat the most significant symptoms of pLGG?

Response options	Count	Percentage
A. Not at all	2	8%
B. Very little	5	21%
C. Somewhat	**12**	**50%**
D. To a great extent	2	8%
E. Not applicable because not using anything	3	13%

4: What are the biggest drawbacks of your current approaches? Select up to 3.

Response options	Count	Percentage
A. Not very effective at treating target symptom	**15**	**28%**
B. Only treats some, not all symptom(s)	8	15%
C. High cost or co-pay, not covered by insurance	7	13%
D. Limited availability or accessibility	6	11%
E. Side effects	9	17%
F. Route of administration	1	2%
G. Other	5	9%
H. Not applicable as not using any treatments	2	4%

5: Short of a complete cure, what TOP 3 specific things would you look for in an ideal treatment for pLGG?

Response options	Count	Percentage
A. Stop disease progression	**15**	**33%**
B. Improve daily functioning	**15**	**33%**
C. Increase energy	4	9%
D. Treat emotional symptoms	6	13%
E. Treat seizures	3	7%
F. Prevent falls	0	0%
G. Other	3	7%