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Decision Making in the Face of Pediatric Incurable High Grade Gliomas:
A Qualitative Ethical Analysis

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Master of Arts

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Decision Making in the Face of Pediatric Incurable High Grade Gliomas:
A Qualitative Ethical Analysis
By Ashley Lanzel, M.D.

Decision making for children and young adults with incurable high grade gliomas (HGGs), like diffuse intrinsic pontine glioma (DIPG) or glioblastoma multiforme (GBM), is difficult, complex, and ethically challenging.

A longitudinal, qualitative study was completed from April 2017 to February 2018 to evaluate factors that play into decision making for children and young adults with HGGs, their families and clinicians. Twenty four of 36 eligible patients were approached. Seventeen enrolled and two withdrew for transfer of care and unavailable, consenting interpreter. Key decision making visits (e.g. MRI reviews) and semi-structured interviews with parents and/or patients were serially audio-recorded. Field notes from clinician meetings, chart notes, and oncologist questionnaires were obtained. Discussions and interviews were transcribed, coded, and analyzed manually and with MAXQDA software until thematic saturation.

An average of 5 encounters, or 2.5 hours, were recorded per patient. Parent and patient interview themes included 1) hope (for a cure, prolonged life, and quality of life), 2) importance of physician recommendations, 3) importance of support systems (family, community, social media), 4) food (as cancer etiology, intervention) 5) finances (personal, research funding), 6) communication (with medical providers, family, community), 7) death, and 8) God (beliefs, prayer, existential questions). While patients, families and physicians all hoped for treatment efficacy, they balanced it with the known poor prognosis. Physicians consistently hoped for patients to live as long as possible as well as possible. Patients and families transitioned more slowly to this hope. Clinician attempts to preserve hope differed between oncologists and palliative care specialists.

From these results, decisions made in this setting are multi-factorial, ultimately reflecting the competing values of decision makers. Optimism about treatment is held in tension with poor prognosis, allowing for functional hope for patients and families. Acknowledging shifting hopes of patients and families allows for changes in goals of care and shared decision making.

Principlism is used to ethically analyze the decision making process, beginning with who makes the decisions to what decisions are made. A clinician communication guide was developed to aid in the multiple difficult conversations for children and young adults with HGGs.

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Dedication

This thesis is dedicated to my husband, daughter, and those impacted by high grade gliomas.

Acknowledgements

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Thank you to the participating patients, parents, and physicians in allowing me to be a part of these special encounters. Thank you to the transcribing services of Matchless Transcription, Lydia G. Cox, M. Lisa Hwang, Melissa S. Hayban, and Margie Dixon, as you were central in making the voices of the patients, parents and clinicians heard.

To my husband, daughter, and parents, you have all been so patient as I have dedicated much time to this project. Your loving intercessory prayers for me have been encouraging. By

the grace of God, the project was able to be completed. As I became a parent during this project, I have learned experientially the bond one feels toward a child, the daily challenges in caring for a child, the sharing of parental responsibilities and decision making with my husband. As parents from the study have reminded me, I cherish the time we have together, however long that may be.

Preface

What is it like to receive abrupt bad news? Let us explore this with a thought experiment. What if you were told your child has an incurable brain tumor? A million thoughts may be rushing through your head: "this can't be happening," "the doctor is wrong," and "not my child." You may wonder or ask, "Now what?" Whether or not you ask that last question out loud, the doctor will proceed to delineate the limited options.

However, while going through these options, you perseverate on the bad news. You cannot keep up with the options, much less weigh them against one another. You do not have fully informed preferences to make a decision, and yet, you may have been given paperwork to sign. This paperwork could be a request for sharing information with other medical institutions, an informed consent document, a do not attempt resuscitation form (DNAR), or a number of other important documents. It feels like you are in a nightmare. You feel overwhelmed. You may be angry that your child has cancer, that your child heard the word 'cancer,' that you have to maintain your composure and put the pieces back together when you get home.

Your hopes that your child would grow up, graduate from high school, obtain a job, get married and have a family of his or her own are shattered. You hope that you can make it through the phone calls telling loved ones the bad news. Oh wait, what did the doctor just say? Shock, anger, doubt, and grief may have prevented you from hearing what was said, cause misunderstanding, or lead to forgetting the options of care, which are the focus of family and friends' questions. These options are what you will research online, assuming you can get past the dismal diagnosis. It is too much. Your child has a death sentence. People expect you to hold it together because you are the child's parent. Your prior mechanisms for holding it

together have been medication, friends, family, and God. Will those be helpful now? You only hope so as you journey forward. Most of all, you just want to sit and cry.

These thoughts and feelings are not just a thought experiment. They are reality for many parents of children with incurable brain tumors like high grade gliomas. It is hard for most parents to imagine anything this bad. Before the diagnosis, the family may have noticed changes in how the child's eyes focus, how the child talks, walks, eats, and sleeps. Their child may have complained of headaches, vomited in the early mornings, or fell behind in school or an activity. Parents may have worried about the symptoms or attributed them to a benign virus.

These symptoms were of a brain tumor that cannot be solved with surgery, radiation or chemotherapy. There are no known cures. There are a few possibilities that can relieve symptoms or prolong life, but, to date, all children with this diagnosis have died within six months to two years. This kind of brain tumor is unthinkable and unutterable. It is devastating.

Because there is no cure, the focus shifts to what decisions are made and how they are made. In this decision process, key players have differing duties, each requiring ethical reasoning. How people perceive their duties and how they ethically reason through the options impacts the decisions made and the level of distress about the outcomes.

For instance, the care for children and young adults with poor prognostic brain tumors relies heavily on their families and their medical providers. How families approach the care of their loved one often differs from the approach of medical providers, as they have distinct duties as family members. How parents define being a 'good parent' weighs heavily on their decision making. Similarly, how physicians define being a 'good physician' influences their recommendations for families. Though families and physicians share a common goal of caring for a suffering person, their viewpoints often diverge on how to best care for that person given

their different roles. Parents may prioritize the spiritual or communal well-being over the physical well-being, while physicians may prioritize the physical well-being. The divergence might only appear at certain times: after cancer progression or near the end-of-life. Other times, the divergence is clear from the first meeting, with conflicting views amongst the family, amongst clinicians, or between families and clinicians.

Acknowledging these differing viewpoints and competing duties aides in providing optimal care, which is defined here as care that best supports a patient and family based on their values, informed by knowledgeable physicians, supplied by available resources, and constrained only by the physicians' ethical duties. Knowing everyone is on the same team enhances communication. When families and physicians position themselves on opposing teams or lack trust in one another, conflict abounds and communication breaks down. Without a solid relationship, quality care, much less optimal care, is difficult to provide.

Having competing duties does not always position the patient, family and physician on opposing teams but rather highlights the complexity of decision making. When an incurable brain tumor threatens to dissolve a person's dignity with progressive debility and diminished cognition, patients and families have decisional priority over physicians in deciding the goals of care, or primary ends, with constraints as indicated above. Physicians attempt to align available care options with those goals, essentially providing the means of care to support the primary ends. Over time, the goals of care may shift either because of family preference or less available options, causing changes to the plan of care. Knowing the competing duties of each decision maker allows for an open discussion in making those changes. Acknowledging shifting decisional priority can aide in shared decision making. Good communication helps prevent and ameliorate conflict.

The goals and their underlying values can be sources of conflict. Examples of conflicting goals include patients and families wanting to "do everything," or prolong life as long as possible while physicians may have a goal of improving quality of life. Underlying values may differ, especially if the patients, families, and physicians come from different backgrounds. For instance, when the patient and family differ in health literacy, spoken language, socioeconomic status, education, world view, culture or religion from their physician, their values may be quite different than the physician's.

Occasionally, conflict is subtle. Parents could have chosen a particular institution and physician who can enroll their child in a clinical trial. Other times patients and families could be healthcare providers, come from similar socioeconomic backgrounds and education level as physicians. The underlying values that informed the initial goals of care may be surpassed by other values and lead to changes in care preferences.

Patients or families who have prior healthcare experiences have influential narratives that shape their interactions after a new diagnosis of cancer. If those narratives are rooted in errors, misunderstandings, or disrespect, acknowledging these obstacles could be crucial in repairing the relationship with the medical field. Alternatively, if those narratives are based on 'medical miracles,' or 'beating the odds,' families may be tempted to 'prove the doctor wrong' again and compromise trust. Acknowledging these narratives does not guarantee a trusting relationship with a healthcare provider but may be a good start in the communication and decision making process, as they uniquely unfold.

Recognizing differences in hopes, backgrounds, values and experiences supports a healthy relationship among patients, families and physicians. This needs to be done in a sensitive and empathic manner to bring patients, families, and medical teams together. Each one

has a story to tell about how communication helped or hindered their interactions. Decision making is complex; communication is essential for providing optimal care. Work is needed to understand the nuances of how decision makers think and how they communicate those nuances.

The goal of the current study is to learn about experiences and viewpoints from patients with high grade gliomas, their families, and physicians about their how decisions are made. Themes will be discussed from the following sources1) audio-recorded clinical visits with physicians, 2) audio-recorded parent or patient interviews, 3) field notes from clinician meetings and clinical encounters, and 4) physician questionnaires. The focus will be on the decision making process, specifically who has decisional priority and authority, delineating duties of physicians and parents. Medical provider moral distress will be explored in the setting of patients and/or parents asking to 'do everything.' Finally, hope preservation and how hope can be functional and lead to perseverance will be discussed.

Principlism will be utilized for ethical analysis of the competing duties of decision makers and provide a framework for clinical application and training that utilizes shared decision making to prevent or ameliorate ethical distress. Key goals of the framework are to improve understanding of patient and family preferences, assist in evaluating and re-evaluating hopes and goals throughout patient care, and promote palliative care consultation. Finally, the over-reaching goal is to provide clarity in prioritizing and balancing the competing principles of optimizing beneficence, decreasing suffering, respecting autonomous rights, and justly providing the care possibilities desired for children and young adults with high grade gliomas.

Chapter 1: Introduction: Overview of High Grade Gliomas and Ethical Concerns

In this introduction, a background overview will be presented about pediatric high grade gliomas and the care options, including a focus on the standard of care which is palliative care. Medical controversies significant to key informants in the empirical study will be briefly highlighted. This is followed by an overview of key ethical dilemmas from diagnosis to end-of-life, with a brief caveat on shared decision making as it is the paradigm of communication and decision making that is promoted by the American Academy of Pediatrics (AAP) and is desired by patient and family informants. After discussing end-of-life issues, there is a brief discussion about the influence of God and religion on decisions as it was a key theme from informants. There is a paucity of literature in this area, but what does exist is found mostly in palliative medicine and end-of-life research. Finally, an overview of principlism will be provided as this ethical framework will be utilized in analyzing the ethical dilemmas that arise in the empirical study on decision making and communication.

Poor Prognostic Pediatric Brain Tumors: Focus on High Grade Gliomas

Despite significant gains in therapy for pediatric cancer and improvement of survival rates, pediatric cancer continues to be the leading disease related cause of death in children outside of infancy. (Siegel, Naishadham, and Jemal 2012) Brain tumors are the leading cause of death among children with cancer. In 2014, brain tumors accounted for 30% of pediatric cancer deaths. (Curtin, Minino, and Anderson 2016) Particularly dismally prognostic pediatric brain tumors are high grade gliomas (HGGs), which include diffuse intrinsic pontine glioma (DIPG), and glioblastoma multiforme (GBM).

Pediatric HGGs are biologically distinct from adult HGGs but carry a similarly poor prognosis. (Fangusaro 2012) HGGs are heterogeneous genetically, epigenetically, and histologically. (Louis et al. 2016) The etiology of pediatric HGGs may be related to an

underlying genetic predisposition syndrome, problems with neurodevelopment, prior cancer directed therapy like radiation, transformation of a low grade glioma, or be sporadic. (Fangusaro 2012)

The World Health Organization (WHO) classifies high grade gliomas as astrocytomas that are grade III or IV based on pathology, with grade IV being GBM. (Louis et al. 2016) The WHO further uses epigenetic patterns of methylation and genetic changes to further subclassify these tumors. High grade gliomas located in the brainstem, specifically in the pons, are called DIPG. There are shared and unique genetic pathways altered in HGGs within and outside the brainstem. (Wu G, Diaz AK, Paugh BS, Rankin SL, Ju B, Li Y...Baker SJ 2014) HGGs in children are aggressive, have poor treatment options, and are near universally fatal. The treatment options available are based on the age of the child and the location of the HGG.

Children with GBM have more available therapy options and a slightly better prognosis than children with DIPG. On average, children 0-19 years of age with GBM have a five year survival rate of 20%; more specifically, the survival rate is 57% one year from diagnosis and 12.6% ten years from diagnosis. (Ostrom et al. 2013) Peak incidence is in adolescence and young adulthood but can occur at any age, including infants. (Fangusaro 2012) For HGGs outside the brainstem, surgery plays a central role as a gross total resection can greatly improve the survival rate but not necessarily morbidity. (Walker et al. 2013)

For newly diagnosed HGGs, standard therapy includes surgery, adjuvant therapy with radiation and/or chemotherapy. (PDQ Pediatric Treatment Editorial Board 2018) Radiation may be delayed in particularly young children (less than three years of age) due to severe neurocognitive effects. Temozolomide is a chemotherapy that has specifically been helpful for HGGs with methylated O6-methylguanine-DNA-methyltransferase (MGMT) overexpression,

both in adults and children. (Cohen et al. 2011) For progressive HGGs, surgery, high dose chemotherapy with stem cell transplant, radiation, targeted therapy, and early phase clinical trials are potential medical options. (PDQ Pediatric Treatment Editorial Board 2018)

DIPG occurs most frequently in children between the ages of five and ten. The median survival from diagnosis is one year and there are no curative therapies. (Warren 2012) Though DIPG composes about 10-15% of pediatric brain tumors, it is the leading cause of death for children with brain tumors, as it is located in a place that is not amenable to surgical resection due to the pons' central role in controlling breathing. (Glod et al. 2016; Rizzo et al. 2015) Despite numerous clinical trials and significant collaborative efforts to improve treatments for DIPG, mortality remains unchanged. (Glod et al. 2016; M. Jansen et al. 2012; Hargrave 2012) Radiation remains the standard of care, as chemotherapy has not led to any benefit in quality of life or median survival. (Glod et al. 2016; M. Jansen et al. 2012; Hargrave 2012; Warren 2012)

Though many researchers are working to improve the number of effective medical options for children with HGGs, there are notable challenges. HGGs are rare, heterogeneous, having an ever-changing classification system, and are protected by the blood brain barrier, making drug delivery more difficult. (Jones et al. 2017) Many institutions collaborate to recruit more children in clinical trials in an effort to ultimately improve outcomes. The question is which patients should be offered and enrolled in a clinical trial. This is based on clinician and researcher opinions, available options, and family preferences. Though who is offered clinical trials and how participation in clinical trials is determined are important areas to evaluate ethically, they will not be a focus here. Along with decisions about participation in clinical trials, palliative care should be standard of care for these children. (Weaver et al. 2015)

Palliative Care and Quality of Life

When pediatric oncology patients are diagnosed with cancer that carries a very poor prognosis, palliative care is essential and may become the primary focus of care. The Center to Advance Palliative Care defines palliative care and the medical subspecialty of palliative medicine as follows:

> "specialized medical care for people living with serious illness. It focuses on providing relief from symptoms and stress of a serious illness. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of palliative care doctors, nurses, social workers and others who work together with a patient's other doctors to provide an extra layer of support. It is appropriate at any age and at any stage in a serious illness and can be provided along with curative treatment." (CAPC n.d.)

Palliative care provides holistic, supportive care for patients and their families. Much literature states that palliative care should be initiated at diagnosis, continued throughout therapy, and persist through bereavement. (Wolfe et al. 2000; Wolfe, Grier, and et al 2000, 200; Weaver et al. 2015) When integrated earlier, patients feel palliative care improves quality of life and anxiety. (Levine et al. 2017)

Though palliative care is the standard of care, scientific journals that delineate care options for pediatric brain tumors do not mention palliative or supportive care (Rizzo et al. 2015; M. Jansen et al. 2012) or mention it only around palliative cancer directed therapy, such as surgery or radiation. (Glod et al. 2016) Perhaps there is an assumption that primary palliative care is being provided; however, it could reflect that palliative care is forgotten in the care of these patients.

When palliative care is included, the involvement and integration of specialty palliative care (as provided by an interdisciplinary palliative care team) varies from center to center based on resources, personnel and institutional support. (Hui et al. 2010) Access to specialty palliative care influences what is available and offered to patients. If there is access to palliative care, it may not be effective if parents have not yet accepted the need for palliative care or if palliative care does not achieve the parents' expectations for their child and family. (Verberne et al. 2017) Many families and providers have the misperception that palliative care is solely hospice care. (Bergstraesser 2013) Once this misperception is corrected and specialty palliative care teams are able to support patients and families through 1) continuity, coordination of care, and providing one reliable point of contact, 2) practical support, and 3) sensitive and reliable attitudes of team members, palliative care becomes invaluable to patients and families. (Verberne et al. 2017)

The utility of palliative care is high given that oncologists are often poor prognosticators, have trouble communicating around palliative care issues, and lack expertise in assessing and treating symptoms associated with cancer, cancer treatment and end-of-life care, especially for children with brain tumors who experience challenging symptoms due to progressive neurological deterioration. (Wolfe et al. 2000, 200; Wiener et al. 2015) Quality of life assessments are often used to help evaluate how well symptoms and distress are controlled.

Quality of life is multi-factorial and has significant personal meaning. Children with DIPG have higher health-related quality of life (HRQOL) per their parents when the children have fewer cognitive problems and less procedural anxiety. (Mandrell et al. 2016) Children report their quality of life is worse with moderate or high intensity cancer directed therapy; conversely, children have better quality of life and psychological scores with oral palliative chemotherapy. (Wolfe et al. 2015) Parental worry is inversely related to their child's HRQOL.

(Mandrell et al. 2016) Similarly, parental psychological distress is high when their children suffer from their therapy. (A. Rosenberg et al. 2016)

Though much more than cancer related symptoms and treatment decisions influence quality of life, they are major factors. Quality of life considerations are important in deciding on treatment options and play a major role in establishing goals of care. When discussing treatment options, palliative care should be considered a standard of care for children with cancer.

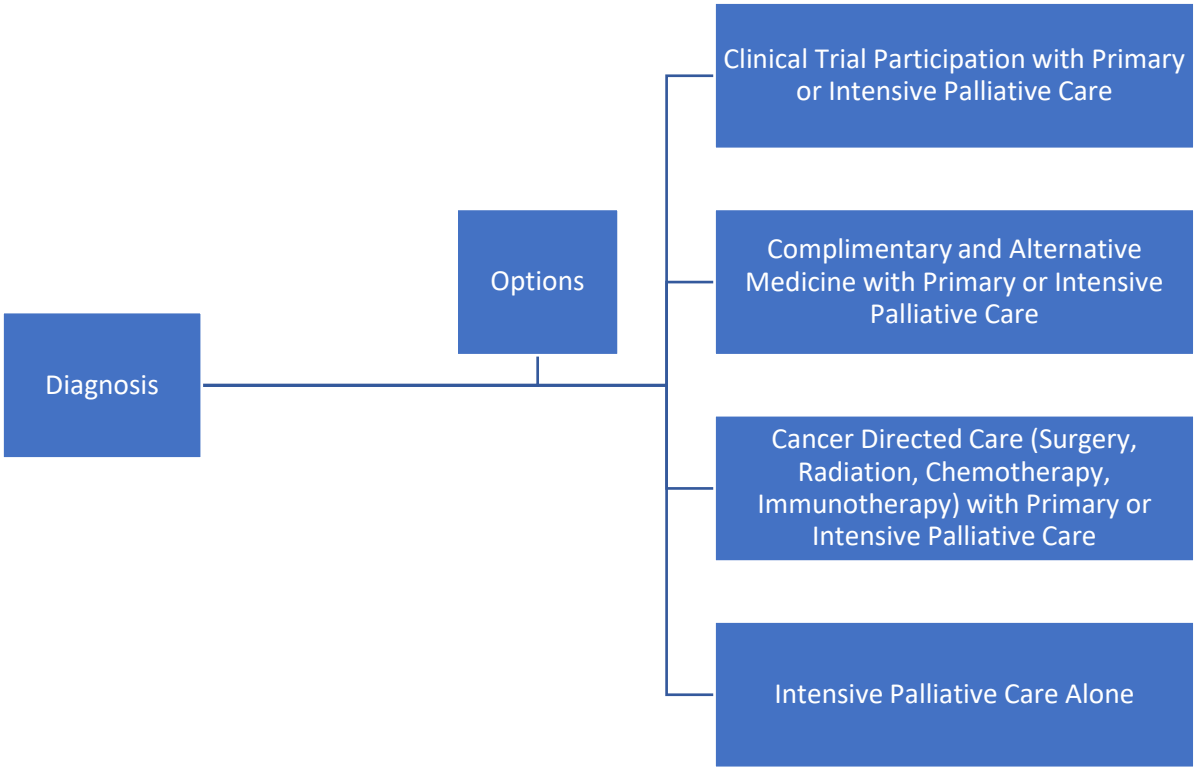
HGGs, Goals of Care and Decision Making

For children with poor prognostic brain tumors, goals of care are often blended: one may hope for a child to live as well as possible for as long as possible yet want to preserve quality of life. These goals may shift over time with more weight given to quality of life. Clinicians may attempt to present families with therapeutic options that align with families' preferences and values. When cure is unlikely, specific options can be limited by resources or provider preferences. Clinical trial participation and complementary and alternative medicine (CAM), are not proven cancer directed therapies, but are options that may be offered to patients. (Munshi, Ni, and Tiwana 2008; M. Jansen et al. 2012) Cancer directed therapy, such as surgical resection or biopsy, radiation, chemotherapy, and immunotherapy, are potential options for symptom palliation, disease control, or life prolongation. (PDQ Pediatric Treatment Editorial Board 2018) Clinical trial participation, CAM, and cancer directed therapy may all be provided with primary or intensive palliative care. A comfort focused approach may involve intensive palliative care alone. Hospice care, a service for children presumed to have less than six months to live, often accompanies a comfort-focused approach.

The process of deciding which path to choose can be quick or take some time based on the many influences impacting these decisions. Influences include the preferences and

experiences of decision makers, as well as the availability, eligibility and feasibility of treatment options.

Figure 1: Options of Care for Poor Pediatric Prognostic Brain Tumors

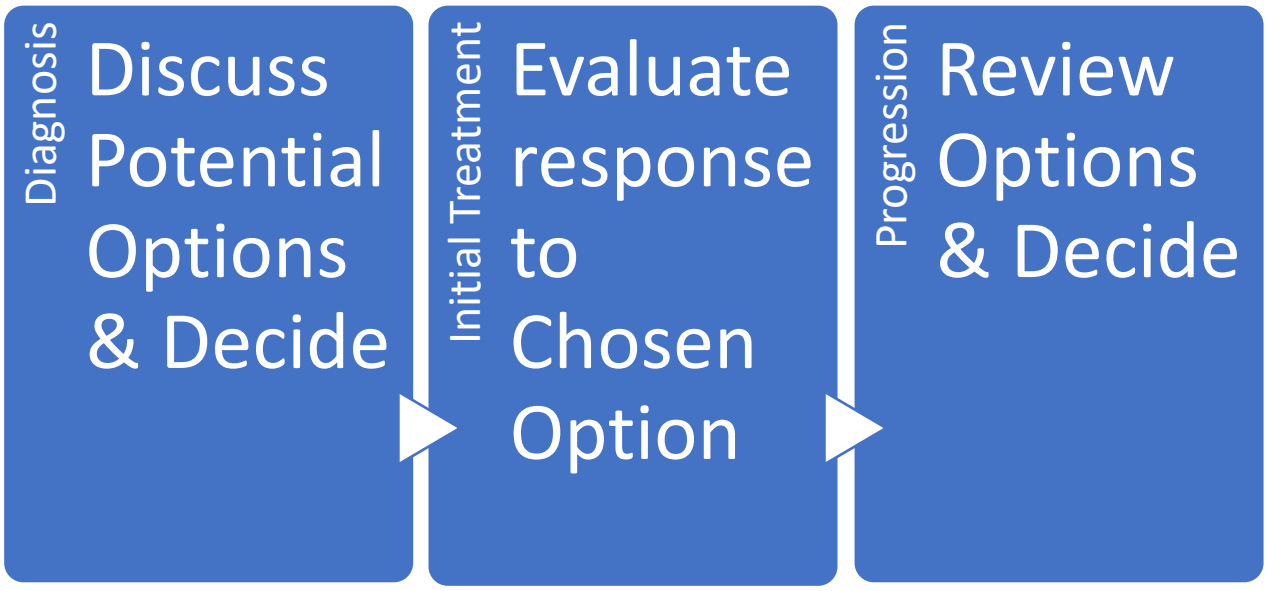


Pediatric patients and their families often struggle with the shock of the bad news (diagnosis, prognosis, and progression), the medical jargon, and the limited cancer directed treatment options. They desire to make the best, most loving decisions for their child. Yet, without much knowledge in the area, families rely on physicians to guide them in the decision making process. Interestingly, there are no studies about whether clinicians have decisional regret about decisions they have made for a patient or have moral distress related to guiding patients and their families through this decision making process. This is out of the scope of this thesis but is important for future research.

Once a cancer directed treatment or clinical trial is chosen, a patient will generally continue with that option until it is time to stop per protocol or progression of disease occurs. During that time, the response to the treatment will be evaluated. If the patient is worse off or not receiving benefit from the treatment (i.e. worsening pain or progression of disease), the selected treatment will stop, options will be reviewed again, and another decision will be made (see Figure 2).

When a child's brain tumor progresses, the discussions differ for several reasons: 1) the options of care change, 2) patients and families have experience with cancer directed therapy or clinical trials, 3) the physician leading the conversation may change, and 4) other psychosocial factors may change. Whether or not there are new providers, goals of care should be reviewed at diagnosis and at the time of progression to guide the care plans.

Figure 2: Decision Making Flow Chart from Diagnosis Through Progression



With each decision for a child's care, potential medical and ethical dilemmas arise. I will explore several of the salient dilemmas that arise in this setting subsequently in this chapter. In later chapters, I will describe the empirical research conducted to evaluate the decision making

processes for children with DIPG, GBM or other HGG, their families and clinicians. I will then describe several ethical challenges that arise and analyze them utilizing principlism.

Controversies in Care: Medical Dilemmas

To Biopsy or Not to Biopsy?

Prior to the development of computed tomography (CT) and magnetic resonance imaging (MRI), biopsy was routinely utilized to diagnose DIPG. Shifts in diagnostic methodology and DIPG characterization have occurred over the past thirty years, though treatments have not changed outcomes. (Vanan and Eisenstat 2015) Classic clinical and magnetic resonance imaging (MRI) findings have been the mainstay for diagnosis the early 1990's. (Puget, Blauwblomme, and Grill 2012; Ogiwara and Morota 2013; Albright et al. 1993) With improving surgical techniques and genetic and molecular characterization of tumors, biopsy of the brain stem lesion has recently become a safe option for diagnostic and research purposes. This option has been controversial as obtaining a biopsy of a brain stem lesion is inherently a life-threatening surgery fraught with ethical considerations on the parts of surgeons, clinicians, researchers, patients and family members. Additionally, a current controversy exists on whether to offer biopsy outside of clinical trials. Recommendations vary by clinician and institution.

Benefits of a biopsy may exist for both patients and the scientific community. Patients may benefit from better pathological and molecular characterization of the tumor, especially if the diagnosis is in question. (Ogiwara and Morota 2013) Research may benefit from having tissue to compare from diagnosis, progression and autopsy to further learn about the disease process. Further, lab-based research on the tissue samples can be used to develop future clinical trials. (Walker et al. 2013) The scientific community hopes that with greater molecular and genetic characterization, targeted therapy be developed successfully.

Burdens of the biopsy range from earlier death to diminished quality of life if a complication occurs. Other possible burdens include inability to enroll in a clinical trial without having a biopsy or inability to access specific investigational drugs if the patient's tumor molecular characterization is not known.

The surgeon may ask whether the risk of death from surgery is important considering the underlying poor prognosis. Would the patient be worse off for having the procedure? Would the patient suffer a preventable adverse event from the procedure? Death from surgery could shorten a patient's life and prevent patients and family members from having important quality time together.

Clinicians wonder if a biopsy should be recommended if no benefit is anticipated for the patient from the biopsy (i.e. change in diagnosis, treatment or survival). Recommendation of a biopsy may be considered if patients and families are interested in a clinical trial that requires a biopsy or if there is a chance of benefit. Because multiple clinical trials do not require biopsy and no clinical trial has been successful in changing the standard of care of palliative care and radiation, clinicians may recommend against a clinical trial requiring a biopsy.

When deciding about the option of a biopsy, patients and families will perceive the risks, benefits, and priorities differently based on their values. If patients and families value clinical trial participation for either altruistic reasons or for personal benefit, they may consider the biopsy to 'keep their options open' despite the life-threatening risk of surgery. Other patients and families may value quality time or feel that biopsy will not change their plan. Most patients and families have mixed goals and choose based on situational complexities and values. Thus, as biopsy is not a current standard of care, clinicians may present it as an option so that patients and families can decide if the procedure is important.

Time Matters: Hydrocephalus Management at Diagnosis Versus End-of-Life

Hydrocephalus, or fluid accumulation within the brain causing increased intracranial pressure, can develop at diagnosis, progression or as a treatment complication for HGGs. Treatment for hydrocephalus can be with surgical placement of a shunt, such as a ventriculoperitoneal (VP) shunt, ventriculoatrial (VA) shunt, third ventriculostomy, and external ventricular drain (EVD), to name a few. Placement of a shunt can be controversial for children with HGGs, depending on the goals of the shunt's placement and the timing of the hydrocephalus.

Relieving the hydrocephalus could improve symptoms, such as headache, early morning vomiting, lethargy, vision changes and gait instability. Efficacy of the VP shunt placement improving symptoms is better when there is a shorter duration between diagnosis of the HGG and shunt placement. (Castro et al. 2017) It remains questionable if it will prolong life, especially for children with DIPG. Survival rate in children with DIPG is similar between those with and without hydrocephalus. (Roujeau et al. 2011) Potential harms of placing a surgical shunt include death, infection, potential need to replace the shunt if hydrocephalus re-accumulates, and rarely, spreading of the tumor to the rest of the body. (Francisco Barajas, Jr. et al. 2015)

Because shunt placement can improve symptoms and quality of life, some clinicians recommend close monitoring for hydrocephalus and early, aggressive intervention. (Amano et al. 2002) These clinicians see it as part of supportive care, especially early in the disease course. However, not all clinicians recommend it, especially at the end-of-life.

Closer to the end-of-life, clinicians sometimes recommend against placing a shunt, as the children will die from disease progression, even if the hydrocephalus is shunted. Symptoms of

lethargy at the end-of-life may not be relieved by resolving hydrocephalus. From this viewpoint, offering shunt placement is an invasive procedure that does not exactly align with comfort-focused care. Instead of improving symptoms, suffering could be prolonged.

Thus, offering hydrocephalus management early in the disease course is less debated than at later stages. If surgeons and clinicians are not willing to offer shunt placement as an option later in the disease course, families should be informed. Clear goals of care discussions are needed prior to discussing hydrocephalus management with patients and families.

Overview of Ethical Dilemmas

Ethical dilemmas can arise in the setting of disclosing the diagnosis and prognosis to the patient and/or family, informed consent and assent, conflict of interest from provider preferences, access to care, decisional priority of patients and families, shared-decision making, relief of suffering, and healthcare provider moral distress. Ethical consultation is often made in the setting of complex patient situations, concerns of physician fiduciary responsibility to patients, care delivery when benefit is unclear, prognostic discordance, moral distress, and religion based refusal of care. (L. Johnson et al. 2015) Here, I will elaborate on prognostic disclosure, phase I clinical trial consent processes, and end-of-life care.

Prognostic Disclosure and Hope

Discussions of diagnosis, prognosis, potential interventions, goals of care and end-of-life care in a pediatric patient with a terminal or poor prognostic brain tumor are difficult. Many physicians find disclosure of bad news and giving recommendations to be distressing and prefer to avoid the discussions. (Wall et al. 2015; V. Miller et al. 2014) Pediatric oncologists leading these discussions often experience internal conflict in attempting to preserve hope and while

conveying accurate information about prognosis with patients and their families. (Sisk et al. 2016)

Even if clinicians have accurate disease based knowledge, they are poor at prognosticating about life expectancy. (Gripp et al. 2007; Brook and Hain 2008) Physicians failed to mention no treatment and/or palliative care options in 68% of informed consent conferences and that the disease was incurable in 85%. (V. Miller et al. 2014) Without true understanding, fewer families were likely to explore palliative care options, but rather request extraordinary measures at the end-of-life and have expectations of a miracle, which was distressing to medical providers. (V. Miller et al. 2014)

Though delivering poor prognostic information is difficult for clinicians, it is vital to future decisions about patient care and does not diminish parents' hope. (Mack, Wolfe, et al. 2007; Mack, Cook, et al. 2007; Mack et al. 2006) In fact, most parents desire to know accurate prognostic information, even if it is upsetting. (Mack et al. 2006) They are still able maintain hope in tension with this upsetting knowledge. Maintaining this hope is evidence of their role in bearing hope and their ability to shift the types of hope they have. (Reder and Serwint 2009)

If not disclosed, parents often quickly learn from online sources what the actual prognosis is. The prognosis is available to anyone with Internet access. However, it is preferential that parents hear the prognosis from their child's physician who can provide guidance, incorporating their knowledge, prior experiences, and the family's specific hopes and worries. The physicians' conceptions of hope may influence their communication with patients and vice versa. (Wolf, Garlid, and Hyrkas 2018) When physicians and patients enter therapeutic relationships longitudinally, "hope becomes an amalgamation, or a rebuilding/rekindling of hope amidst hopelessness." (Wolf, Garlid, and Hyrkas 2018)

Communication strategies to facilitate prognostic awareness have been developed by palliative care providers. (Jackson et al. 2013) When discussing goals of care, providers should inquire about a child and family's hopes and worries, and probe deeper if the predominant hope is cure. Asking what else a family is hoping for can elicit additional hopes. Families may express "seemingly conflicting hopes [as] part of the process of accepting the reality of this very sad situation and finding ways to live with it from day to day." (S. J. Friedrichsdorf et al. 2015) Medical providers should listen empathetically.

Jackson *et al.* (2013) describe a coping pendulum, where patients vacillate between expressing hopes that are likely to be realized and hopes that are not. Similarly, patients may swing from denial of illness to the reality of illness. In cultivating prognostic awareness, clinicians must assess the current level of prognostic awareness, help the patient envision a poorer health state, and decide based on the urgency of the situation how much information to deliver. For patients ready for the information, clinicians should provide that information. For those not yet ready, clinicians should align with the patient, name the dilemma of not addressing prognosis, and wait until the patient is ready to hear this information. The conversation can then transition to 'hoping for the best and preparing for the worst,' with anticipatory guidance about what "getting worse," looks like.

When making these important decisions, it is vital to diminish decisional regret when possible. Parents have less decisional regret when 1) receiving high quality information and detailed prognostic information from a trusted oncologist and 2) holding their perceived ideal role in decision making, which is often as a primary decision maker guided by physicians. (Mack, Cronin, and Kang 2016) Thus, physicians should not struggle with the ethical dilemma of preserving hope versus truth telling as parents are capable of maintaining hope and receiving

truthful news simultaneously. Additionally, physicians should inquire the parents' desired involvement in decision making and support that role if it is appropriate in the form of shared decision making.

Ethical Concerns of Involving Children in Prognostic Disclosure and Decision Making

Inviting children into discussions about diagnosis, prognosis, decision making, and end-of-life care is promoted professionally in the field of pediatrics. The American Academy of Pediatrics states, "The child should participate to the fullest extent possible, given his or her preferences, cultural and spiritual tradition, illness experience, developmental capacity, and level of consciousness." (AAP 2013) Current practices favor truth telling over non-disclosure, albeit in a way that is acceptable to caregivers (i.e. who tells the patient, where the patient is told, etc.). (Cole and Kodish 2007; Coyne et al. 2013; Sisk et al. 2016) However, this was not always promoted.

Previously, it was thought that withholding information from children about death would protect them in the paternalistic form of therapeutic privilege. There was concern that knowing the bad news would be harmful to the children. Theoretically shielding children from this knowledge would decrease their worries, preserve their hope, and be good for them. (Sisk et al. 2016) However, this is not the case.

Myra Bluebond-Langner completed one of the first investigations on how children perceive their terminal prognoses and death, publishing *The Private Worlds of Dying Children* in 1977. (Bluebond-Langner 1978) This groundbreaking work explored how children with leukemia, then a terminal diagnosis, viewed their diagnosis. She exposed the fact that children knew of their prognosis, even if parents and healthcare providers went to extensive lengths to 'protect' the children from that knowledge. This news began a wave of change that facilitated

more open communication with children about their diagnosis and prognosis. It opened the doors to provide a shared experience and meaningful time for children and their families at the end-of-life.

Children actively dying may experience 'total pain,' including physical, psychological, social, and spiritual pain. (Saunders 1964) Children fear suffering, being alone at the time of death, worry about those surviving them, and desire to make the most of the lives they have left. Addressing these sources of pain, rather than have children perseverating on these fears can be beneficial. Having an end-of-life care discussion in a transparent manner allows children to experience the love people have for them. While discussing emotionally challenging topics can be hard, it is not particularly injurious to children if done in a developmentally appropriate manner. (Last and van Veldhuizen 1996) Thus, the benefit to harm ratio sways to greater benefit in incorporating children in these discussions.

Truthful disclosure in a developmentally appropriate manner and in an acceptable manner to parents is beneficial not only for the children, but also for families. Parents who talk honestly with their children about death have less decisional regret than those who do not. (Ullrich et al. 2016) Open communication can provide a means to promote familial healing, including for well siblings who can be overlooked or not involved during a child's cancer journey. (A. R. Rosenberg et al. 2015; Houtzager et al. 2004) The sibling's psychological adjustment depends not on the knowledge of the poor prognosis, but rather on the sibling's ability to empathize, coping strategies, birth order, closeness to the patient, and familial functioning. (Labay and Walco 2004; Houtzager et al. 2004) The process of getting to open communication can remain a challenge, but leads to patient and family-centered decision making, especially when it matters most. (Sison et al. 2017)

Though the pendulum has swung from no disclosure to full disclosure, more complexities exist on a case by case scenario. (Sisk et al. 2016) Additionally, specific recommendations on how to involve children in the decision making process are lacking. Considerations that need to be made when involving children in medical decisions include those for the child, parents, and the parent-child relationship. Child considerations include the child's age, development, illness experiences, views of illness and options for care, and actions to protect parents. (Bluebond-Langner, Belasco, and DeMesquita Wander 2010) Parental considerations include the parents' legal and moral responsibility for the child, the parent's positions on their child's care and treatment, their child's place in the decision making process and what their child should and can be told. (Bluebond-Langner, Belasco, and DeMesquita Wander 2010) Parent-Child relationship considerations include the lack of autonomy children have and their deference to authority figures or likelihood of dissent from parents' sanctioned decisions; usual decision making routines between parents and their children, differing knowledge base about illness and treatment options, along with social and cultural factors. (Bluebond-Langner, Belasco, and DeMesquita Wander 2010)

Children have emerging autonomy and capacity, but are legally minors, requiring surrogate decision makers, who are often parents or legal guardians. Without legal decision making power, children's voices may be lost despite recommendations to involve children when appropriate, possible, and culturally sensitive. (Villanueva et al. 2016) Ethically, healthcare providers try to ensure that surrogates make decisions in the best interest of the child. At times, the best interest of the child may be unclear or complicated. At other times, the surrogates may have conflicting or competing interests that interfere with making decisions in the child's best

interest. Each situation should be evaluated in context to determine the most ethically sound decision.

Respect for persons is a key ethical concept to honor. For healthcare providers, it is important to ask parents, guardians, or significant family members what information is preferred and how they would like to receive information. Parents are more likely to allow discussion of terminal illness or impending death with their children when they become aware of the benefits. Clinicians have to work to avoid harm by talking with children in a sensitive manner and honoring parent preferences for information delivery. Respect for patient and family values is essential in supporting a therapeutic relationship with healthcare providers, so the physician may have to proceed carefully if the family rejects honest information sharing.

Phase I Clinical Trials and Ethical Concerns Around Informed Consent

Participating in phase I clinical trials or palliative radiation may be the only available options for a patient with DIPG and family who wishes to pursue cancer directed therapy. Families often choose participation in phase I trials with the hope of a potential benefit, the advancement of science and care for future patients. (Yap et al. 2010)

The purpose of a phase I trial is to establish the maximum tolerated dose, biologically relevant dose (for biologic agents), and dose limiting toxicity. In pediatric phase I trials, cancer control occurs in less than 10% of novel single agent trials and about 20% of trials combining novel agents with chemotherapy. (Lee, Skolnik, and Adamson 2005) A more recent prospective study of the risks and benefits of pediatric phase I trials in oncology showed an objective response rate of 10.29%, but with significant discrepancy with solid tumors having an objective response rate of only 3.17% compared to hematological malignancies of 27.9%. (Waligora et al. 2018)

Understanding the efficacy of a drug is the purpose of a phase II trial. Yeh *et al.* in 2016 demonstrated that when pairing single agent phase I trials with phase II studies, response rates were highly correlative; interestingly, they found that thirteen phase II studies took place despite the preceding phase I studies having an overall response rate of 0%. (Yeh, Huang, and Cohen 2016)

Adverse effects are common in phase I trials with 25% experiencing a severe toxicity, 17% with dose related toxicity, and 0.5-2.09% dying from treatment. (Waligora et al. 2018; Kim et al. 2008; Lee, Skolnik, and Adamson 2005; Shah et al. 1998; Decoster, Stein, and Holdener 1990) The average rate of severe or life-threatening event is 1.32 per person. (Waligora et al. 2018)

Thus, participation in phase I trials has little potential benefit and some associated risk, especially for children with poor prognostic brain tumors. Participants hope for some benefit even if they do not realistically expect it. This often leads to participation, especially if there are limited or no options for cancer directed care. A reasonable person could choose to participate in the clinical trial if options for cancer directed care are limited. (F. G. Miller and Joffe 2008) Choosing an option and being optimistic about one's choice helps one cope. Balancing hopes with worries is also appropriate. Having limited options may put one at risk for manipulation but does not necessarily infringe on the voluntariness of clinical trial participation and the validity of informed consent.

The process of enrolling in a clinical trial may be a whirlwind, but often occurs over a series of discussions rather than an isolated informed consent discussion. The content of the informed consent discussions can vary from provider to provider, notably around the perceived benefits and focus of a trial. (Simon et al. 2004; S Joffe et al. 2001)

The AAP states that informed consent process involves: "disclosure of information to patients and their surrogates, assessment of patient and surrogate understanding of the information, and their capacity for medical decision making." (Bioethics 2016) The information disclosed includes: 1) the patient's diagnosis and prognosis, 2) the nature of the treatment or intervention (including risks, benefits, and probability of success), and 3) the alternatives (including the option of no treatment or comfort measures). (Bioethics 2016) The discussion must be developmentally, educationally, and culturally appropriate. The consent process must take place before treatments or interventions and be long enough to provide time for patients and their surrogates to ask questions. (Bioethics 2016)

Some of the challenges that arise in pediatric settings around informed consent include, but are not limited to: language barriers, low education level or health literacy, emotional distress, religious or cultural views, manipulation from healthcare providers, parents, or legal guardians. (Breese et al. 2007; Simon et al. 2004) While clinical research informed consent documents should be written at or below an eighth grade reading level, this is not always accomplished. (Villafranca et al. 2017)

Attempts to improve the informed consent process are ongoing. To improve the informed consent process, many have advocated providing training to physicians and researchers, with focus on information delivery and attention to patient and parental preferences. (L. Johnson et al. 2015; Baker et al. 2007; Yap et al. 2010; Baker et al. 2013)

Several studies have been completed assessing communication, along with patient and parental understanding after an informed consent discussion. Hazen *et al*. in 2015 showed that in pediatric phase I oncology trials, risks were discussed 95% of the time and benefits about 88% of

the time. Therapeutic benefit was frequently emphasized along with the positive impact on quality of life (88%). (Hazen et al. 2015)

Both Simon *et al.* (2004) and Truong *et al*. (2011) compared the informed consent processes in pediatric and adult oncology centers. (Simon et al. 2004; Truong et al. 2011) While pediatric oncologists spent a longer average time disclosing information about the trial, parents had lower understanding of the rationale of treatment, risks and benefits of the clinical trial and standard therapy, the concept of randomization, treatment alternatives, and ability to receive therapy if not enrolled in the trial. Those with improved understanding often had participated in prior clinical trials, had a child with relapsed/progressed disease, had the consent discussion as an outpatient, a delayed time point from the new or relapsed diagnosis, discussed the consent with the principal investigator, and spent more time in the consent process.

Since Applebaum *et al*., first defined therapeutic misconception in 1982, ethicists have debated if therapeutic misconception exists and have attempted to further clarify and more precisely define the alternatives to therapeutic misconception. (Applebaum, Roth, and Lidz 1982) For a person to have therapeutic misconception, that person misconceives the purpose of the clinical trial to be for personal, therapeutic benefit rather than for generalizable knowledge. Therapeutic misestimation, alternatively, occurs when a person incorrectly overestimates benefit or underestimates risk. (Pentz et al. 2012) Further, therapeutic optimism occurs when subjects believe that they are more likely to benefit and less likely to experience risk than others enrolled in the clinical trial. (Lad and Dahl 2017)

Many of these concepts have been grounded in evaluating the informed consent process with discreet questionnaires rather than qualitative interviews. This can be problematic due to the "psychologist fallacy" and "discursive perspective." (Weinfurt 2013) The "psychologist

fallacy," occurs when the researcher substitutes his or her point of view for a participant's response. This egocentric bias in interpreting data is difficult to eliminate. The "discursive perspective," occurs when participants answer questions based on a desire to establish an attitude within themselves. In other words, they answer based on what they hope will happen rather than what has been disclosed to them. Therefore, questionnaires incompletely captured individual understanding and over-estimated misunderstanding. Ongoing quality studies are needed given the risk of increasing therapeutic misunderstanding related to phase I trials related to the language of 'targeted therapy' and the designs of phase I trials that may include the pairing of an experimental drug with standard chemotherapy. (Reeder-Hayes et al. 2017)

Being optimistic about a therapy is not always problematic, especially in the context of a general positive outlook or dispositional optimism. (L. A. Jansen et al. 2016) Dispositional optimism can assist children and young adults with cancer and their parents in promoting resiliency, finding benefit in the face of adversity, engaging in healthier behaviors, improving health related quality of life and psychosocial functioning. (A. Rosenberg et al. 2014; Molina et al. 2014; Gardner et al. 2017; Okado et al. 2016; Mannix, Feldman, and Moody 2009; Sulkers et al. 2013) Increasing levels of hope and quality of life are correlated with decreased levels of depression and anxiety; thus, preserving hope or using hope as a framework for choosing interventions may benefit overall well-being after a cancer diagnosis. (Germann et al. 2015)

If participation in a clinical trial is the only cancer directed therapy option, allows for hope preservation, and aligns with patient and family goals, then presenting a clinical trial to the patient and family is reasonable. Informed consent must be approached carefully as children and their parents are vulnerable and are susceptible to bias or manipulation from a physician-investigator who has a known or potential conflict of interest. (A. Rosenberg 2016)

When overt conflict of interest exists, it does not always interfere with the informed consent discussion, especially if the provider is transparent and does not provide a strong recommendation. Yap *et al.* (2010) noted that 64% of 103 pediatric oncologists presented phase I trials as an option rather than a strong recommendation and felt reluctant to influence decisions of families about these studies.

Separate from overt conflict of interest, the clinician can have an undue influence on the decision making for the child's care by making recommendations when there is no established standard of care. Each oncologist has his or her own medical opinions, values and underlying 'ethical standards.' These underlying values and standards influence the recommendations provided to patients and their families. (Hinds et al. 2005)

Those oncologists participating in Hinds *et al.* 2005 study reported consistently that patients and families choosing a Phase I study, terminal care, or do not attempt resuscitation (DNAR) orders were "consistent with my ethical standards." (Hinds et al. 2005) The physicians thought that the ethical option was chosen in each situation. It is unclear if the physicians influenced the decisions based on their own biases, values or preferences or if they believed all options were equally ethical and if all options are reasonable, physicians are less likely to have moral distress over the choices made by patients and their families. In the same study, parents perceived the way oncologists introduced phase I trials as "not trying to sway [them] one way or another/support any decision." (Hinds et al. 2005) In end-of-life decisions, patients and parents noted that oncologists helped "identify and respect [their] preferences." (Hinds et al. 2005) This extended to DNAR decisions, where oncologists "asked [parents] to do what [they] believe is right for [their] child." (Hinds et al. 2005) For all of these decisions, oncologists supported

patients and parents alike, a value that most oncologists find satisfying about their work. (Hinds et al. 2005)

Finally, phase I trial enrollment did not preclude quality end-of-life care in one institution where palliative care resources are robust. (Levine et al. 2015) This claim seems counterintuitive based on the observations I have had in my clinical training and in the empirical work done for this study. Even if palliative care services are robust, referrals can be late and preclude quality end-of-life care. A predictor of late palliative care referral includes intensive treatments and cancer directed care at the end-of-life. (Kaye et al. 2018) The discrepancy may be based on the differences of resources, personnel and institutional support for phase I trials rather than palliative care.

Shared Decision making

Patients and families ought to have greater decisional priority for terminal and poor prognostic cancer. (Whitney et al. 2006) Most parents desire to make decisions together with the oncologist (66%) or to make treatment decisions after considering the oncologist's opinion (25%). (Mack, Cook, et al. 2007) Only 8% of parents preferred the oncologist make the decisions, and no parents wanted the oncologist making decisions with little or no input from them. (Mack, Cook, et al. 2007) Only 1% preferred to make decisions with little or no input from the oncologist. (Mack, Cook, et al. 2007) Shared decision making is valued by parents of children with cancer and can best be accomplished with accurate prognostic understanding. It is also recommended by the AAP. (Adams, Levy, and Council on Children with Disabilities 2017)

To help patient and their families make the best decisions, healthcare providers can provide information in an empathic manner and use collaborative, shared decision making. Specifically in pediatric oncology, shared decision making interventions are sparse. (Coyne et

al. 2013) However, it is of the utmost importance, especially at the end-of-life. (Hinds et al. 2005)

End-of-Life Care for Children and Young Adults with HGG

Parents of children with brain tumors at the end of their child's life focus on 1) parental coping with maintenance of hope and resilience; 2) parental struggles, such as balancing competing responsibilities and talking to their child about death; and 3) parental hardships such as lack of financial and/or community resources 4) parental dilemmas such as trying to achieve a home death while optimizing symptom management. (Zelcer et al. 2010) Parents rightly focused on home-based palliative and oncology care, as it is associated with improved quality of life, an increased likelihood of having fun, experiencing events that add meaning to life, and dying at home. (S. Friedrichsdorf et al. 2015)

End-of-life care for children and young adults with HGGs is particularly challenging whether they die at home, in hospice, or in the hospital because symptoms and debility progress until death. Managing these symptoms and debility can be difficult for healthcare providers and be especially distressing for patients and their family members. Moreover, uncertainty or conflicts in prior decision making can manifest in changes to prior care plans when patients are acutely dying.

A recent publication by a Canadian group describes end-of-life care of 41 children with DIPG who died between 2001 and 2010. (Hasan et al. 2018) In this retrospective cohort study, they evaluated the last three months of life for these patients who died from disease progression. Similar to other cohorts, about 50% of the patients received cancer directed care and within the last month of life, 30% of patients received cancer directed care within the last month of life. Fifty-six percent died at home. Importantly, DNAR discussions were documented but not

always followed. Eighty percent of the patients had documented DNAR discussion a median of 28 days (IQR 11-68) before death. Of the 33 discussions, 30 (91%) agreed to a DNAR. Those not agreeing to DNAR received resuscitation. Three patients received resuscitation and after resuscitation had their first DNAR discussion. One child who had a DNAR order began to acutely die and parents called emergency services. This child also underwent cardiopulmonary resuscitation. Interestingly, none of the 29% of patients without a DNAR received CPR. As the authors point out, "a lack of a DNR in end-stage cancer may concern clinicians who fear that CPR may lead to child suffering, parental regret and provider moral distress." However, they later then go on to question the importance of a DNAR as the existence did not orchestrate the care the patients ultimately received. While their point is well taken, it is unclear what the foundational discussions of diagnosis, prognosis and goals of care were for these patients. This could reflect that DNAR discussions are more of a check box to complete rather than flowing out of goals of care.

There is a clinician rhetoric that DNAR conversations should occur with the patient and/or family early in the disease course and be led or moderated by the clinician who knows the patient and/or family the best (Sanderson, Zurakowski, and Wolfe 2013); however, late or absent discussions about code status are not uncommon. (Hasan et al. 2018) Common barriers cited by Sanderson *et al*. in having the DNAR discussions often focused on the parents: "unrealistic parent expectations," "lack of parent readiness," and "differences between clinician and patient/parent understanding of the prognosis." Conversely, the following were never or rarely considered a barrier: "lack of importance to clinicians," "laws and regulations," "concern about the patient receiving less attention from the health care team once resuscitation status discussions

begin," "lack of clinician time," "ethical considerations," "conflict between patient and parent," and "clinician concern about losing the trust of the patient."

Palliative Care as an Example: Cultural and Religious Considerations in Decision Making

Culture and religion are important to patients and their families in decision making and end-of-life care and should be considered by healthcare providers when discussing care options. (Wiener et al. 2013) People have beliefs that are dynamic and individual in nature, and thus cultural and religious beliefs are not generalizable. Cultural humility, rather than assumption, is needed when interacting with patients and families. (Tervalon and Murray-Garcia 1998) Further learning about a patient's and family's religious and spiritual beliefs may help in the healing process. There is a paucity of literature in this field, but greater attention has been given to it in the palliative care field than other fields. (Puchalski et al. 2014; Balboni et al. 2013) The holistic view of the patient in palliative care and hospice allows for viewing the patient as a person in the spheres of biopsychosocial and spiritual health. Even from a research perspective, most quality of life evaluations do not include spirituality, but do reference hope, suffering, and transcendence. Demographic information recorded in a person's chart or from a checkbox on a survey does not adequately capture the importance of religion, faith tradition, spirituality, and community or how to address within healthcare the true beliefs of a person.

Ethical Challenges and Principlism

Principlism is often applied to clinical and research ethical challenges such as those outlined above. Principlism is an ethical theory promoted initially by Tom L. Beauchamp and James Childress in which essential moral norms of a pluralistic society, such as America, can practically be applied in a non-hierarchal way to evaluate ethical dilemmas. (Beauchamp and Childress 2013) Principles are general guidelines based on the common morality. "Based on

considered moral judgments and the way moral beliefs cohere," the four clusters of principles that Beauchamp and Childress determined were essential to biomedical ethics are:

> "*Respect for autonomy* (a norm of respecting and supporting autonomous decisions), 2) *nonmaleficence* (a norm of avoiding the causation of harm), 3) *beneficence* (a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs), and 4) *justice* (a group of norms for fairly distributing benefits, risks, and costs)." (Beauchamp and Childress 2013)

Though this theory was first promoted in the 1970's it has a historical background that extends to medical ethics in the nineteenth century with concepts of nonmaleficence and beneficence. (Beauchamp and Childress 2013) About the time the first edition of Principles of Biomedical Ethics was published, the Belmont Report formalized research ethics principles of autonomy, beneficence, and justice. (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978) The foundational principles are rooted in, consistent with, or not in conflict with various moral theories and epistemic justifications related to moral decision making. (Bulger 2007) Thus, principlism accounts for moral pluralism.

It takes a middle ground with not only competing moral theories, but also competing principles. Principlism offers plasticity in moral decision making by balancing the competing *prima facie* principles. This is similar to W. D. Ross's idea of *prima facie* duties, in which conditional duties would be proper duties (one's actual duty) if they had no other competing duties of moral significance. (Ross 1930) It flexibly accounts for situational complexities and nuances in specific ethical dilemmas. This strength is also a limitation in that inconsistent judgments can arise when utilizing principlism.

In balancing these competing principles, different solutions can be elucidated with each moral dilemma or with the same moral dilemma given to a different group of people. While some argue that this is inadequate treatment of relativism and has promoted medical consumerism, (Donaldson 2017) principlism often leads to practical solutions that lead to the least amount of distress for those particular parties involved. (Beauchamp and Childress 2013)

Principlism is an accessible moral theory that is often used in pediatric ethics curricula along with casuistry for case based analysis of ethical dilemmas. (Opel and Olson, 2012) With the prevalence of principlism in medical curricula, clinical settings, and research, the use of it to analyze empirical, narrative results will be helpful in translation to clinicians. To some this may be counter-intuitive as principlism and narrative ethics can be in tension; instead, principlism and narrative ethics can inform one another. (McCarthy 2003) One cannot apply a principle unless the facts of the case or situation are well understood. This thesis will thus use principlism in analyzing data from the concordant empirical study, which is delineated in the next chapter.

Chapter 2: Empirical Study: Purpose and Methodology

Learning from the Decision Makers: Description of the Qualitative Study

Purpose

The purpose of the empirical study was to investigate the communication and decision making processes over the illness trajectory for pediatric and young adults with HGGs, their parents, and physicians, namely oncologists and palliative care specialists.

A Priori Objectives

1. To evaluate the decision making and informed consent processes for cancer directed therapy for children and young adults with HGG and their families with the pediatric oncology team.
2. To evaluate if palliative care improves understanding of comfort-focused care and hospice options along with family-centered decision making for pediatric patients with DIPG, GBM or other HGG.
3. To evaluate how decision making, hopes and goals change over an illness trajectory for children and young adults with HGG.
4. To compare the actual care of patients with HGG with the previously stated preferences and hopes when there is and is not a palliative care consult.

Hypotheses

1. Children and young adults diagnosed with a HGG are more likely to receive treatment recommendations from the pediatric oncology team that favor Phase I trials or other cancer directed therapy over palliative care and hospice, given the tension between hopeful intervention and acceptance of end-of-life.
2. Though there is a risk for conflict of interest with patients receiving care from physician investigators and a risk for therapeutic misconception during the consent process, appropriate informed consent is obtained and therapeutic misconception is minimal.

3. Palliative care involvement helps facilitate family-centered discussions and decisions. Families of children and young adults with HGG who have palliative care involvement have a better understanding of prognosis, end-of-life care options, and receive care that is concordant with their goals more frequently than those who do not have a palliative care consult.
4. Families' hopes shift over the course of an illness, transitioning from hopeful intervention with cancer directed therapy to a comfort focused approach. The shift to a comfort focus occurs earlier for families when palliative care is involved.

Methodology

A longitudinal, qualitative approach was used to evaluate how goals of care, hopes, and decision making change over the course illness for patients with HGGs and their families. With progressive illness, multiple difficult discussions were anticipated for these patients, starting at diagnosis and continuing through end-of-life care. We sought to assess the content and structure of these discussions and evaluate if therapeutic misconception, misestimation or optimism permeates decision making or if decision making is free of this problematic understanding, with patients and families balancing the knowledge of the poor prognosis with hope and an optimistic outlook. We also aimed to learn the important influences on decision making, including the impact of physician recommendations and communication.

Qualitative data was obtained in the form of personal accounts and experiences of parents, and when appropriate of patients, which reflect on communication with physicians, express insights into the decision making process, and reveal present and future hopes and worries. Serial audio-recording of key decision making clinical encounters (e.g. MRI reviews or end-of-life discussions) and one-on-one semi-structured interviews with parents and several adolescent and young adult patients were obtained.

The open-ended, semi-structured interviews were developed based on informed consent questionnaires. (S Joffe et al. 2001; Truong et al. 2011) The questions aimed to evaluate the parents or patient's decision making processes, hopes, fears and suggestions on how to improve physician-parent/patient communication and support decision making. See Appendix A for the semi-structured interview guide.

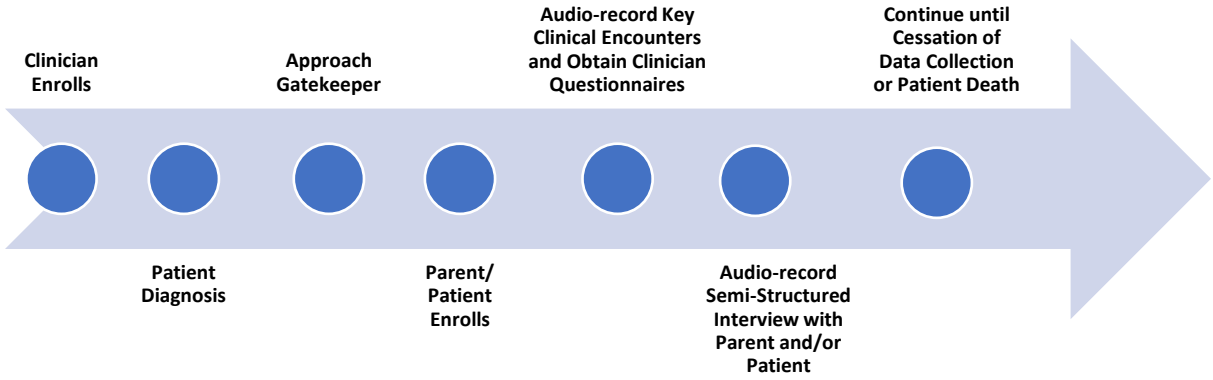
Quantitative surveys of parents and/or patients were not used as they would not be able to provide the thick data of personal accounts, experiences, and decision making process that were needed to answer the study questions. Additional reasons include: 1) burden of additional time for completing questionnaires, 2) risk of external influences on questionnaire completion (i.e. other people helping complete the questionnaire), 3) risk of literacy level influencing ability level to complete, 4) low response rates, and 5) the lack of a validated instrument capturing all domains of care, ranging from phase I or cancer directed therapy to palliative or end-of-life care.

Field notes from neuro-oncology meetings reviewing patients, clinical encounters and chart notes were obtained and analyzed. If subspecialty palliative care was involved, attempts were made to audio-record interactions with the supportive care clinic or the Pediatric Advanced Care Team (PACT). Comparison was made between the desired care and the actual received care based on preferences expressed in audio-recorded clinical encounters and interviews and the charted received care in the patient's chart.

Oncologists and palliative care clinicians were queried via questionnaires after each audio-recorded key decision making clinical encounter. Questions focused on each patient's disease status, prognosis, patient preferences and family dynamics in decision making, and the physician's hopes and worries for the patient. Physician questionnaires for oncologists and palliative care specialists are located in Appendix B. Information from patients, parents and

physicians allows data triangulation to identify key themes. Figure 3 demonstrates the experimental design in a timeline schema.

Figure 3: Experimental Design



Audio-recorded clinician encounters and parent/patient interviews were centrally transcribed. *A priori* and inductive codes were generated independently by two investigators (AL and RP). Deductive codes derived from the interview guide and concepts in the literature. Inductive codes were derived from the data based on new issues, topics, ideas, or opinions. The codes were further defined and developed based on the meanings that participants attached to the coded ideas. Codes were classified based on their topics and underlying concepts.

At a code book meeting, the two investigators compared and discussed the codes with a third investigator (KB) until consensus was achieved. Inter-coder reliability was reviewed. Discrepancies in coding were evaluated and updated until coders agreed on the final code book. The coded transcripts were analyzed manually and with MaxQDA Analytics Pro 2018

Qualitative software using constant comparison method until code saturation, the point where no new codes arise. Codes were analyzed and key themes emerged based on frequency of occurrence and emphasis by participants.

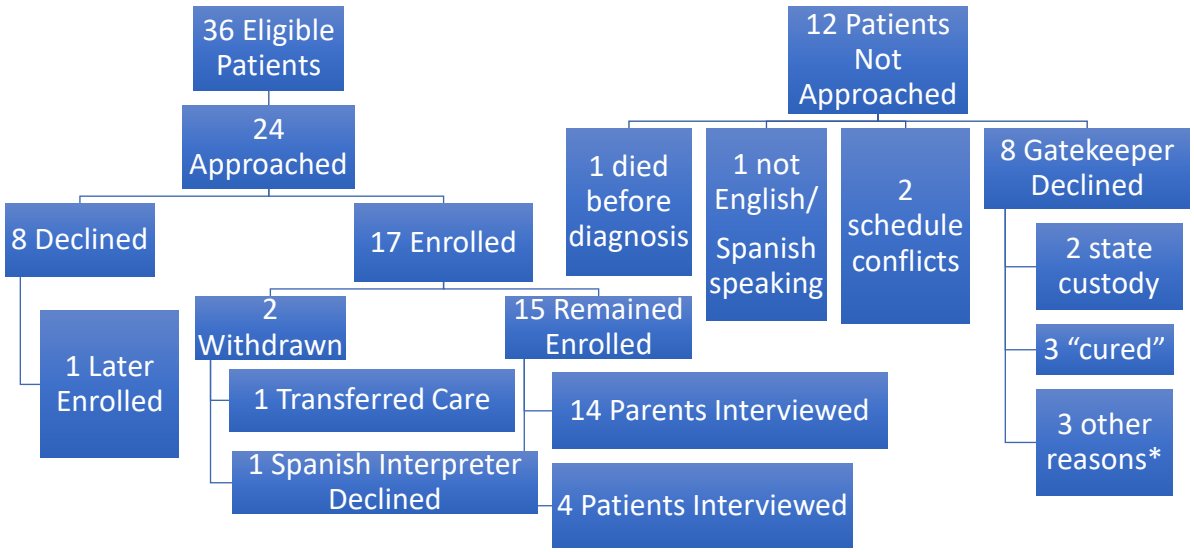
Eligible Participants and Enrollment

Eligible participants included: 1) pediatric/young adult oncology patients (ages 0 to 21 years old) at Children's Healthcare of Atlanta with a diagnosis of DIPG, GBM or secondary HGG, 2) their parents, 3) their neuro-oncologists, and 4) their palliative care specialists. Primary language of participants was either English or Spanish. Recruitment of eligible patients occurred through primary neuro-oncologists who served as gatekeepers in allowing or not allowing access to patients. Accrual occurred over ten months, from April 2017 until January 2018.

Of thirty-six eligible participants, twenty-four were approached. Eight initially declined, however one enrolled later. Seventeen patients enrolled initially, but two later withdrew: one for transfer of care to another center and the other not having an available Spanish interpreter to consent to having his or her voice audio-recorded. Fifteen remained enrolled at the end of the study (Figure 4).

Subjects able to participate in semi-structured interviews were: 1) patients with HGG (ages 8-17) with no cognitive impairment who provided assent and had parental permission to participate 2) patients with HGG (ages 18-21) with no cognitive impairment and provided consent, and 3) parents of patients with HGG who provided consent. One researcher (AL) interviewed thirteen mothers, one father, and four patients. While four fathers and one step-father were present at key decision making visits and agreed to be audio-recorded, they were not specifically interviewed. They deferred to the mothers for participation.

Figure 4: Patient Enrollment



Eligible healthcare providers included neuro-oncologist attendings (n=5, 4 enrolled), neuro-oncology fellows (n=2, 1 enrolled), hematology-oncology fellows (n =14, 1 enrolled), and palliative care specialists (n=6, 2 enrolled). Consent for audio-recording was also obtained from two developmental therapeutics nurses and one advanced practice provider. No interpreters provided consent to audio-recording. Questionnaires were completed only by the oncologists or palliative care specialists caring for the patients (n=7).

Institutional Research Board and Ethical Considerations

This protocol was approved by the Emory University and Children's Healthcare of Atlanta Institutional Review Boards (IRBs), and the pediatric hematology oncology program, neuro-oncology program, palliative care team, and interpreting services leadership team. Institutional practices for informed consent and assent were followed. Participation did not impact treatments offered to the patient or care received at the institution. Healthcare provider participation did not impact their employment or training status. Study participation was voluntary for patients, parents and clinicians. Participants who revoked consent or assent were notified that records would be destroyed and not analyzed.

Potential risks and discomforts from participation in the study included: 1) distress from discussing emotional topics such as end-of-life care, 2) discomfort from audio-recording, and 3) provision of time for interviews. Possible direct benefits from participation included development of greater insight into hopes, wishes and decisions being made. No compensation was provided for participants. Data from audio-recordings, field notes, chart notes, and questionnaires were de-identified, kept private and confidential, and securely stored per institutional guidelines.

Chapter 3: Results and Brief Discussion

Demographics

Demographics of patients, parents and physicians are listed below. Quotations denote respondent answers as they are not standardized but rather obtained from open ended questions in interviews or on questionnaires.

Table 1: Patient Characteristics

	Included Patients, N=15, n (%)	Excluded Patients, N = 21, n (%)
Sex	Male 11 (73)*	Male 13 (62)
Age, years	Average 9.2 (SD 6)	Average 9 (SD 6.4)
	<6: 4 (27)	4 (19)
	6-10: 6 (4)	4 (19)
	11-17: 3 (2)	7 (33)
	>= 18: 2 (13)	6 (29)
Race	White: 8 (53)	10 (48)
	African American: 4 (27)	6 (29)
	Asian: 1 (7)	3 (14)
	Other: 2 (13)	2 (9)
Ethnicity	Latino/Hispanic Origin: 2 (13)	1 (5)
Insurance	Medicaid Only: 7 (47)	6 (29)
	Private Insurance Only: 6 (40)	11 (52)
	Medicaid + Private Insurance: 2 (13)	4 (19)
Diagnosis	DIPG : 9 (60)	6 (29)
	GBM: 4 (27)	14 (66)
	Secondary HG: 2 (13)	1 (5)

Table 2: Options of Care Patients Received

	Included Patients, N=15, n (%)	Excluded Patients, N = 21, n (%)
Surgery	No Surgery: 8 (53)	3 (14)
	Biopsy: 3 (20)	7 (33)
	Resection: 5 (33)	12 (57)
	Re-Resection: 2 (13)	1 (5)
	VP Shunt/EVD: 3 (20)	5 (24)
	Port: 4 (27)	2 (10)
	G-Tube: 1 (6)	0 (0)
Radiation	Radiation: 15 (100)	18 (86)
	Re-irradiation: 6 (40)	3 (14)
Chemotherapy	Standard: 3 (20)	5 (24)
	Multiple courses: 3 (20)	5 (24)
	Palliative: 2 (13)	1 (5)*
	Compassionate Use: 3 (20)	0 (0)
Clinical Trial	Phase I [one]: 7 (47)	3 (14)
	Multiple Phase I: 2 (13)	4 (19)
	Phase II: 1 (6)	1 (5)
PACT Consult	7 (47)	7 (33)

*Two patients had discussed palliative chemotherapy, but did not start it prior to death.

Table 3: Parent Interview Participant Characteristics

Parent Participants in Semi-Structured Audio-Recorded Interviews, N = 13, n (%)		
Parent Respondent	Mother: 12 (92)	
Average Age, years	36 (SD 5.4)	
Race	White: 8 (62) African American: 3 (23) Asian: 2 (15)	
Ethnicity	Latino/Hispanic Origin: 1 (8)	
Preferred Primary Language	English: 12 (92)	Spanish/Bilingual: 1 (8)
Relationship Status	Single: 1 (8) Married: 9 (69) Divorced: 3 (23)	
Sexuality	Heterosexual: 12 (92)	Bisexual: 1 (8)
Highest Level of Education Leve	Bachelors Degree(s): 4 (31) Some College/Associates Degree: 5 (38)	High School: 2 (15) Graduate Degree: 3 (23)
Employment Status	Part-Time: 1 (8)	Full Time: 7 (54)
Financial Status	"Struggling, Rocky, Lower Class, Relying on Family & Friends": 4 (31) "Able to Pay Bills, Ok, Lower Middle Class": 3 (23)	"Able to Pay Bills and Do What Want, Upper Middle Class": 2 (15) "Pretty Well, Upper Class": 4 (31)
Number of People in Family	Average: 4.3 (SD 1.5)	
Religion	Atheist: 1 (8) Baptist: 3 (23) Catholic: 2 (14)	Non-Denominational: 3 (23) None: 3 (23) Seventh Day Adventist: 1 (8)
Church/mass attendance:	"Don't believe in going to church": 4 (31) Attend Regularly: 2 (15)	Rarely Attend: 2 (15) Attend Frequently: 5 (38)
Spirituality	Pray: 11 (85) Sing/Worship: 1 (8) Devotional/Read Scripture: 2 (15) Meditation/Good energy: 2 (18)	Write notes: 2 (18) Diet: 1 (8) Teach Kids: 2 (18)
Life Outlook	Optimist: 6 (46) "Positive Realist": 3 (23)	Realist: 3 (23) Pessimst: 1 (8)
Life Stressors	Work: 1 (8) Finances: 1 (8) Patient Siblings: 1 (8) Nones: 5 (38)	Spouse laid off work: 2 (15) Insurance: 1 (8) Living with Ex-spouse: 1 (8) Over 50 of them: 1 (8)
Healthcare Provider in Family	Yes: 5 (38)-no physicians	
Familial Experience with Serious Illness	Yes: 11 (85)-Cancer, Congestive Heart Disease, Chrohn's Disease, Dementia, Diabetes , Early Death, Thrombotic Thrombocytopenic Purpura)	

Table 4: Patient Interview Participant Characteristics

Patient Participants in Semi-Structured Audio-Recorded Interviews, N= 4, n (%)		
Sex	Male: 3 (75)	
Age, Average, years	17.5 (SD 3.5)	
Race	White: 1 (25) African American: 2 (50) Other: 1 (25)	
Ethnicity	Latino/Hispanic Origin: 1 (25)	
Preferred Primary Language	English: 4 (100)	Bilingual (English/Spanish): 1 (25)
Relationship Status	Single 4 (100)	
Sexuality	Heterosexual: 4 (100)	
Highest Level of Education Level	High School: 2 (50) Graduated High School: 1 (25) Some College: 1 (25)	
Employment Status	Employed: 1 (25)	
Financial Status	"Hard not working; worried about bills": 1 (25)	"OK": 3 (75)
Number of People in Family	Average: 5 (SD 1.8)	
Religion	Baptist: 1 (25) 7th Day Adventist: 1 (25) Jehovah's Witness: 1 (25) Mixed (Catholic & Islam): 1 (25)	
Spirituality	Pray: 4 (100)	Attend church/meeting: 4 (100)
Life Outlook	Optimist: 1 (25) Realist: 2 (50)	Positive Realist: 1 (25)*
Life Stressors	Finances: 1 (25) Difficulty Walking: 1 (25)	School: 1 (25) Appearance: 1 (25)
Healthcare Provider in Family	Yes: 2 (50)-no physicians	
Experience with Serious Illness	Yes: 3 (75)-Self & other family members	

*Initial answer: ("Optimist & pessimist at the same time-hope for the best, prepare for the worst," but at a later date changes answer to positive realist)

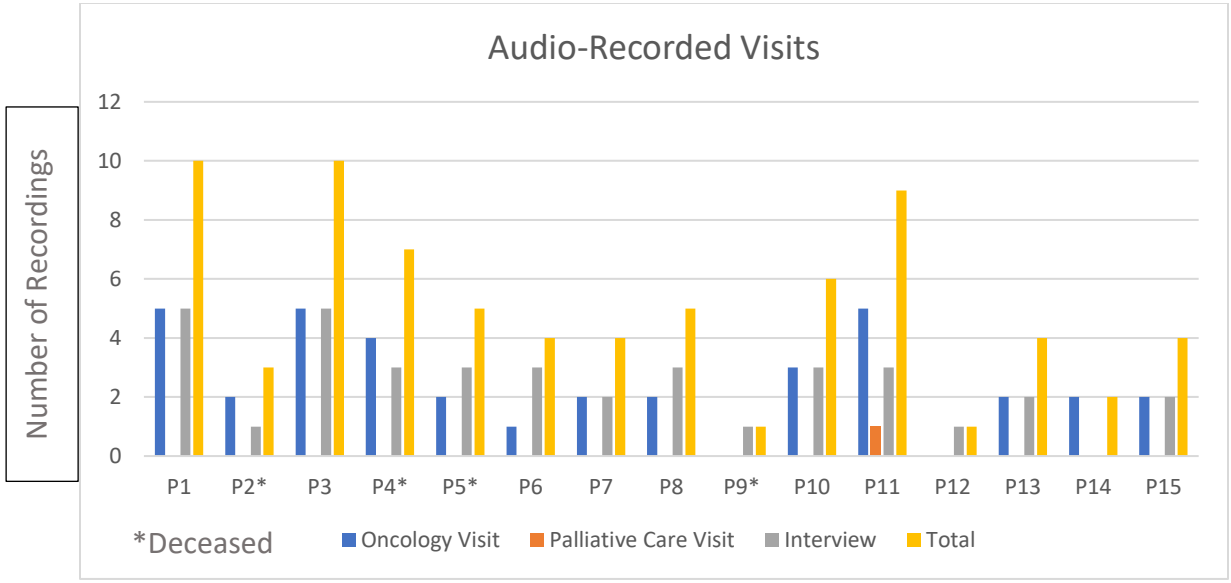
Table 5: Neuro-Oncologist Characteristics

Neuro-Oncologist Demographic Characteristics, (N = 3 completing questionnaire), n (%)		
Sex	Male: 2, (66)	
Age, Average, years	52.3 (SD 5.5)	
Race	White: 2 (66)	
	Asian: 1 (33)	
Ethnicity	Latino/Hispanic Origin: 1 (33)	
Primary Language	English (100)	
Relationship Status	Married: 2 (66)	Divorced: 1 (33)
Sexuality	Heterosexual: 3, (100)	
Highest Level of Education	MD: 1 (33)	MD + Graduate Degree: 2 (66)
Employment Status	Employed Full Time: 3 (100)	Attending Neuro-Oncology: 3 (100)
Financial Status	"Employed Full Time": 1 (33)	
	"Upper Middle Class": 1 (33)	
	"Top 3%": 1 (33)	
Number of People in Family	Average: 4 (SD 0)	
Religion	"Agnostic/Non-Practicing Catholic": 1 (33)	
	Practicing Catholic: 2 (66)	
Spirituality	Attend Mass: 2 (66)	
	Meditate/"commune with nature": 2 (66)	
Healthcare Provider in Family	Yes: 3 (100)-mostly physicians	
Familial Experience with Serious Illness	Yes: 3 (100)-Cancer,Congestive Heart Failure, Dementia, Diabetes, Early Death, Renal Failure	
Life Outlook	Realist: 2 (66)	Pessimist: 1 (33)
Stressors	Family: 2 (66)	Financial: 2 (66)
	Work: 2 (66)	Work-Life Balance: 1 (33)
Training	Informed Consent: 3 (100)-observation/experience	End-of-Life Care: 1 (33)-observation/experience

Results

Seventy-five independent encounters were audio-recorded, with an average of five encounters per patient (Standard Deviation 2.9), with each patient having an average of 2.5 oncology visits (Standard Deviation 1.6) and 2.5 interviews (Standard Deviation 1.4) [Figure 5]. Patient subjects were identified by P, followed by their enrollment number (i.e. patient 1 = P1). Due to scheduling conflicts and missed appointments, no physician encounters were audio-recorded for P9 and P12; and one physician encounter was audio-recorded for P6. Due to scheduling conflicts, no semi-structured interviews were obtained for P14 and only one structured interview was obtained for the following patients: P2, P9, P12, and P13.

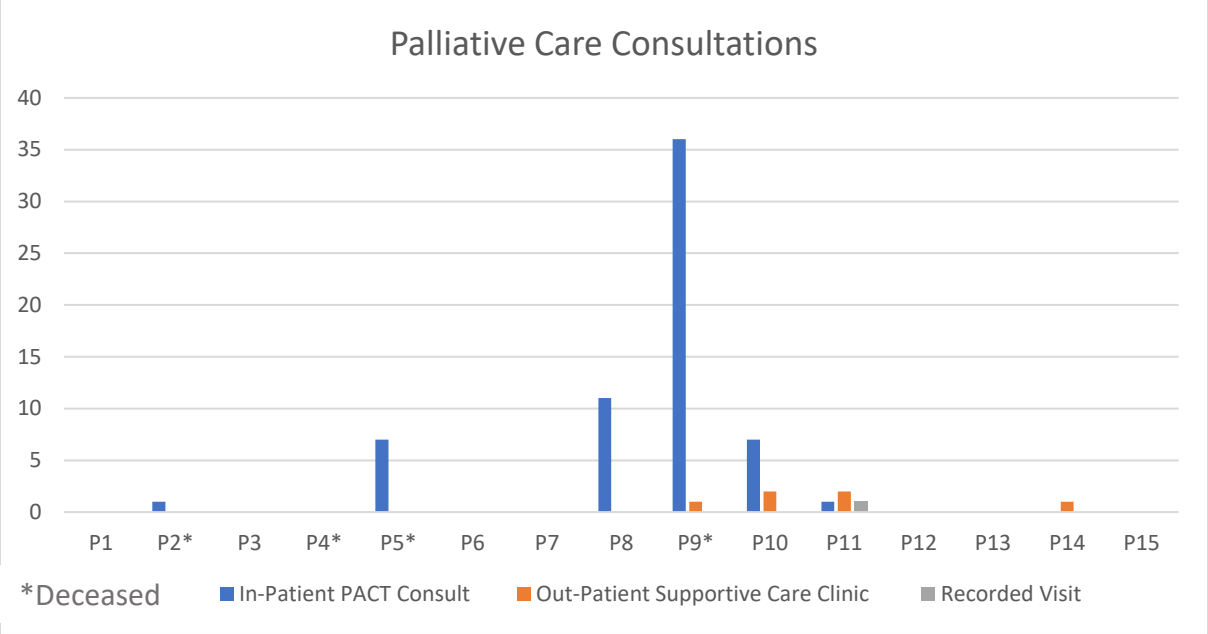
Figure 5: Audio-Recorded Visits Per Patient



One palliative care visit was recorded (P11) even though 47% (7) had a palliative care consult by the end of data collection. One patient had an in-patient consultation by the pediatric advance care team (PACT) prior to this study. During the study, five patients had in-patient PACT consults and four patients had out-patient supportive care clinic visits. Audio-recording

palliative care visits was difficult as only two PACT providers enrolled in the study, schedule conflicts with timing of palliative care consultation, and lack of principle investigator notification. In-patient consultation was more difficult to schedule than out-patient visits. Most consultations were in-patient.

Figure 6: Palliative Care Consultations Per Patient

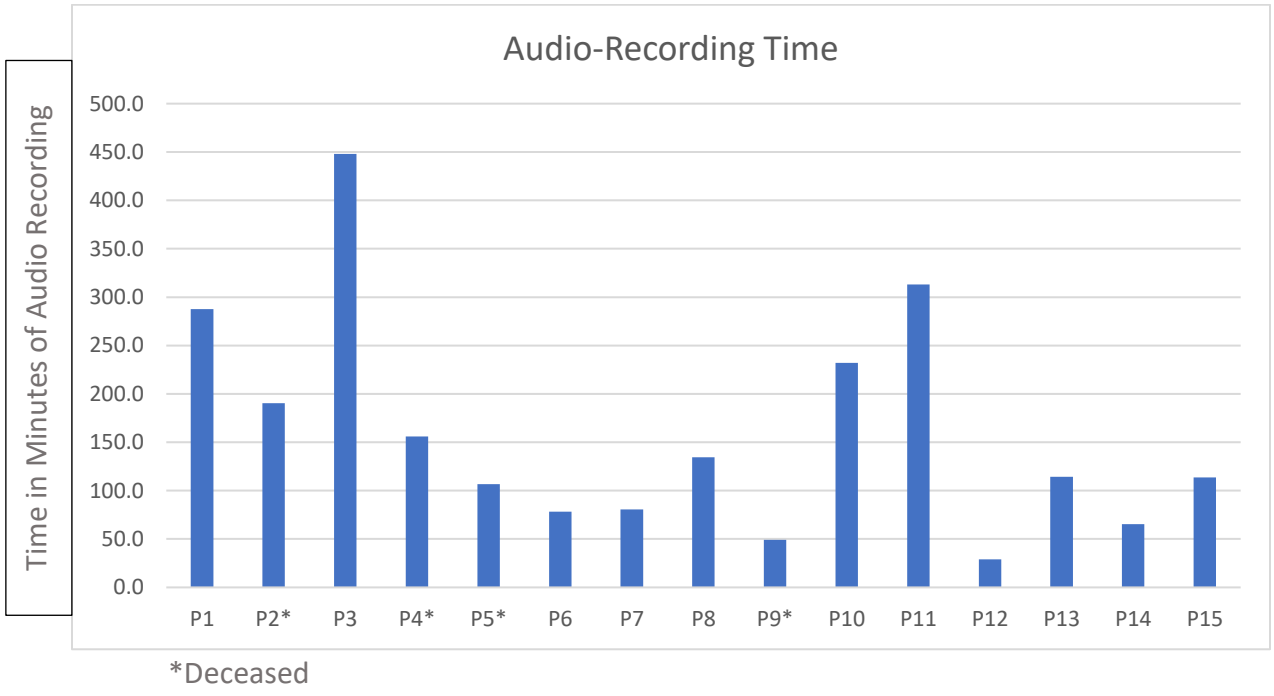


The 75 audio-recorded encounters generated 40 hours (2,398.9 minutes) of transcribed data, with an average of 2.7 hours (159.92 minutes, Standard Deviation 115.9) recorded per subject. The average length of encounters was 27.3 minutes (Standard Deviation 11.8). Audio-recording times ranged from a minimum of 7.8 minutes to a maximum of 91.3 minutes for clinical encounters, a minimum of 1.9 minutes and a maximum 94 minutes for interviews, and a minimum of 23.8 minutes and a maximum of 928 minutes for encounters with combined clinical visit and interview. On average, a clinic visit was 28.6 minutes (Standard Deviation 18.2). On average, an interview was 36.7 minutes (Standard Deviation 22). Audio-recordings of

encounters that included combined clinic visits with interviews were 61.5 minutes on average (Standard Deviation 29.9).

The wide range of audio-recording time was secondary to 1) differing ranges of clinical encounter times, 2) patients or parents spending more time answering questions in the first interview and less time in subsequent interviews, 3) the investigator permitting families to answer "no changes" for an interview without answering all of the questions, 4) time constraints on patients or families for the interview, 5) technical difficulties with the audio-recorder not capturing an entire encounter, and 6) missed clinical encounters and interviews with patients or parents.

Figure 7: Audio-Recording Time Per Patient



At the time of the study completion, four patients died: P2, P4, P5, and P9. Of those who died, two died in the hospital, one of which had enrolled in hospice services previously. Two died at home with hospice services in place. The four deceased patients had DNAR orders.

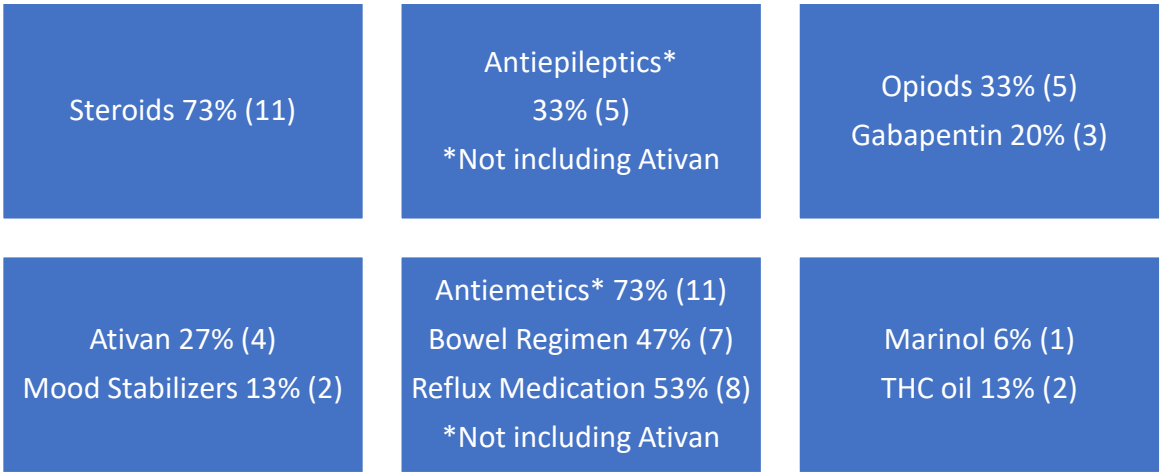
Three had documented DNAR orders at least one month prior to death, with the earliest documentation being six months prior to death. None were intubated, underwent mechanical ventilation, or spent time in the intensive care unit. Three of the deceased patients had discussions with a healthcare provider about Physicians Orders for Life Sustaining Treatment (POLST). Two had documented limitations of life-sustaining treatment in the form of Physicians Orders for Life Sustaining Treatment (POLST) while the third never had the forms completed. One of the two completed POLST forms was directed with a clinician other than a physician. No surviving patients have DNAR or POLST orders written.

Hospice was discussed with 53% (8/15) of patients and 27% (4/15) received hospice services. Three of the four deceased patients received hospice services. Three families planned to have limited autopsies post-mortem, but only two had autopsies completed. These two patients died in the hospital.

Outside of the initial diagnostic discussion, clinicians did not bring up life-expectancy again until patients had progressed significantly and were presumably at the end-of-life; however, parents may bring it up in a way of demonstrating they have beaten the odds. For instance, parents would mention that it has been a year or almost two years from diagnosis. At a time of significant progression, parents may have been told that death would be eminent, yet their child survived (n=6). During audio-recording, clinicians over-estimated life-expectancy 66% of the time (2/3 patients). In one patient encounter, a clinician stated the child had several months to live, yet that patient died nine days later. Another clinician estimated the patient would die in 12 weeks; the child died 8 weeks later. For a third patient, the oncologist did not give an exact life-expectancy yet talked about how the compassionate use drug or brain tumor progression could cause an acute event. That oncologist was surprised that the child died two

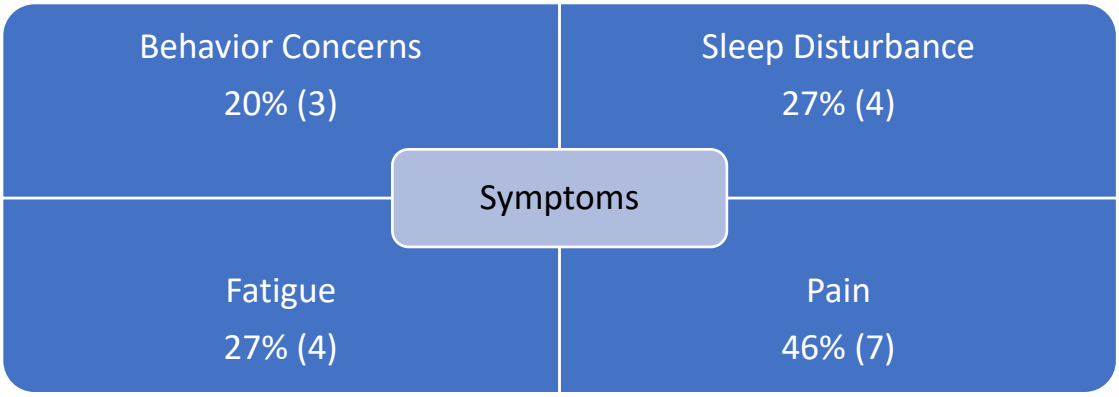
days later. P9 did not have an audio-recording discussing life-expectancy with clinicians, but at clinician meetings physicians focused on what progress the patient had made rather than deterioration toward death.

*Figure 8: Symptom Focused Medications Patients Received^*



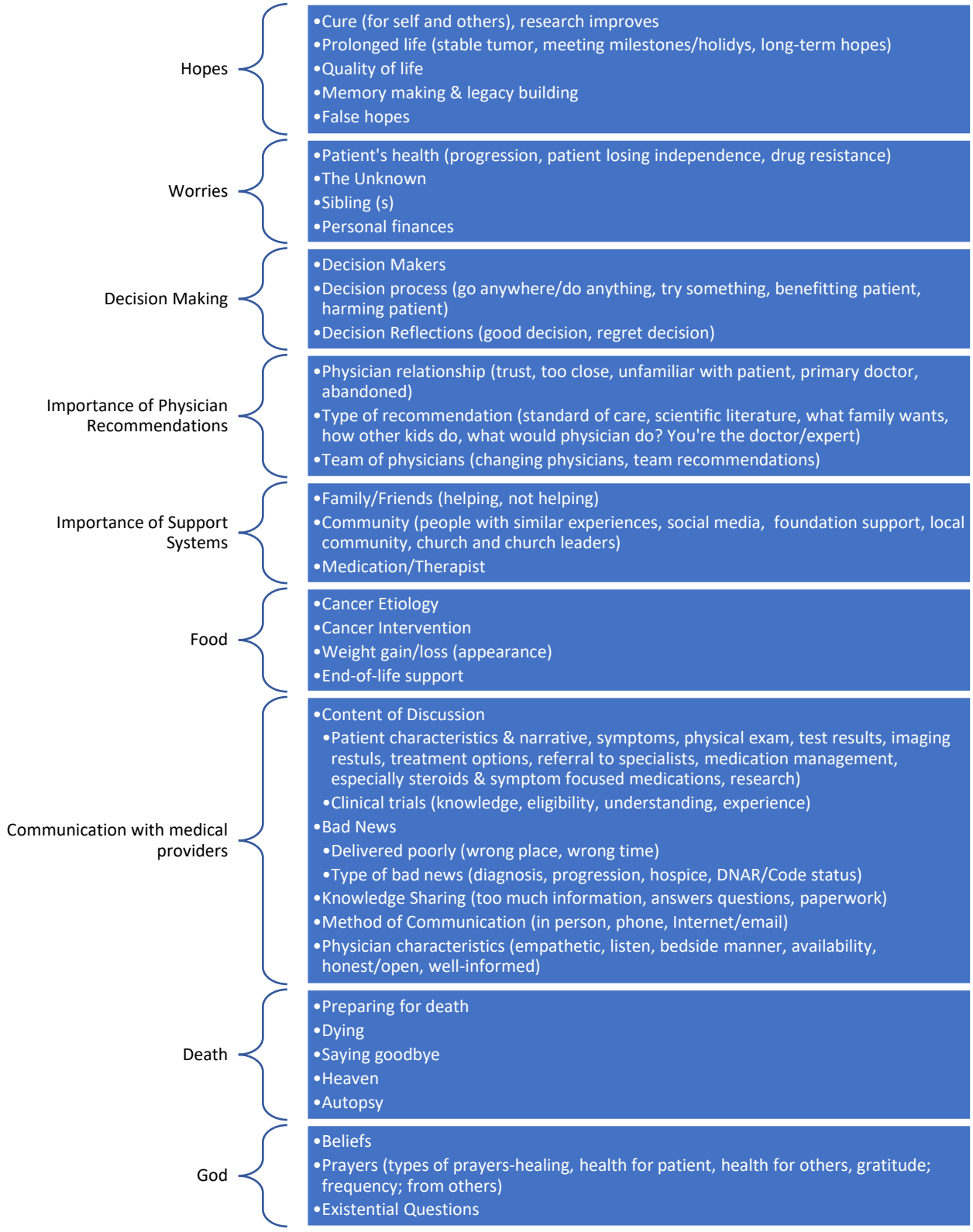
^Data obtained from chart review.

*Figure 9: Patient/Parent Reported Symptoms^*



^Data obtained from audio-recorded patient encounters and chart notations. These were not asked specifically in the interviews and were not a primary focus of the study. Results here may be falsely low.

Figure 10: Themes, Codes, and Subcodes



Interview Themes

Parent theme categories were identified based on emergence of new ideas, mentioning more than two times, and emphasis by the informants. Themes were identified from analyzing the codes, with emergence of underlying concepts that related the codes to one another. Parent and patient interview themes included 1) hopes (for a cure, prolonged life, quality of life, memory making and legacy building, and false hopes), 2) worries (patient's health, the unknown, siblings, and personal finances), 3) decision making (decision makers, decision process, decision reflections), 4) importance of physician recommendations (relationship with physician, type of recommendation, team of physicians), 5) importance of support systems (family, community, medication/therapist), 6) food (as cancer etiology, intervention, weight gain/loss, end-of-life care), 7) communication with medical providers (content of discussion, bad news, knowledge sharing, method of communication, physician characteristics), 9) death (preparing for death, dying, saying goodbye, heaven, autopsy), and 10) God (beliefs, prayers, existential questions).

Patient and Parent Responses to Interview Questions

Tell Me About Your Child's (or Your) Illness

Patient and parent narratives are powerful when recounting when the patient was first diagnosed and prognosis was revealed. Their personal stories demonstrate the impact of how the information was delivered, received, and interpreted. With knowledge of limited treatment options, some families indicated that they would spend a significant amount of their time, money, and resources in exploring any potential treatment option for their loved one. Others would rely primarily on the oncology team to provide options of care.

Table 6: Patient and Parent Responses

Patient and Parent Responses, N = 16, n (%)
Prognostic Understanding
All patients and parents acknoweldged the poor prognosis and that there was no cure: 16 (100).
Options for Care
•All patients began with a cancer directed therapy (chemotherapy, surgery, radiation) or clinical trial: 16 (100) •After intial therapy: Waiting: 3 (19) •At progression: Clinical trial as Only Option: 3 (19), Surgery: 1 (6) No option: 1 (6)
Did the doctor recommend one of the options? What did he or she say? Did you think this was a strong recommendation or just a suggestion?
Continue what we are doing. Stay on clinical trial: 5 (31), Come off trial with progression: 3 (19), Continue compassionate use drug: 2 (12.5), DNAR/POLST: 1 (6)
What option did you pick and why?
Clinical trial, radiation, chemotherapy, surgery, compassionate use drug as it was our only option: 14 (88)
Tell me all about how you made the decision.
Influences on decision: Family members: 16 (100), Friends 2 (12.5), Church: 2 (12.5), God: 12 (75)
Who usually makes big decisions in your family?
Myself: 10 (62.5), With spouse, together as a team: 3 (19), Other Family Member: 2 (12.5)
What do you wish you could know that you have not discussed yet?
Nothing, just wish child did not have illness: 16 (100)
What do you wish you did not know or wish that you had not been told? Is there anything you wish your child was not told?
Nothing: 16 (100)
What do you think is the best outcome?
A cure, miracle, or healing: 16 (100)
What is the worst outcome?
Death: 16 (100)
What are your fears?
The drug isn't going to work: 1 (6), Death: 16 (100)
What do you hope for right now?
A cure: 16 (100), Make a milestone/memory: 6 (38)
How could we improve conversations like the one you had with your child's doctor? We welcome any suggestions!!!
Nothing: (75), Decrease the waiting time: 3 (19, Decrease the number of people in the room: 1 (6)

Clinical Trial Understanding and Experience

The clinical trial experience often involves having multiple long appointments, labs, tests, imaging, completing diaries, and waiting for dispensing medication. Patients and families embrace the intensity when they perceive it to be their "only option." One family expressed their hope that the medication would work and that his tumor would disappear, but they knew that it would not. They struggled to get their child to take medication and reinforced that the study drug was to "get him better." They hoped that because he was on a higher dose than other children who progressed, that it would work for him. This family knew that non-adherence would mean stopping the trial. All they could do was to work with their child to take the medication, continue the clinical trial and pray.

Parents of patients on clinical trials connected and talked with one another in person or on social media. Many parents reported that they compared notes and talked about how other children were doing. They tried to connect the patients' medication doses with their good or poor responses. They discussed the options their children had tried, other available options, where trials were open, eligibility, and wash out periods. They become savvy in navigating difficult healthcare systems and online informational sites to prepare for the next clinical trial. They developed "game plans" for care and wished that medical providers had explicit "game plans" for progression, even though they understood that their providers may not have a plan since no other options are available.

Improving Conversations and Care

Overall, patients and families believed they were being cared for at a superb institution with both quality care and good communication from healthcare providers. However, some

families indicated that if needed they would look elsewhere for second opinions (especially if their insurance company would pay for it), and other potential treatment options.

Though patients and families were mostly satisfied, several had concerns and complaints about communication, especially around sensitive topics. Some patients reported that bad news, such as diagnosis, progression, and end-of-life conversations, were abrupt, were delivered in the wrong place, had the wrong people present, and had too much content. Trying to shield their child from certain knowledge or the word cancer (instead using "the bump," "the owie," or "the spot"), this request may not have always been respected.

Patients and parents wanted medical providers who would be familiar with them. A few parents did not like how the oncology team operated. They did not like the lack of transparency in how a primary oncologist was chosen for them. Some parents indicated that they sometimes wished they could pick their medical providers rather than randomly being assigned to a provider. Most parents did not appreciate seeing different providers at each visit rather than having a consistent oncologist. With the team approach, however, they could see different providers if they did not like their assigned medical provider. All patients and parents appreciated the collective team recommendations.

Treatment Options

Many families feared progression and simultaneously wished that they could do something to prevent progression. For parents of three patients who completed radiation, with or without a study drug during that time period, they anxiously awaited progression. To them it seemed paradoxical that patient progression was needed prior to administration of a cancer directed therapy or another clinical trial enrollment. Rather than hoping that the prior therapy or clinical trial 'worked,' they had mentally moved on to the next idea or therapy plan. This helped

them prepare for progression; it would 'soften the blow.' Two mothers recalled being devastated at the first post-treatment MRI that continued to show the tumor. They believed that as symptoms improved the tumor and MRI should have also improved, even to the point of cure. Only after recognizing that the tumors would not go away, could they shift to thinking about the best and worst case scenarios.

Four parents focused on how unfair it is that there are limited treatment options given how far technology and medicine has come. They believed that more research funding would lead to more progress. Two parents in particular became visibly angry when describing the funding disparity for adult and childhood cancer research. They felt progress has been made on adult cancers but none has been made on DIPG. It was important to them to participate in research to further scientific knowledge in addition to the hope that their children would personally benefit.

Influence of Social Media

Many parents found social media, especially Facebook, highly beneficial. Some parents noted that from posting on Facebook, they received free meals, gifts, activities, and fundraising. Several parents posted about their child's wish for a particular gift or experience for a holiday or birthday. Community members would go out of their way to ensure that the milestone event was spectacular. Additionally, nearly all families benefited from Go-Fund-Me pages to aid in medical expenses. Patients and their parents looked to provide mutual or altruistic support of others as well. If parents saw a need in clinic, they would share this with the community and generous donations would be given. Two families were able to initiate large donations to the clinic or to children in hospice.

On Facebook, they were invited to special groups for DIPG or high grade gliomas. They became part of a tight knit international communities whose members experienced similar challenges. One mother said, "To me it helps a lot because people don't know. Like if you're not going through it you don't know." Parents connected with one another and even began praying for one another. Parents shared their ups and downs of the disease process, specific clinical trials, and novel therapies from other countries, especially Mexico.

One mother said that though she reads medical journals and understands them the best that she can as a well-educated non-medical person, she was able to obtain helpful knowledge through Facebook as well. There she could follow patients and their parents through their journeys of compassionate use medications, clinical trials or cancer directed treatments. Several other parents mentioned similar things, citing that people would post pictures, videos, all of the interventions they had tried, in addition to MRI scans and physical updates.

Learning about other people's experiences had benefit both in informing their decision making and providing peace about the care they were providing as parents to their child. One father recounted a mother's account on Facebook and the impact it had on him:

> "[She said, 'We didn't leave a stone unturned. We looked at every treatment, went to everything. Said, you know, we spent almost $ 3 million doing it. She said I can promise you that we'll never think that we didn't do everything, but there's nothing you can do. She was just like in the end, if you live longer because of it, it's just because of the type and the way the tumor's sitting. If you live shorter, nothing slows it down. Nothing stops [death], you know, from happening….And then at the same time people like that post on there, it sounds terrible, but you know, also gives us some comfort that we're not screwing up. You know, I mean, we're sitting over here and we don't have $3 million…I

mean, there's some people that's even worse off than we are, you know, and they're sitting there thinking you know, I've heard them. I've heard people say it. I've seen them say on that page that you know, my kid's going to die because I can't afford to save them. That's not true. These people had $3 million and tried to do everything, you know, other people do. So—that makes us feel better, because our biggest scare is can we live with ourselves if we don't do something, like if—we're trying to decide on Mexico. Well, if we don't go, are we not going to be able to live with ourselves because we didn't?"

Another mom demonstrated the conflicting thoughts about Mexico (where treatments would be about $300,000), and the importance of the decisions made for her daughter:

"The reasonable side of me is like, 'no that's a bad idea.' I don't know the language. They don't have the standards we have. They're asking for a boat load of money up front. You know, so all of these are red flags. But then you see the parents and the parents are like, 'my son's using [his legs] and he wasn't using them before. And my daughter's talking. Or, my child doesn't have to have a NG tube anymore'…When we see these other kids who we just here thought that they were promising in what they were doing, you know, the treatment that they were having and then they die. It's hard…. For [our daughter] we have means to do anything. If we don't have the money, we'll get the money… As a parent, knowing that you may have to be without your child one day, you have to be able to live with decisions that you make and know that you did everything you could. And for me, doing everything I can doesn't mean prolonging things for her…. And it's not a criticism to those parents in any way, but some parents have done more than I think I would do to prolong life. Because to me, quality of life, to me, is more

> important than being physically present… I want her to be here for my whole life, but it's not up to me."

The connection with others through Facebook was seen as a "blessing" but at other times, painful. Many parents followed other parents of children who were dying or had already died from DIPG or HGG. They could not delete "friends" or the group as they became connected to the other children. One mother said:

> "It's very hard because we, every day, see kids die that we've connected with their families, or have prayed for. And that's been…really hard, 'cause we grieve [our daughter]. We try not to you know, because she's alive, but we can't help it. We're only human."

Some parents wondered why physicians did not join the groups or know much about the information on the websites. They wished that physicians had an online presence so that physicians could validate the type of information that was on-line and demonstrate care for their child (especially when a child had a particular Facebook page).

Not all parents posted on social media. One mother did not want others to think the specific treatments her child was receiving would work for other children. Some other parents stopped posting due to negative outcomes they experienced. One family posted a Go-Fund-Me page on Facebook. This led to using the word 'cancer' around the child even though the family was trying to protect him from that language as the child was struggling with the cancer related deaths of loved ones and his own mortality. Another mother learned the reality of the prognosis from Facebook:

> "I found out how in depth, how bad these babies get. You know, pretty much through the Internet, Facebook and all of that. I mean that's what I wish I didn't know is how bad it's going to get later, you know, if it comes down to that."

Influence of Religion and God

If a family indicated that prior to the diagnosis they practiced a religion or spirituality, that practice supported the family during this difficult time and provided guidance and peace in decision making. Many parents became even more engaged with their religious groups. One mother asked her friends to provide scripture so that she could be surrounded by it all the time. Friends ensured that she had framed scripture to put around the house, especially at the kitchen sink where she does the dishes. She said that helped tremendously.

Many families stated the God influenced their decisions and prayer was important. One mother said:

> "We're always asking for guidance, and you know, clarity with what to make. Not—you know, most the time or I guess at that time when we started on that chemo it was kind of like, you know, we just left it in [God's] hand and whatever [He willed] was-you know, it was just going to be."

Prayer was a central focus of nearly all parents. Several parents said they constantly prayed, and "never really said an Amen." Two parents who were agnostic would pray that the cancer never comes back and would pray before a major procedure or MRI as a family that "things be ok." The mother said, "I probably pray once a week. It's more like a mental, uh meditation, I guess. It's more of like putting good energy out there...I say, 'whatever forces are out there, please let her be ok." Many thought that prayers from others were helpful. One

mother wanted to ensure that others prayed specifically for a miracle with the belief that you must ask to receive:

> "I'm hoping for a miracle. I know that and believe that miracles are real…I mean that's my hope and prayer is for a miracle. If I don't have that and we don't get a miracle then my hope is that she doesn't suffer... And people are always like, 'Well, what can we do?' And I want them to pray for a miracle. I don't want them to just pray that she's home or that she doesn't suffer. I want everybody to pray for a miracle. I put my thoughts down [on Facebook] and make sure that I'm clear with the people who love and care about [her] for what we need for them as far as their prayers go."

However, one mother who believed in God but did not believe in church found it unhelpful when people said that they "would pray for them":

> "I feel like I'm just sitting around waiting for death. And there's nothing that anyone can do besides, 'I'm praying for you,' which, eh…I've learned that that's one of my trigger words…. Because to me prayer is begging. Cries. Don't beg for my child. Help me get answers. I'm not looking for a miracle. I'm looking for answers. I'm looking for tangible things that I could do for her while she's here. Even if it's just, 'Hey, I know you guys are not doing anything. I'm coming over just to sit with you.' That's what somebody needs, not prayer. What makes a person's prayer different than mine? [I've got] a one on one relationship. Doesn't make any sense to me. I'm already begging enough because she's mine. So why's my prayer different from yours?.... I'm not praying anymore…. It's hard. I don't get it. Cries. It just makes no sense to me. I don't know—I feel like I did something or karma, or – and I can't think of anything that I've ever did to anybody that's so horrible that I have to lose my child. Cries… I begged God for her. So

> what? Prayer doesn't do anything. [She's going to be] taken away… And that's all—And I mean, --And I get how, you know, a lot of people say that, you know, because they don't know what to say but they don't have compassion and sympathy, so you only say, you know, what you've taught, and that's, 'Oh, I'm praying for you,' you know, and especially if you're a Christian or you have that religious background, you know, I'm praying, it's like okay, pray. I don't know what kind of relationship you have with him (God), you know? Laughs. So, I don't know, if I want you praying for me or not. But what people really want is someone to stand next to them, hold their hand, let them cry, especially if you are losing a child or a loved one. A lot of people just want somebody just to be there. I don't like being alone, especially when I'm with her, you know what I mean? Because I can't hold my emotions, you know? And so, if someone was just here with me so I can go and, you know, release a little bit and come back, and sit with me, and laugh, and watch a show, or you know, that would mean the world to me, you know."

A spiritual leader's recommendation was important for about one third of patients and families. Spiritual leaders were pastors or heads of religious groups but could also be vocal community members or friends. One family talked about a teacher who a "big time Christina" and was influential in their family's life. She would support decisions the family was making. She would not only come to the hospital and pray with the family, but she would also be available to other students and their families. Families took their children to healing prayer services with priests.

They also took to heart recommendations religious leaders would preach about. One religious leader showed a video on the connection of food with cancer. Along with that video, the leader preached about the importance of diet and the link to both faith and health. That

sermon took place close to the time of the patient's progression. The patient enrolled in a clinical trial and changed his diet. When asked if they were going to stop one of them, they said, "No, because we don't know which one is working."

Influence of Food

Families had a complex relationship with food. Some believed food was the etiology of their child's cancer, like certain dyes. Others believed it could be an effective cancer treatment, alongside other complementary and alternative medicine options. Families and patients focused on weight gain associated with steroids. Though the steroids helped with symptoms (headache and vomiting), they had other undesirable side effects, like mood swings, acne, elevated blood pressure, and weight gain. Eight patients started restricted or 'healthy' diets to try to lose weight or stop further gain. These diets were often organic, vegetarian, or vegan. Some mothers ensured that their child had "good meals," with no fast food. One mother meticulously prepared meals for her child but forgot to make herself food. If a clinical trial medication required certain food to enhance absorption or if a child would only take a pill with a certain food/drink, families went to great lengths to obtain that specific food/drink.

Life Outlook, Hopes and Fears

Most patients and families had optimistic life outlooks or were "positive realists." If they personally were not optimistic, someone else in the family was. Parents often balanced one another, with one being optimistic and the other being pessimistic or realistic. Many patients and parents embraced the "fight against cancer." Most patients rarely complained and bravely underwent procedures related to clinical trials or cancer directed care.

Similar to a pendulum, patients and families swung from one side to another with hopes for cures, to fears of suffering and death, to focusing on the day at hand. They all hoped for full,

long lives, but also had hopes of making memories, building legacies, and caring for each other. Parents worried about their child dying from the tumor, and how their other children would cope. Parents went to great lengths to learn how to care for siblings. One family moved to a new house so that their dying child would not share a room with a sibling.

Reflections on Participating in this Research Study

Fourteen families (93%) expressed that this study was beneficial to them as they were able to express their feelings in a safe place. They saw value in the study in that it could change how healthcare providers communicate and improve the local healthcare system. They appreciated learning about their decision making processes which often were illustrated within semi-structured interviews. Family members heard from their children what as important to them and what they hoped and feared. Interviews often occurred during clinic downtimes, helping the time pass more quickly; however, if it was late in the day, families were in a rush to leave clinic. Many families were flexible to talk on the phone. No one felt participation was a burden or desired to be removed from the study.

Review of Oncologist Responses

In this study, oncologists acted as gatekeepers to the patients. Oncologists expressed to me that they were stressed from busy days, multiple difficult conversations per day, and other life concerns. If they perceived that a patient or family was overwhelmed, they protected the patient from another research study. Enrolled patients were often early in the disease course, after both diagnosis and discussion of clinical trials. This was secondary to difficulties in coordinating schedules and balancing the levels of patient, family and provider anxiety. Once patients and families enrolled, attempts were to be present at key clinical encounters and medical meetings reviewing patients. Some of the patients had conflicting encounters and were not able

to be audio-recorded. For the forty-one audio-recorded neuro-oncology visits, twenty-five, or 61% had accompanying completed physician questionnaires. Here I will delineate the oncologist responses to the questionnaires, which only represents a portion of information I learned from these physicians. See the below table that delineates the five neuro-oncologist responses in twenty-five questionnaires for fourteen patients (no questionnaire for P9). Several physicians provided more than one answer, so that the total number of response may be greater than twenty-five.

Table 7: Neuro-Oncologist Questionnaire Responses

Neuro-Oncologist Questionnaire Responses, N = 25, n (%)
What is the patient's diagnosis?
DIPG: 16 (64), Progressive DIPG: 1 (4), HGG: 1 (4), GBM: 5 (20), GBM/NF1: 1 (4), GBM, infant, epitheliod: 1 (4)
Do you expect this child to live longer than 6 months?
Yes: 18 (72), No: 7 (28)
Did you offer a Phase I trial?
Yes: 6 (24), Total No: 19 (76); Qualifiers-"Not Yet": 1 (4); Not Eligible: 3 (12): None Available: 1 (4); Progressed & taken off trial: 1 (4): Already on from institution: 8 (32); Already on from outside institution: 1 (4)
Did you offer cancer directed therapy (radiation, chemo-not on trial)?
Yes: 12 (48); radiation 2 (8) re-irradiation: 1 (4), chemo 1 (4); No: 13 (52); Already on: 4 (16); Not option: 1 (4)
Did you offer palliative care?
Yes: 11 (44), Primary palliative care: 1 (4); No: 14 (56); Previously with palliative care & hospice but now withdrawn per family request: 1 (4)

Neuro-Oncologist Questionnaire Responses, Continued N = 25, n (%)

What did you recommend?

Start Clinical Trial: 2 (8); Continue Current Clinical Trial: 8 (32); Continue Current chemo: 2 (8); Radiation: 1 (4): Re-irradiation: 1 (4); Palliative Chemo/Avastin: 1 (4); Compassionate Oral Chemo: 3 (12); holistic/CAM: 1 (4); Referral to another specialist: 1 (4); Other medication adjustment: 1 (4); Start hospice: 1 (4): continue hospice: 2 (8); Observe: 1 (4)

What option did they pick and why?

None picked yet: 3 (12), Start Clinical Trial for "hope" of prolonged life & QOL: 2 (8), Start Clinical trial with few other options & family signed consent: 1 (4): Continue Clinical Trial with no progression: 3 (12), Continue Clinical Trial because of good response and doing well: 2 (8), Continue current clinical trial because mom is committed to trial: 2 (8), Continue clinical trial because of "hope for a miracle" or "looking for a cure: 2 (8), Enroll in hospice, sign POLST, and consent for autopsy because "mother wanted hospice and made clear her decisions": 1 (4), Compassionate use drug and palliative care/hospice to maintin current quality of life as long as possible: 1 (4); Compassionate use drug because "there's nothing to lose": 1 (4), Continue Comassionate use drug because it is working: 1 (4), Treat with radiation to help with symptoms: 1 (4), Standard treatment with radiation and chemotherapy: 2 (8), Standard treatment with radiation: 1 (4), Continue observation post clinical trial as patient is not eligible for another clinical trial and no other clinical trial is available: 1 (4)

Who do you think is the primary decision maker in their family?

Mom: 17 (68), Dad: 5 (20), Both Parents: 2 (8), Patient: 1 (4)

Who do you think influenced these decisions the most?

Mom: 10 (40), Mom's own background, beliefs, and core values: 1 (4), Mom's education: 1 (4), Dad: 5(20), Parents: 1 (4), Other family member: 1 (4), Friend: 1 (4), Oncologist: 3 (12), Patient: 1 (4)

What do you think is the best outcome? Why?

Prolonged stabilization, progression free survival: 12 (48), Longer Quality of Life: 10 (40), Supportive care to alleviate suffering: 1 (4), Symptoms: 4 (16), Clinical improvement to baseline: 1 (4) Quick tumor progression to lessen suffering: 1 (4), Cure: 1 (4), Patient has a specific experience: 3 (12), Wean patient off steroids: 1 (4)

What do you think is the worst outcome? Why?

Rapid Decline/early death: 13 (52), Worsening quality of life: 12 (48), Severe side effects of medication: 2 (8), Severe symptoms: 2 (8), Family won't accept anything other than cure: 1 (4), Prolonged suffering: 1 (4)

Neuro-Oncologist Questionnaire Responses, Continued N = 25, n (%)

Do you try to preserve hope? If so, how?

Offer/Discuss Clinical Trial Participation: 11 (44), Research: 1 (4), Waiting on Test Results: 1 (4), Emphasizing unclear course: 2 (8), Listen and support family: 1 (4),Talk about 'Rare Responders'/Positive Outcomes: 3 (12), Relay Hopes of Medical team: 2 (8), Concentrate on Child's Acheivements/Positives: 2 (8), Not asnwered: 2 (8)

What are your fears for the patient? For the family?

Rapid Deterioration/death: 5 (20), Short Progression Free Survival: 9 (36), Poor Quality of Life 3 (12), Go to Mexico: 1 (4), Family losing child: 2 (8), Tumor recurrence: 1 (4), Secondary Malignancy: 1 (4), Worsening depression: 1 (4), Patient failing school: 1 (4), Placement of VP shunt: 1 (4), Family seeing child suffer: 1 (4)

What are your hopes for the patient? For the family?

Long Progression Free Survival: , Good Quality of Life: 10 (40), Durable response to treatment: 1 (4), End-of-Life symptoms controlled: 1 (4), Peaceful death: 1 (4), Go to school: 1 (4), Good holiday: 2 (8)

Would you call yourself an optimist, a realist, or a pessimist?

Optimist: 1 (4), Optimist/Realist: 1 (4), Realist: 14 (56), Pessimist: 9 (36)

If you could re-do the conversation, what would you do differently? If so, how would you change it?

No: 18 (60), Not Much: 2 (8), Don't Know: 1 (4), Would Make Change: 4 (16).

Examples of changes: "I would provide better guidance of what to tell child about current condition, death, and dying." "I would keep personal recommendations out of the conversation." "I would have involved the father more." "I would not tease the patient about his belt buckle."

How could we improve training for physicians to have difficult conversations like the one you had with patients and/or families?

Observation: 10 (40), Classes/Seminars/Videos: 5 (10), Experience/Practice: 10 (40)

Most oncologists recommended phase I clinical trial participation early in the disease course. If a patient was doing well and had no evidence of progression on a clinical trial, no other options were discussed. If a patient progressed, palliative care emphasized. Some made recommendations based on the patient's and/or family's goals. One oncologist recommended steroid-sparing palliative chemotherapy (Avastin), holistic prescriptions, and cannabis oil. Physicians sometimes made recommendations for medications to manage symptoms, equipment, or referral to other specialists. Some discussed cancer directed options like re-irradiation for symptom control and improvement of quality of life, but rather would recommend hospice enrollment.

Oncologists perceived that decisions were made by mothers (68%), fathers (20%), both parents (8%) and the patient (4%). These decision makers seemed to be influenced by parents and family members (68%), patients (4%), friends (4%), (28%), physician recommendation (12%), their own educational background, beliefs, faith and core values (8%).

Oncologists believed that families chose clinical trial participation because it "offers hope for a miracle," there were "few other options," "it will increase [the patient's] chance of survival," "prolong [the patient's] survival," or even the family was "still looking for a cure." Parents would be "committed to the clinical trial." Oncologists perceived that families chose comfort focused options after tumor progression or were burdened by symptoms. In some cases, oncologists thought that parents picked compassionate use drugs and palliative care to <u>maintain</u>[1] current quality of life for as long as possible or because they had "nothing to lose."

[1] All emphasis of underlining or bold font within quotations is original to the physician informants.

Physicians perceived that parents chose the patient and family's preferred treatment plan; however, parents comments did not always align with this. For example, one physician remarked, "They wanted hospice. Mother signed POLST form and then consent for autopsy. Mother had made her decisions and was clear on what are the important things for her." Though the oncologist had just met the family and did not have a goals of care discussion with the family, the oncologist felt that the mother's goal of care was based on "quality of life" and influenced by the poor prognosis. However, these statements did not align with the family's comments. The family perceived that communication was abrupt and unexpected. Instead of taking the oncologist's recommendation to enroll in hospice alone, the family chose re-irradiation, another clinical trial, and compassionate drug use along with hospice enrollment.

One physician who "offered palliative care" to three patients never actively consulted the specialty palliative care team through supportive care clinic and only twice referenced potential hospice enrollment. Possibly, this physician mean offering primary palliative care. Some patients were never offered palliative care during recorded study visits, likely due in part to the "good performance status" of the, patients. One patient who had specialty palliative care consultation and hospice enrollment, was later removed from hospice due to clinical improvement and parental request.

The best outcomes identified by oncologists focused on quality of life, symptom control, tumor control, and quantity of life. Only one physician mentioned cure, and qualified this statement by stating, "a small % are cured and although this should have relapsed by now there is no indication of tumor 1.5 [years] from diagnosis." Other best outcomes included: prolonged stabilization, clinical improvement back to baseline, prolonging a good quality of life without suffering, maintaining interaction with others for as long as possible, and overall survival beyond

two years since diagnosis. Occasionally specific outcomes were listed for specific patients. An example of a specific outcome was for a patient to walk independently, play, and run with siblings again. Weaning steroids off steroids was considered a best outcome, especially if neurological symptoms, such as hemiparesis also improved. If children's disease had progressed, oncologists believed the best outcomes would be for "amelioration of symptoms, supportive care to alleviate suffering, quick tumor progression to lessen suffering."

The worst outcomes identified by oncologists were: rapid decline, severe side effects of disease, a trial that did not add benefit and led to added side effects, disease progression less than one year since diagnosis or shortly after radiation (the "expected" course), or tumor recurrence. If there was disease progression, oncologists believed the worst outcome would be prolonged suffering and death within 3 months. Oncologists worried that a "family [would] not accept anything other than [a] cure," a family would choose "aggressive interventions at the end-of-life," or that a compassionate use drug could hasten death from a "catastrophic side effect… (low likelihood but possible)."

Oncologists hoped for the following for their patients: prolonged quality of life, prolonged life, preserved good quality of life, prolonged progression free survival, survival greater than two years from diagnosis, and that patients live without pain or fear for as long as possible. They also hoped that the clinical trial medication would provide the opposite of "early death." Hopes were framed against uncertainty:

> "I hope that parents and siblings enjoy quality time with the patient since there is uncertainty on how long the response is going to last. My hope is that the patient continues to improve clinically and that this is a durable response with this new regimen."

In response to another patient who was doing favorably, the physician said, "at this particular juncture we are cautiously optimistic." Some oncologists framed their hopes in relation to the family's goals of care or with patient's goals. For instance, one oncologist hoped that a patient would have his wish of an enjoyable holiday. If a patient's disease progressed, oncologists hoped for quick tumor progression and minimal suffering, which they believed to be the family's hope as well. They also hoped that at the end-of-life, symptoms would be well controlled, and that the patients would die peacefully. Oncologists also hoped that patients would avoid prolonged suffering, poor quality of life, and loss of interaction with others; they hoped that families would avoid "losing their child and seeing their child suffer."

Oncologists feared the patient's deterioration and death (20%), family's coping with death (8%), poor quality of life 12%), short progression free survival (36%). They feared that patients would die around the holidays (8%). They also feared tumor recurrence due to the "inability to cure if recurs" and even secondary malignancy. One oncologist feared survival would be less than anticipated but balanced that with hopeful knowledge that the patient "has already beaten those odds." Oncologists feared the medications would have no effect. If a patient seemed to have a response to therapy, physicians feared the patient would later stop responding. Some oncologists feared the family would lose hope if the patient deteriorated or that patients would have worsening depression and anhedonia or fail school. Oncologists feared that patients and family members would pursue aggressive treatments, such as VP shunt placement. At disease progression, physicians feared patients would have slow and painful deterioration. They feared the patient would get "sicker," have decreased quality of life as a result of a new drug and lose ability to interact with others.

Physicians believed that they preserved hope through offering participation in clinical trials, noting "we are learning new things every day so prolonged life could offer [an] opportunity to [try the] next trial/new drug prescription." They told parents that other options were available if progression occurred, and that molecular testing would provide more information about the outcome. Some believed that "New trial → hope." Oncologists stated they preserved hope "until [the patient] is no longer eligible for trials."

Some oncologists felt they preserved hope by focusing on an uncertain prognosis and toxicity profile. Others focused on the positive achievements of the patients to preserve hope. They encouraged parents to work with their children and to concentrate on one day at a time. Still others said they preserved hope by sharing with the patient and family their mutual hopes.

Twice oncologists did not answer the question of "did you preserve hope and if so, how?" when a patient had disease progression. Another physician challenged the question: "Before we preserve hope, the question is what is hope? Hope for what???? Once you clarify this, then you can take the next step." Only one oncologist stated hope preservation was through "listen[ing] and support[ing] the patient and family."

One physician engaged in shared decision making regularly. This physician was willing to work with families in managing treatment options that were based on limited, existing evidence. For one particular patient, that physician hoped that "we have 'stumbled' upon a treatable form of GBM, even though the particular type of GBM was described as being very aggressive. This oncologist worked with the family in facilitating proton radiation at another institution and negotiating the non-standard chemotherapy. The child tolerated the therapy well and has continued to surprise the medical team.

When oncologists were asked what they would do differently, some oncologists interpreted the question of changing the conversation to mean changing the treatment course. One physician commented, "I would not change it. So far have been lucky in having prolonged quality of life without disease longer than expected." Sixty percent of the time, oncologists would make no changes to the conversation. When stating that they would not change or re-do the difficult conversation, they sometimes commented that they presented the "reality of diagnosis/prognosis," offered hope through a clinical trial, needed to hope for the best, and offered palliative/supportive care. When news was good, conversations were not difficult and there was nothing to change.

An oncologist reported wanting to involve other family members in the conversations more. Another would not have teased a patient. A different oncologist would have provided "better guidance [for the family on] what to tell [the] child about [her] current condition, death and dying," and questioned giving "my 'personal recommendation,' [but] I think [the] family understood what I meant so [I] likely [would] not change much."

Almost all oncologists lacked formal training on informed consent or end-of-life discussions. One acknowledged the importance of training: "Some physicians are shy and avoid exposure to those difficult conversations during training, then when they have to do it as attendings, you can see how this part is weak." Oncologists had many suggestions on how to improve training for fellows, junior and senior faculty, most of which followed the paradigm of 'see one, do one, teach one.' Time was needed to listen and observe other expert providers, like palliative care specialists or senior faculty having "upfront conversations" (diagnosis), and discussions around decision making for treatment." They preferred observing multiple **different experts** in both real and simulated patient conversations. Oncologists were open to being

observed, supervised and directed by experienced providers discussing their strengths and weaknesses both one-on-one and in groups. Several oncologists emphasized "experience, experience, experience," "practice!" and being the "person delivering the bad news, not only the person sitting in the room listening." One oncologist mentioned personal reflection on experiences as well.

A few oncologists mentioned watching videos, attending classes, conferences, or seminars on difficult conversations was mentioned by a few physicians. The curriculum should include what is helpful and unhelpful when conducting a difficult conversation and should occur after some real-life experience with difficult conversations. Importantly, one oncologist emphasized that these difficult conversations are not just one conversation; they occur over a series of encounters and additional work is needed to thread the conversations together.

Review of Palliative Care Responses

The two palliative care specialists provided greater detail in their responses to questions in a total of five completed questionnaires. They framed their answers with the patient's specific situation and goals. They provided narrative and contextual explanatory answers.

Table 8: Palliative Care Questionnaire Responses

Palliative Care Questionnaire Responses, N = 5, n (%)
What options for care did you discuss with the child and/or family?
•Hospice care: 1 (20), Symptom management (pain control, nutrition, consitpation, fevers): 1 (20), Rehabilitation: 1 (20), Chemotherapy: 1 (20), Phase I study enrollment: 1 (20), Advance Directive: 1 (20), End-of-Life: plan who is present, memory making: 1 (20), NG tube: 1 (20), Post-death options: bathing patient, being with patient as long as desired, autopsy: 1 (20)
Did you discuss hospice?
•Yes: 4 (80), No: 1 (20)
•"No (or not yet I should say). At that time, it was not consistent with the goals. In addition, as he was making the decision to enroll on a Phase I trial, and would continue to need to have frequent visits/ adhere to the rules of the trial, it did not seem like it would be a good fit. "
What did you recommend?
Focus on comfort: 1 (20), Focus on good quality of life on clnical trial (school, friends, decrease steroids): 1 (20), Family permission for respite: 1 (20), Think about hospice: 1 (20), NG tube trial-stop if does not lead to improvement: 1 (20), DNR/DNI put on chart: 1 (20), Hospice would have been recommended if it was not in place or was a realistic possibility: 2 (40)
What option did they pick and why?
•Natural death without attempts at resuscitation with comfort focused goals and desired "peaceful" death: 1 (20), Remained in the hospital for death because not able to be "safely" discharged: 1 (20), NG attempted but immediately removed due to patient discomfort: 1 (20), DNR/DNI put on chart: 1(20), no decision made yet about hospice: 1 (20)
Who do you think is the primary decision maker in their family?
•Mom: 3 (60), Patient with mom: 2 (30)
•"In this family, the mother was the primary decision maker. P5's father was also involved and participated in decision making, but the mother was the primary driver. I think dad harbored a lot of guilt over not having been a better father to her and was trying to make up for lost time."
•"P9 is legally the primary decision maker, although he makes decisions in conjunction with his mother. He wishes to bypass his father as a primary decision maker. On his advanced directive he intends to completed to be his mother, followed by his sister, followed by his grandmother. This will supersede the state order which would be mother/father, followed by sister."
•"His mother, but with very strong influence by his grandmother."

Palliative Care Questionnaire Responses, Continued, N = 5, n (%)

What do you think is the best outcome? Why?

Comfort until death: 4 (80), Enroll in clinical trial: 1 (20)

- "I think the best outcome for a child with a well-known terminal brain tumor is a comfortable, happy life until they die, also peace for the family that maintaining as normal a life as possible despite disease is the best way to “fight” for their child."
- "The best outcome here was that we allowed her to be comfortable, loved, and cared for until she died peacefully. It was also “good” that she didn’t have attempts at resuscitation as this would not have been successful due to her underlying condition and only would have caused additional pain and suffering (which her parents were trying to prevent). They had a ton of family and friends around who came to be with her and this was also a good outcome."
- "The best outcome for P9 would be that he gets what he wants. I think this means that he gets discharged from the hospital, get some of his strength back, does not feel a burden to his family, spends more time at home, and eventually dies with hospice (or in the hospital if desired) but in a comfortable manner with focus on pain relief and being peaceful. "
- "At that time, the best outcome was for him to enroll on the trial, have some benefit that would allow him to wean steroids so that he can have less steroid s/e and get back to seeing friends, wearing his clothes, and going to school."

What do you think is the worst outcome? Why?

Suffer: 2 (40), Die in the ICU: 2 (40), Long term life support: 1 (20), Increase steroids: 1 (20)

- "I think the worst outcome is for a child and family to suffer needlessly with false hopes and magical thinking that aggressive chemotherapy will make their child “the one to survive”
- "Some people might say that the worst outcome here was that she died. But I believe that that was her only outcome and our job was to usher her there peacefully. If she had died in the ICU getting coded, that would have been a poor outcome since it would be contrary to her family’s wishes."
- "The worst outcome is hard to define, because are not sure he has defined it for himself. I think that ending up in the ICU, on a ventilator, or long-term life support would not be what he wishes for himself. It is definitely not what his mother would want."
- The worst outcome for him would be progression that entailed going up on steroids. The worst outcome for the mom/grandmother (I believe, it’s a bit of a presumption based on what they told me) would be to watch him suffer greatly and then still have him die "

Do you try to preserve hope? If so, how?

- Yes: 5 (100); Focus on patient/family's hopes: 3 (60), Intensive symptom management: 1 (20), Give examples of hopes that provider or other people have in similar circumstances: 1 (20)
- "You can always hope. To the last breath, even beyond that. You often have to help the family shift what they are hoping for. With P5 we hoped for good time with her siblings and a comfortable death. Mom hoped for her legacy."
- "His mom noted that she has many hopes for him including cure, growing up, graduating, going to college, and getting married. She wishes that he could spend more time being a "normal teenager". We validated that it is okay to still hope for those things."
- "In this setting (at the EOL), there is still hope – for peace, forgiveness, time together, time and courage to say goodbye, for her comfort/ to not suffer, and to transition peacefully to death. Here, there was hope preserved in the form of a limited research autopsy – that this would help other children in the future."

Palliative Care Questionnaire Responses, Continued, N = 5, n (%)

What are your fears for the patient? For the family?

None: 2 (40), Patient has less time than perceived: 1 (20), Progressive symptoms: 1 (20), Patient to feel like being a burden: 1 (20), Missing patient's voice: 1 (20)

- "My only fear when patients come in for EOL care is that it won't end up being as peaceful as they would like. Death is never as pretty as one hopes, and we try to do a good job preparing them for what it will look like, how the body will change, what we will do to manage symptoms vs what is not 'fixable' at this point. My fear for the family during death is their ability to cope, to grieve openly, and how they will enter bereavement. The moment of death and that experience does factor in to hope people grieve. "
- "My fears that P9 has much less time than we think he does. I worry that his oncologist may not have the same estimation of his prognosis that we (palliative care and rehab) do. I worry that he will only become more and more symptomatic, and lose the ability to the use his arm. If he can no longer type, or communicate for himself, or help with his care is in some way, I feel this will only add to his feeling of being a burden. I worry that P9 will continue to be externally worried about his

What are your hopes for the patient? For the family?

- Peace, coping and a healthy bereavement: 3 (60), Patint regains self-confidence to enjoy life, spend time with friends and go to school: 1 (20), Better symptom control: 1 (20), Better disease control with palliative chemotherapy: 1 (20), Better understanding of wishes before not able to communicate: 1 (20), Discharge from hospital: 1 (20)

Would you call yourself an optimist, a realist, or a pessimist?

- Staunch realist: 2 (40), Realist: 3 (60)

If you could re-do the conversation, what would you do differently? If so, how would you change it?

- No change: 1 (20), Earlier timing (in disease course) of conversations: 2 (40), Have more time with patient/family: 1 (20), Ask if friends/family should step out or if it was okay to speak in front of them: 1 (20), Ask mother if she would like to participate: 1 (20)
- "I wouldn't change anything. We covered a lot of ground in terms of his symptoms, goals of care, code status, advanced directive and decision making, and hospice. This was to his primary team."

How could we improve training for physicians to have difficult conversations like the one you had with patients and/or families?

- Setting a framework for establishing a trusting relationship: 2 (40), Practice with an expert available (simulation lab, role play): 2 (40), Didactics: 1 (20), Rotation with palliative care: 1 (20)
- "It is important for physicians to not walk into difficult conversations with a presumption they will "check a box" by the end, what I mean is that they shouldn't see it as a failure if they walk away without "the DNR", acceptance of hospice, acceptance of disease etc. It is about setting the framework for establishing a trusting relationship, partnership if you will, to walk this difficult journey with the parents and children going through it."
- "They need to realize that these conversations don't just go wonderfully because people are innately good at this, or just born with that skill. It comes with practice: in a sim lab, in role play, with a palliative care clinician. Ideally, they should watch themselves on video and see how it feels to them/ see if they can follow the conversation, the logic, the jargon, etc. They need communication training, ways to have better conversations. They could even call a palliative care team member to help "prep the conversation."
- "This needs to be integrated throughout medical education, starting at the medical school level and extending through the attending level."

In describing patient and family understanding about diagnosis or prognosis, palliative care specialists relayed the multiple, often competing opinions of several family members. For one family, an aunt only wanted to hear the positive, so she stepped out of the room when prognosis was discussed. Another patient and his mother knew that "he was dying from the day of diagnosis…he was lucky to have time between then and the time of his death [as] no day was a given;" however, "until a few days before his death, Dad was reluctant to admit that [his son] was at the end of his life. He felt that everyone was too gloomy and negative. He was convinced that his son would turn around." Their family dynamic was such that the father was not a strong presence in decision making, and thus, was "an afterthought." As the mother knew the disease was fatal, she already had a burial plot for her son. Here, the family dynamics influenced the tensions of maintaining hope, remaining positive and accepting reality of a terminal illness.

Palliative care met the patient, mother and father where they were. This patient and family pursued cancer directed therapy and intensive supportive care until his death. Palliative chemotherapy was a "last ditch option," that the patient wanted to continue. At the same time, he discussed his advance directive and end-of-life preferences. He was open to hospice but was reluctant due to prior experiences with home health services which lacked nursing continuity. He was reassured that in hospice, he would have a primary care nurse.

Options of care and recommendations depended on the patient's situation. If hospice was a service that the palliative care providers thought the patient and family could benefit from, then they would discuss it when the patient and family were ready. One family requested to enroll in hospice "before they really needed it." They had decided not to put their daughter through aggressive interventions. However, as the child neared death, her safety and comfort were the main focus. Palliative care focused on symptom management (pain control, fluid/nutrition

status, constipation, fevers), presence of family, memory making, post-death care (bathing the child, being with the child for as long as desired) and confirmed the family's desire for an autopsy. The palliative care providers gave parents the permission to "just be the parents" and love their child and allow the healthcare providers to be the "nurse." The family's goals were clear: comfort care and natural death without attempts at resuscitation. Those goals were met by healthcare providers and was thus the best outcome. Other good outcomes were 1) having family present, 2) relieving the father of guild over not being more involved, and 3) completing a limited research autopsy which may help other children in the future (as per the family's desires). The palliative care provider notes that some people would say "the worst outcome here was that she died. But I believe that was her only outcome and our job was to usher her there peacefully. If she had died in the ICU getting coded, that would have been a poor outcome since it would [have been] contrary to her family's wishes."

Palliative care recommendations did not undermine the oncologist recommendations, but rather attempted to support the patient and family. However, palliative care specialists did have some underlying suppositions that differed from the oncologists. For instance, one palliative care specialist framed best and worst outcomes based on the nature of the problem:

> "I think the best outcome for a child with a well-known terminal brain tumor is a comfortable, happy life until they die, also peace for the family that maintaining as normal a life as possible despite disease is the best way to 'fight,' for their child. I think the worst outcome is for a child and family to suffer needlessly with false hopes and magical thinking that aggressive chemotherapy will make their child 'the one to survive.'

Compared to oncologists, palliative care specialists better estimated when a patient would die. For one patient that was told days before that she would have weeks to live, the palliative

care specialists prognosticated it would be days to maximum of weeks. Yet, palliative care specialists supported the patients' and families' goals and hopes. One patient was enrolled on a clinical trial with strong family support. While the patient initially seemed ambivalent about enrolling in the trial, he later expressed that he hoped it would help him achieve a goal of graduating. Thus, the palliative care specialist focused on achieving good quality of life on the clinical trial: "focusing on school, friends, decreasing steroids (per his wish as he hates the side effects of acne and weight gain), and giving his family permission to take breaks and have respite time." Thus, the palliative care specialist assessed that the best outcome for that patient would be weaning steroids, so that he could have "less side effects, get back to seeing friends, wearing his clothes, and going to school." The worst outcome for the patient would be "progression that entailed going up on the steroids" while for the family members would be "watching him suffer greatly and then still [having] him die." "Best and worst outcomes" were framed by palliative care specialists around the desires of patients and families, noting the best outcome would be that the patient "gets what he wants," and the worst outcomes as those the patient and family do not want.

Preserving hope is a critical part of palliative care. In fact, two palliative care providers wrote very similar responses: 1) "There is always something to hope for. Though hopes may change over time, there is always hope," 2) "You can always hope. To the last breath, even beyond that. You often have to help the family shift what they are hoping for." Palliative care specialists learned what the patient and family's hopes were and then validated that it was okay to still hope for those things. Preserving hope, for some patients, meant focusing intensely on symptom management to maintain hope that symptoms can be managed. In study responses, palliative care specialists referenced the hopes of patients and family members. One mother's

hopes for her child were cure, growing up, graduating high school, going to college, and getting married. She also wished that her son could "spend more time being a 'normal teenager.' Another mother hoped for her daughter to have a legacy.

Questionnaire responses revealed that the patient and family hopes of palliative care specialists mirrored the hopes of the patient and family. Hopes for the patients included: regaining self-confidence to enjoy life, comfort, independence for as long as possible, peace, being home, controlled symptoms, achieve good disease control with cancer directed therapy, rehabilitate with an understanding of unlikely return to baseline, good time with siblings, forgiveness, time together, courage to say goodbye, and to transition peacefully to death. Hopes for family members included peace, healthy coping, and a good bereavement outcome.

Fears of the palliative care specialist were also patient and family centered. One provider's fear at the patient's end-of-life was that dying would not

> "end up being as peaceful as [the family] would like. Death is never as pretty as one hopes, and we try to do a good job preparing them for what it will look like, how the body will change, what we will do to manage symptoms, and what is not 'fixable' at this point. My fear for the family during death is their ability to cope, to grieve openly, and how they will enter bereavement. The moment of death and that experience does factor into how people grieve."

Another palliative care provider worried that a patient's voice was being lost by not having separate conversations with medical providers, observing that, "he seems to be protecting his mother, and she is doing the same for him." Another patient stated that his biggest worries were for "his comfort and his mom's ability to 'survive' without him. He wanted her to be okay. When he was convinced she would be okay, then it would be his time." While the patient was

hoping for his mother to demonstrate that she would be oaky in her bereavement, the mother hoped her son would have "peace and happiness in heaven."

Palliative care specialists tried to go "at the pace of the family." When reflecting on re-doing a conversation, one palliative care specialist would have liked more time with the patient and family. In the out-patient setting, palliative care providers see the patients after a busy clinic visit with the oncologist, obtaining study labs, reviewing the study drug diary, checking the number of study drug pills in a bottle and dispensing new medication. In the in-patient setting, timing was centered on having important conversations with the patient earlier, when he was better able to communicate for himself. One palliative care specialist would have asked if the parents wanted other family members to step out during the conversations or whether it was okay to speak in front of them (though the family's demeanor seemed to support the latter). At the end-of-life, a palliative care provider would have inquired if a parent wanted to help remove the medical equipment post-mortem.

Insights palliative care providers gave on improving training for physicians in difficult conversations were:

> Provider 1: "It is important for physicians to not walk into difficult conversations with a presumption they will 'check a box' by the end, what I mean is that they shouldn't see it as a failure if they walk away without 'the DNR,' acceptance of hospice, acceptance of disease, etc. It is about setting the framework for establishing a trusting relationship, partnership if you will, to walk this difficult journey with the parents and children going through it."
>
> Provider 2: "People need a framework. Then, they need to realize that these conversations don't just go wonderfully because people are innately good at this, or just

born with that skill. It comes with practice: in a [simulation] lab, in role play, and with a palliative care clinician. Ideally, they should watch themselves on video, see how it feels to them, and if they can follow the conversation, the logic, the jargon, etc. They need communication in [post-graduate] training, [including] ways to have better conversations. [Oncologists] could even call a palliative care team member to help '[prepare for] the conversation."

Another provider mentioned the integration of didactics and simulations throughout medical education, starting at the medical school level and extending through attending level. Palliative care rotations were encouraged, especially to learn how to structure a goals of care conversation.

Figure 11: Comparison of Oncology and Palliative Care Responses on Hope

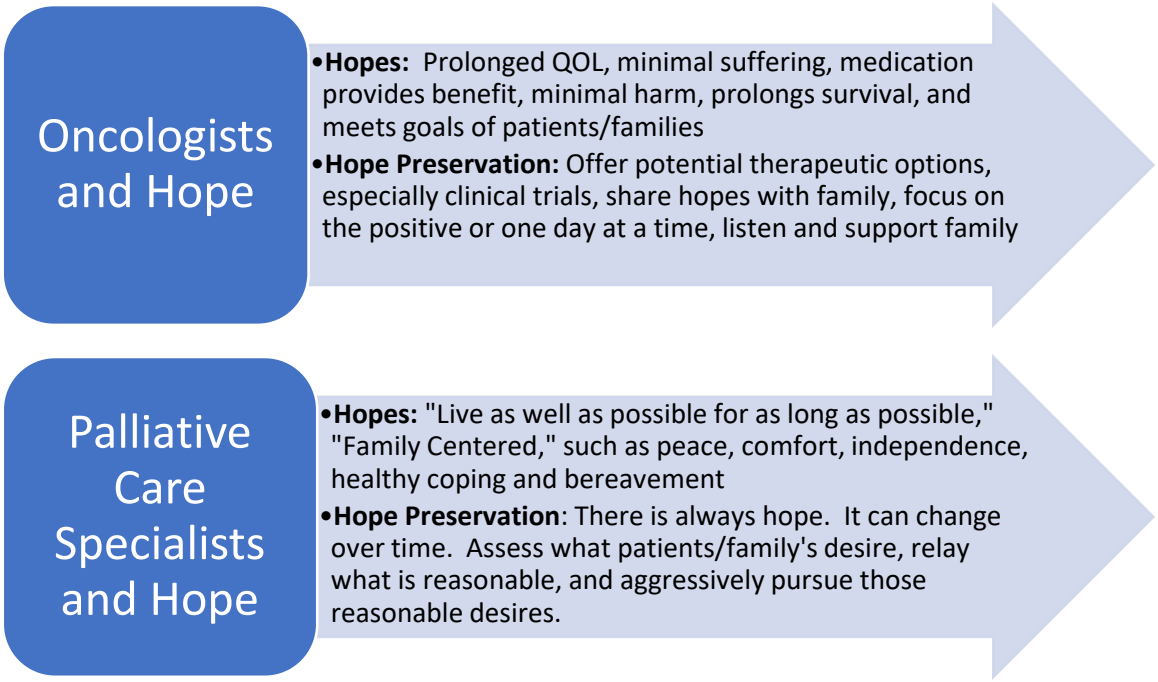
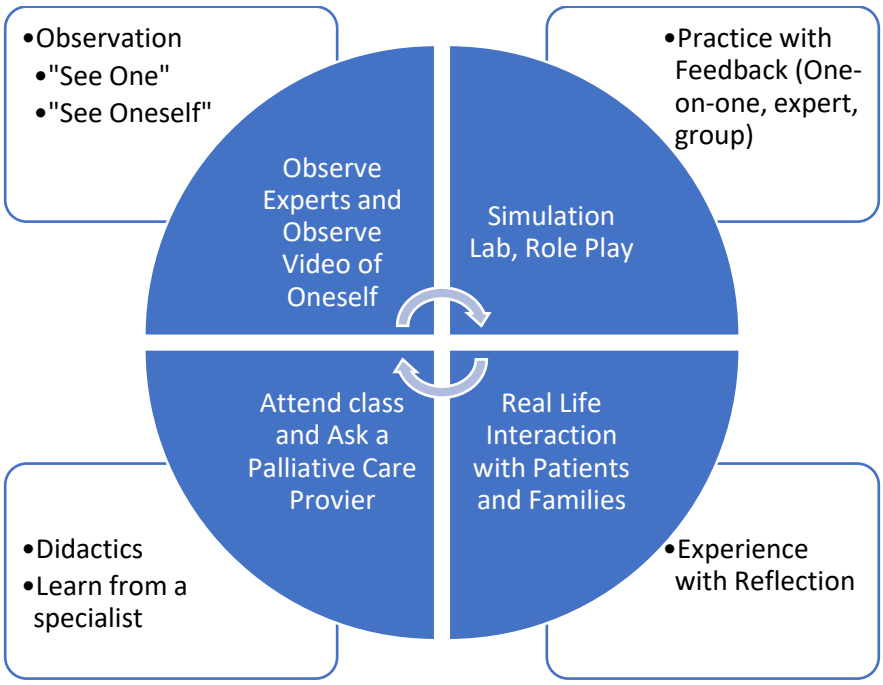


Figure 12: Summary of Communication Training Recommendations



Limitations and Considerations

This is a qualitative study based on a small sample size of patients at a large academic medical institution. Selection bias exists in several ways. Patients presenting for a "second opinion only," who were not followed at the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta were not approached for study. Patients came specifically for clinical trial participation; thus, patients interested in comfort care approaches could be underrepresented. Non-English-speaking patients and those in state custody are not represented but are vital in learning how to better support decision making and effective communication. As many patients or parents answered questions weeks, months, or years from initial diagnosis or specific decisions, recall bias is expected. The triangulation of interview data with chart and physician accounts may help in alleviating some of this bias.

Not all eligible pediatric patients (by age) were interviewed due to available time or parents not wanting their child to participate. Patient participation was lower than anticipated. The number of participating physicians was also small and exacerbates selection bias. As some physicians completed questionnaires in a delayed rather than immediate fashion, recall bias is again possible. Significant missing physician data resulted from incomplete questionnaires and demographic sheets.

The longitudinal nature of the study led to difficulties obtaining data continuously. Some important conversations were not captured in this study as they were not anticipated or a recorder/investigator was not available. Specifically, the audio-recorder and the back-up recorder did not work for four clinic visits and two interviews. Field notes were taken at three of the clinic visits and both interviews.

Although plans were made to follow patients and families starting at diagnosis, patients were captured at different stages of disease course and not followed from beginning until end. Two patients were lost to follow up or withdrawn if transitioning to other centers for care.

Summary of Results

Patient and family decisions in the setting of HGGs are multi-factorial, ultimately reflecting the competing values of decision makers. While patients, families and physicians all hoped for treatment efficacy, they balanced it with the known poor prognosis. Though data is limited, patients and families demonstrated the knowledge that investigational agents would not be therapeutic or curative, though they hoped they would be. Physician investigators would also have hopes of investigational agents working but would balance those hopes with the known prognosis as well. Thus, therapeutic misconception, misestimation and optimism are likely not present when taking into account dispositional optimism, hopes, worries, and understanding.

Optimism about treatment is held in tension with poor prognosis, allowing for patients and families to have hope that is functional. This 'functional hope' is an unfulfilled desire (realistic or unrealistic in achievability) that allows a person to proceed with daily life despite difficult circumstances. Hoping for a cure is not necessarily a false hope, rather a hope that allows a patient or parent to face the day and all of its difficulties. Functional hope allows for hopes to shift or swing over time per the needs of the moment. Oncologists too can have functional hope in that they are not paralyzed by the deaths of children but continue to press on in caring for patients and seeking out potential treatments through research.

Physicians did not cause patients or families to lose hope. On the contrary, patients and families had many hopes which may or may not have aligned with their medical providers. Physicians consistently hoped for patients to live as long as possible as well as possible. Patients and families transitioned more slowly to this hope from hope for a cure. Hopes shifted at different times for each person. Acknowledging shifting hopes of patients and families could improve communication about goals of care and shared decision making.

Patients, families and physicians agreed that communication and decision making are important. Training physicians in communication skills and shared decision making is desired in experiential and didactic education and evaluation.

Chapter 4: Difficult and Distressing Decisions for Care

Decisions to Make

Decisions, decisions, decisions. There are many decisions to make when a child has a HGG. Medical providers decide the breadth of options for patients by obtaining information and collaborating with specialists. Options generally include surgery, radiation, chemotherapy, and/or immunotherapy. A patient could eligible for clinical trials or compassionate use drugs. Patients and families make a decision based on their preferences and values. Some may choose intensive phase I trials, while others choose a comfort-focused approach. With a life-changing diagnosis, the patient and family have to make many other life changes, like changing jobs, finances, and schedules. Many people have opinions about what decisions could and should be made, who should make the decisions, and what influences those decisions? Information from parent and patient responses will be used to answer some of these questions empirically.

Decisional Priority

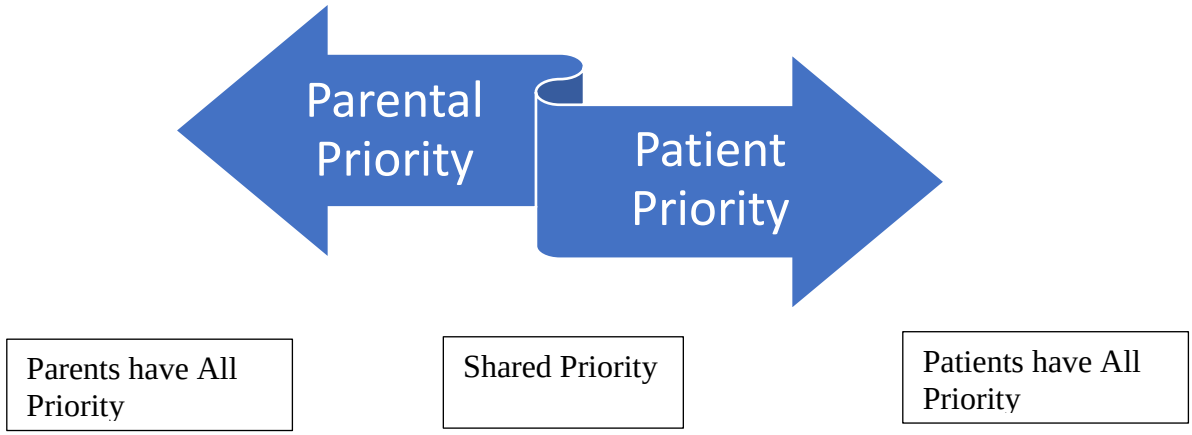
In the setting of paternalistic medicine, physicians have decisional priority and authority. In the setting of patient and family centered medicine, patients and families have decisional priority and authority. Where is the balance? Shared decision making occurs when there is a collaboration among physicians, patients and families to come to a decision regarding care. Families bring their knowledge of their child and values. Physicians bring their medical expertise.

Whitney et al. described a decision making model in pediatric oncology that utilized consequential rationale, whereby decisional authority and priority could shift from physicians to families based on whether one best option, probability of cure, existed. (Whitney et al. 2006) In this model, if cure exists and only one option of care is available, physicians should have decisional priority and authority. If there is no cure and multiple options for care exist, patients

and families had decisional priority and authority. This model's main limitation is that the patient and family are treated as a unit, rather than distinct decision makers. (Andre 2006)

With children having evolving autonomy and capacity, they also have evolving roles in decision making ethically, but not legally. For physicians, there is a tender balance in respecting the autonomy of the parents and the evolving autonomy of the child. Some argue that only the autonomy of the parents should be respected, as they are the legal, surrogate decision makers. Others would state that the child's desires should be respected as capacity develops, giving more respect to a mature adolescent than a young preschooler. Still, others state that it is the child's body and the child's life, so only their desires really matter. There are extremes on this ethical spectrum of decisional priority, ranging from giving all of the priority to the parents to all of the priority to the patient.

Figure 13: Representation of the Patient/Parent Priority Spectrum



Parents did not always agree on the care of a child, especially at the end-of-life. For three patients, mothers were all physically with their children day in and day out. Their fathers were less frequently around. Mothers would desire a more comfort focused approach, but fathers would still be requesting significant interventions be done, such as VP shunt placement or to continue a full code status. This caused distress for the patient and medical team until conflicts

were resolved. The VP shunt was not placed for one patient. Two other patients had DNAR orders placed and at the time of death, fathers did not insist on chest compressions or invasive procedures.

When two divorced parents disagree about the care of the child, is a physician obligated to prioritize the court's ruling about the decision maker? If parents are not divorced, who is the primary decision maker? It likely depends on the family unit's architecture. Some parents work as a team in co-parenting. Others still take leads on certain types of decisions. This consideration did not arise in clinic visits as either the primary decision maker attended the clinic visits or the divorced parents worked together as a team.

One couple was getting a divorce when their child was diagnosed with DIPG. They decided to live together, go on vacations together and attend clinic visits together for her sake. A point of contention was how to answer the child if she asked if she was dying. The oncologist did not have a straightforward answer for a precocious school age child and deferred to palliative care specialists, but ultimately recommended to "let the child lead." The mother was worried about this method but agreed that she wanted to be honest with her child. The father, on the other hand, did not ever want his daughter to be told that she was going to die. He was willing to say that "We are all going to die" or that the treatments were not working and that they were looking for others.

There are some important, practical considerations when ethically determining who has decisional priority, even if the decisional authority is legally prescribed. First, parents (and some patients) like shared decision making. (Mack, Cronin, and Kang 2016) This does not necessarily have to be 50% physician and 50% family. It could be 90% physician and 10%

family or vice versa. Families like to have honest answers, know the potential care possibilities, and be involved participants in the decision making process. (Mack, Cronin, and Kang 2016)

Second, the involvement of the child depends on many factors, with cognitive capacity being the most important one. Infants will not be included *a priori*. No infants were involved in this study, but one child was diagnosed with GBM as an infant and clearly was not involved in the decision making. Another patient had severe developmental delay and was non-verbal. This patient was also not included in decision making.

For preschoolers, some information may be shared, but their ability to weigh in on complex decisions is insignificant. A three-year-old boy could weigh in on preferences for food, games, and participation in the physical exam, but parents dictated what food he received, when his schedule (when nap time would be), and availability of a game. If he would not pay attention, a game would be taken away. He would be rewarded if he did well in participating. He may see his MRI with parents, but the meaning of the pictures was likely not known to him. One four-year-old patient was always given a choice of a game to play in clinic, the type of necklace she wanted to make her mother using her fingerprints, and the type of book about dying that she wanted to read.

For school age children and pre-teens, parents may desire to share generalities but not specifics with the child. Parents balance being honest with causing more anxiety for the child. One mother went to great lengths to hide specific information from her son. She would call and email the oncologist multiple times before a visit and remind the oncologist outside of the room to not go over the MRI results in front of the child as it caused him to worry. He would be told generalities about the tumor but not specifics, such as necrosis, radiation effects, bleeding, bright

spots, etc. The medical language used by physicians led to more distress in the patient than when a parent revealed information in a more sensitive manner.

However, this can lead to more anxiety for these children if they believe that something is being hidden from them. For instance, one school age boy was told that he had DIPG or a brain tumor. He was not told that he had cancer. He associated that word with death as a close relative died recently from a different type of cancer. When people outside of his family mentioned that he had cancer, it caused many problems for the child. He only focused on the negative things rather than the positives. Though he went from not being able to play his favorite video games and not being able to walk to doing both activities with some impairment, he only focused on his inabilities. His pain in his back and head seemed to get worse and his intake of analgesics increased. These hallmarks of distress may have been prevented if the family was forthright about the diagnosis rather than providing tailored information. Ethically one could provide generalities rather than specifics about medical information, however, the missed generality of a cancer diagnosis is a significant breach in trust.

Oncologists spend more time speaking directly to the teenage/young adult patients than other family members, which is different for younger patients. Adolescents and young adults are more likely to be included in decision making since they have their own beliefs and opinions. They may wish to share their opinions privately or defer decision making to their parents. One teenager seemed ambivalent about decision making when his family members were present, but privately he would become more involved. Another teenager was glad to be considered and somewhat involved in the decision making, but he felt relief that his mother was really paying attention and acting as the primary decision maker. It took the stress off of him.

A young adult patient attempted to not have her parents around for decision making as they would become very anxious and cause her stress. She had been primarily supporting her family by working and had been acting as a 'responsible adult' for several years. She did not want them to be present to discuss decisions or make them as she would likely not agree. Another young adult patient actually experienced a transition in decision making about his cancer and end-of-life preferences from his parents to himself. He felt that his mother knew his preferences and values. They talked about them regularly. He trusted her judgement not only because she had made decisions before, but because she listened to him and knew what he wanted. The degree to which children participate in decision making relies on the type of decision, the level of cognitive and emotional development of the child, and the family structure.

"You're the Doctor

Parents and patients are vulnerable in making decisions as they have less expertise and power than physicians. They do not have authority to prescribe chemotherapy or enroll their children on clinical trials. However, they can look for clinical trials and have the authority to sign documents, such as informed consent and release of information forms. All parties are advocating for the patient's best interest but may perceive differently what the best interest is. Shared duties and authorities between physicians and parents (and adult patients) permits shared decision making but does not necessarily guide the process. Additionally, responsibilities may not be fulfilled by the parties and authority can be abused. Thus, one must ethically perform one's duties as a physician, parent and patient in order for shared making to function.

Though parents like to be involved in decision making, they want to know what the doctor thinks. Several families would gather information from many sources and then inquire the oncologist's opinion about the information. Other times, parents wish for more assistance in

guiding difficult decisions, such as limiting life-sustaining technology. One mother would often say, "I don't know, you're the doctor." This statement would come when her child had a rapid decline, when she was flustered or did not know what to do. Despite saying this, she was very active in making decisions for her child. She led efforts in searching for clinical trials, advocated for her child to have re-irradiation, agreed with DNAR orders, and met with hospice.

She trusted most physicians, but not all. She questioned physicians who recommended plans of care that did not align with her child's primary neuro-oncologist's recommendations. She was astounded when an Emergency Department physician said, "If it was my child, I would stop the steroids." After noting significant hydrocephalus, the doctor asked, "How do you feel about a shunt?" This question came after another physician had abruptly given the mother POLST forms to sign. When given the forms, the doctor said, "don't do a shunt." The mother was wondering why the Emergency Department physician did not see in the chart that she did not want a shunt. This caused a lot of discord at home because the patient's father wanted a shunt to prolong life and improve symptoms of headaches and vomiting. The mother said "a shunt is not going to cure his DIPG." She was concerned about additional harm, as the child would have to go through significant surgery and be in the hospital instead of being at home. So, she responded to the Emergency Department physician:

> "I'm not putting a shunt in my child who's already terminal. He was like, 'Well you know it might be good for someone who has spina bifida.' I'm like, 'He doesn't HAVE spina bifida! Like, he's got a brain tumor.' I don't know…"

She was less trusting of doctors who were unfamiliar with her child, especially when making uniformed or poorly informed comments. The familiar pediatrician also lost her trust and respect over time. When the patient went to get labs, the oncologist had ordered at the

pediatrician's office, they would say that he needed a physical exam there, even though he was being seen by multiple physicians every week on a clinical trial. The pediatrician's office would comment that he had gained weight, that his vision or balance was off. She would write down that he had "BRAIN CANCER," but they would still push. She concluded that, "You don't go to the pediatrician if you have cancer. You don't."

There are lessons here. For children interfacing regularly with the healthcare system, parents learn how to navigate the system and become experts in their child and their child's disease. They develop educated opinions that are valuable in determining care. When children have cancer, their medical home becomes the cancer center. Oncologists can improve families' stress levels by communicating well and working as a team.

Goals of care discussions are important for planning the next steps in decision making. These discussions often occur with the physician who knows the patient and family best. Other physicians may defer major decisions to the primary team unless it is time sensitive. When they need to provide complete care for a patient or to know certain information, they should ask open ended questions rather than making strong statements. Physicians should reflect on the big picture when making recommendations to support the patient and family.

"You're the Parent"

As parents look to physicians' recommendations because of their knowledge base physicians also defer to parents for certain decisions. Examples where physicians would say, "You're the parent," include what the eats and wears, how the child is disciplined, the destination chosen for a child's Make-A-Wish trip, if the child goes to a healing service, or practices a particular religion, etc. Medical decision making is often not deferred to the parent unless one is determining goals of care and end-of-life planning. Other times, physicians may feel

uncomfortable with allowing parents to be the primary decision makers, especially if the decisions do not align with their own personal beliefs and values and if the decisions seem to cause more harm than good for a patient.

One general example is pain management. If parents avoid providing analgesics and the patient appears in pain, clinicians may have moral distress over this. While they do not want to overstep the parent's wishes, they do not want the child to continue in pain unnecessarily, especially when they are capable of relieving pain. Rarely, and not in this study population, suffering and pain is important to the patient and/or family's view on life after death. If a family believed suffering and pain could bring a better life after death, families may be willing to permit pain. Therefore, an ethical dilemma and moral distress persist until resolution.

Physicians have the authority to intervene if the child is being harmed or they believe that parents are making decisions that are not in the best interest of the child. When considering the over-arching goals of care and end-of-life care, parents often have priority in driving the type of care given to their child. However, the physician has the authority to either carry out that care or not. For the most part, pediatricians often provide the care parents (and sometimes patients) request, even if with reservation. One special consideration is 'doing everything.'

Doing Everything': The Physician's Fear and the Parents' Desire

Several families in the study seek to "do everything." They will go from one institution to another looking for all cancer directed therapies and cure. Six of fifteen patients (40%) went to more than one institution for cancer directed care, in the form of clinical trials or complementary and alternative medicine. When they find medical providers, who engage in highly specialized techniques or research for scientific advancement, the hope of better cancer therapy is a shared

goal. Even this shared goal appears differently through the optimistic family-lens compared to the realistic/pessimistic physician scientist lens.

The shock of the cancer 'treatment' not working resonates on a deeper level with the parents compared with physicians. While highly personal for parents and physicians in the study, the aftershocks have repercussions of differing weight and meaning. For families, the treatments failed. Their loved one died, but they did all that they could. For the physician scientists, the treatments failed, and they failed. A patient died and they could not prevent it. They are not necessarily closer to developing a cure, though they hope to be. Some family members raise funds for research or help other families going through a similar process. The physician scientists, however, continue searching for this evasive cure and life-prolonging treatment with less toxicity.

If a parent's philosophy on parenting is that caring for a child involves providing all the means necessary to promote life, then they will seek to 'do everything,' and 'leave no stone unturned,' seeking the best treatments for their child. As one father reflected on the family who spent over three million dollars and the mother who said they would find money, giving the child the best possibility of sustaining life longer, and perhaps even better. In this quest for treatments for incurable illness, parents will expend significant energy and resources to obtain this goal, even if they have observed other parents doing the same thing for effective treatments, in this quest for treatments, parents will expend significant energy and resources to help their child. They will do this even if they observe other parents doing the same thing. It is part of their mantra. They cannot stop. They have a duty to care for their child and nothing will stop the them, sometimes not even the child's other parent.

Ethically, a parent willing to 'give in' and focus on quality of life, may disagree with the 'do everything' standard. Parents in the study wishing for less intervention would often defer to the parents wishing to 'do everything,' except the account of where the father wanted a VP shunt and the mother did not. Acknowledgement of differences of opinion may lead to conversations around the goals of care from patient and family perspectives.

Is 'doing everything' normal? It does appear that new science advancements are leading to more being done. This leads us to ask, 'just because we can, does it mean we should? Doing everything will not change the eventual outcome in an incurable illness. The child will die. Could there be a net harm in doing more interventions to a person who is dying? Yes! The child's life may be shortened. Some interventions may lead to increased time, allowing a loved one to come say goodbye. And yet, people who receive comfort focused care may live longer and better than those without this focus. (Temel et al. 2010)

One main goal of parents and physicians alike is to provide care to a suffering child. Shifting the hopes and goals from doing everything to cure the cancer to doing everything to keep the child comfortable is a large shift. It takes time for that transition and many conversations. Despite numerous conversations, parents and patients indicate they may still choose to "do everything" until the end. One father likened the care of his son to playing sports. He would ask the doctor about the "game plan" and ask if it was time to "throw a 'Hail Mary.'" This question may bring distress to the medical provider who fears the decreased quality of life with utilization of medical technology and develops distress from 'poor' allocation of resources. If distress occurs, consultation with the ethics team or palliative oncologist may be helpful on a case-by-case basis. While awaiting expert consultation, it may be helpful for medical providers to reflect on their hopes and worries for the patient and inquire from parents and patient about

their hopes, expectations, and worries. This could be the first step in mediating distress and unrealistic expectations, not only for care but also in fulfilling one's role as a patient, parent, or physician.

Chapter 5: Hope Preservation

When a child has a HGG, all families hope for a cure. This hope persists until the day the child dies. Every parent interviewed in this study expressed this sentiment. At the same time, they knew that their child would die. Parents were desperate to believe that a cure could happen not only for their child, but also for other children. They prayed for a miracle and they hoped that medications, radiation or surgery could lead to a cure. For one mother, a clinical trial drug was her "only hope for [her son's] surviving this" but ultimately left the outcome to God. She said, "hopefully He (God) lets my baby stay here with me."

Most parents and patients maintained positive outlooks and balanced them with knowledge. For instance, one mother who considered herself a realist talked about hope often:

> "Hope is plastered all over the house and it's-I have it tattooed on my hand so I can look at it. So, I definitely have a ton of hope, but I-you know, I do know what statistics say and you know, I do know what the reality of this is… Which makes it difficult to be a realist, because everybody around you is an optimist and you're not."

She later said, "I think that the optimism, the positivity is what is keeping him here…the hope is what's keeping him here."

All physicians considered themselves a realist or pessimist. One oncologist was exceptional in calling herself an optimist when she delivered good news and a realist when she delivered bad news. Thus, the outlook may be related to the cancer itself or one's mood. If it is related to cancer, oncologists may be desensitized by the many children who die. Physicians did not hope for a cure, except in very rare cases when patients had proven to be an exception. One physician said:

> "She's clearly doing something different than the rest, and let's hope that maybe she does everything completely different in that regard... she's off on an island to herself, and I wouldn't, at this point, I wouldn't assume anything, you know? So, let's just hope that maybe this one is cured… no reason to suspect otherwise at this point."

When this patient broke the rules, the physician felt able to hope alongside the family. Another physician, felt like she "won the lottery," when a patient responded to a compassionate use drug. That physician hoped alongside the family, but also worried about drug resistance. The quickly brought herself back to a more realistic position, not allowing herself to develop false hope.

Both patients had something unique about their situations and both received non-standard treatments. Though oncologists saw success with these tailored regimens, they do not support veering away from standard of care often. When there is no known benefit, high risk of harm, and no gain of generalizable knowledge (as would be in a clinical trial), treatments that break the rules are not often recommended.

Most physicians in this study hoped that clinical trials would work but reminded themselves and others that prior clinical trials failed. They would then count how many children were the exceptions over a period of time. If a clinical trial seemed to be going well, the physician would remind people that statistically there will be an exception, but the exception is not the rule. Other ways physicians held realistic or responsible hopes was hoping for something that would predictably happen. For instance, they would hope for decreased tumor size at the end of radiation, but not necessarily months after radiation. One physician said when reviewing the MRI at the end of radiation, "Obviously we got the results we were hoping for. The tumor is a little bit smaller." Thus, the hope was not unrealistic.

Though physicians did not always hope for the same things that patients and parents did, they wanted to preserve hope without giving false hope. The more patients and parents focused on cures, the more physicians would make statements that aligned with ambiguity or doubt. However, these statements were made with care.

Hope preservation takes work. Parents expressed to me in interviews that they worked to preserve hope themselves as it was important to "keep the hope" especially if they were feeling that "their hopes were shot." They did rely on physicians to preserve hope. One father said that he "always feels like there's still hope, even if we don't have it right now." Thus, parents hoped to hope again and would later take steps to develop a new hope.

Parents also hoped for support from others. They would share disappointment if people did not provide that support or if the support was not "what they hoped." Here, expectations are not fulfilled but they are able to still hope. Thus, they are not in despair.

Parents did not want to give false hope to their children, similar to physicians. Patients did not always embrace the philosophy that parents embraced. One patient said, "I don't really like the whole, 'well, you might get better' You know, you just have to hope. I don't really like that. I'm just kind of like, if I get better, great. If I don't, oh well, but yeah." That patient instead was still hoping to go back to work, buy a house, achieve other life milestones, lose weight gained from being on steroids, and spend time with friends. Another patient also wanted to buy a home, travel, and spend time with friends and family.

The hopes of patients also stimulated and fostered hopes in other people. A child's hopes also led to others working to fulfill those hopes. When a child would hope to be a superhero, people would work to introduce that child to that superhero. Parents would also hope for certain milestones. They hoped a child would make it to a vacation, then to a holiday, then to a

birthday, and then even to kindergarten. When kindergarten started, they then had to permit themselves to have new milestone hopes. Thus, as time passes, hopes change. People may have worries and challenges along the way, but they work very hard to preserve hope.

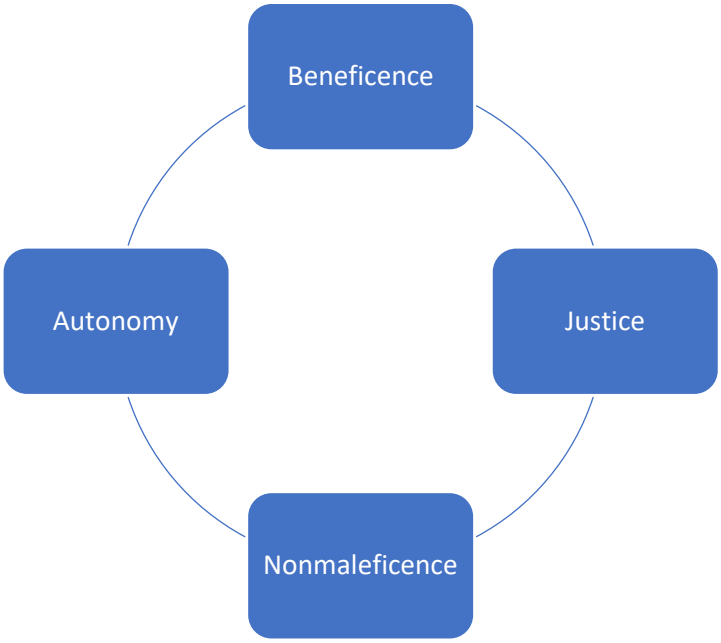
This work to preserve hope becomes a duty for physicians and parents alike. It is a caring act to allow and even encourage others to hope, as great benefit can come when hopes are fulfilled. However, supporting false hopes can lead to despair and thus significant harm. Unfulfilled hopes can also lead to despair, possibly explaining why people hope for the miraculous and also more achievable hopes. Achievable hopes allow people to function daily. They are functional hopes, similar to the miraculous, in that they inspire people to persevere. A functional hope may motivate action. True hope preservation leads a person who is resilient despite difficult circumstances.

Chapter 6: Ethical Reflections and Analysis with Principlism

Principlism

In this final chapter, the principlist approach will be used to analyze decision making dilemmas that arose from the study. This analytic approach is most helpful with its basis in common morality and its use by physicians and researchers. The principlist framework recognizes that there are competing obligations and rights. It is flexible and uses an extension of W. D. Ross's idea of *prima facie* obligations and rights, whereby an obligation must be fulfilled or a right must prevail, unless there are obligations and rights of equal or greater weight. Thus, when deciding what one ought to do, one must weigh out the competing obligations and/or rights. (Beauchamp and Childress 2013) The obligation fulfilled or right honored is the one of greatest weight or contextually the highest consideration. The principles of autonomy, beneficence, nonmaleficence and justice are of equal importance but compete against one another in ethical dilemmas. Though each principle is to be balanced with the others, Americans often prioritize autonomy over the others, leading to an unbalanced approach. (Wolpe 1998) Similar to how patients, parents and physicians balance the competing notions of poor prognosis and hope, these ethical principles balance one another out; however, hope for a cure may be in the forefront regularly. In this chapter, each principle will be delineated and discussed with relation to its importance in decision making for children and young adults with HGGs. How these principles are balanced will be examined in particular cases.

Figure 14: Ethical Principles



Autonomy: Respecting Persons

The word autonomy has Greek origins and means self-rule. (Beauchamp and Childress 2013) There are multiple theories of autonomy, but Tom L. Beauchamp's and James F. Childress' three-condition theory will be used. The three conditions for an action to be autonomous are intentionality, understanding and non-control. (Beauchamp and Childress 2013) Though intentionality is or is not present, understanding and non-control may ambiguously be present as they may be present by degree. Thus, "the lines between adequate and inadequate degrees of understanding and degrees of control must be determined in light of specific objectives of decision making." (Beauchamp and Childress 2013) Special considerations are needed regarding decision making for pediatric patients as they are developing capacity and have various degrees of controlling influences, especially from parents and physicians. Relational autonomy takes into account the social context of decision makers rather than the isolated individuals and can be helpful in analyzing decision making in pediatrics. (Walter and Ross

2014) However, parents answered study questions individually as they were often the primary, surrogate decision makers for the patient. Young children and adolescents did not see themselves as active decision makers in their care. Young adult patients acted as individual agents making decisions.

Respecting autonomy, or respecting a person's self-rule, often involves: telling the truth, respecting privacy, protecting confidential information, obtaining consent for interventions, and helping others make important decisions. (Beauchamp and Childress 2013) These are all essential to the decision making process for patients with HGGs. The diagnosis, prognosis, and treatment options need to be honestly communicated to allow patients and families to prioritize goals of care and what decisions need to be made. Physicians need to protect the privacy of patients and families, specifically, the patient's information, body (especially during a physical exam), location and personal space. In regard to decisional privacy, physicians should limit access of others to the knowledge of a patient's and family's choices and decisions. Confidential information that patients and families relay should be kept private, unless patients and families request the sharing of information to further the patient's care, which often occurs in the setting of physician referral or insurance coverage. Consent to procedures and interventions is needed. The consent should be voluntary (without manipulation) and patients and family should receive accurate information in a way that is understandable about the purpose, benefits, risks, and alternatives of the procedures and interventions. Conflicts of interest should be made transparent by an investigator. Additionally, when patients and families inquire about guidance in decision making, it should be provided in a non-manipulative manner to allow decisions to reflect the application of their own values and preferences to the available knowledge from an expert

provider. These are some general principles about autonomy. Further examination of the principle of autonomy derives from study participants.

One patient expressed that his individual autonomy in decision making was important to him. He developed that autonomy legally with turning eighteen, but also ethically developed it as he increased his knowledge and understanding. He underwent many treatments for his HGG, with chemotherapy and radiation. Around the same time, he went to college his HGG progressed. He commented:

> "After that I became secluded… I decided to move to Portland with my aunt and did everything on my own. Mom just let me go. It was a good example [of how] I deal with my illness. While I was up there on my own, [I sought] out treatment options, like intra-arterial chemo, which would have put me in a vegetable state. I'm glad I didn't do that. About 3 weeks after I decided to come back here and get treated by [my primary doctor]."

Since then, he had another progression. He said, "Right now, I'm all good mentally. [I have] recovery of my left side and all throughout." He went on to discuss that his past experiences, his oncologist's recommendations, and his family impacted his perspective and the decisions he made. He reflected that the decision making shifted from when he was first diagnosed to now. His parents initially made decisions and now he makes them. His grandparents and parents raised him to be independent. He wanted to do things himself and be well informed. Though his family helped him all the way, he declared that "it's been mostly my decision because they want the best for me." He said that he made decisions not for his mom, dad, family, or friends. He made the decision for himself, doing what makes him happy. Though it was no one else's decision to make, he felt like he had 100% support from his family.

He described how he embraced his individual, autonomous decision making. His family members also embraced his functioning as an autonomous decision-maker. They listened to what he wanted and his wishes were met. He discussed "everything" with his mother and he trusted her to act in his best interest if he was ever not capable of making decisions. He reinforced this with completing an advance directive, listing her as his surrogate decision maker.

Another young adult on the study embraced her autonomy as well. She had become quite independent. At the time of her diagnosis, she had graduated high school, worked at an office for several years, bought a car, and was supporting her family by paying rent and other bills. She had her father present when clinical trials were discussed. She said it was mostly her decision, but it helped having the approval of her family and the physical nod of her father next to her. When her tumor progressed and another clinical trial was mentioned, she did not accept it. She did not want to take pills every day. Though others would have joined, she decided that the trial did not align with her quality of life.

Most of the patients on the study were not young adults. Adolescents had more influence on the decision making than young children, but clearly were not making the decisions. Adolescents may be involved in most of the discussions with physicians. However, not all healthcare providers involved the adolescents in the discussions of major treatment decisions. For instance, one nurse came to a family to discuss clinical trials. She spoke directly to the patient's mother and did not acknowledge the adolescent. After the nurse explained two clinical trials, the mother asked, "Who makes the call" on deciding which clinical trial the patient should enroll in. The nurse then responded:

> "That's a great question. So, I think it's a partnership between you guys and [your doctor]. So, the two of you guys can sit down together and look at what's your

> expectation, like what fits better for your lifestyle. So [your doctor] can have that conversation. She of course can definitely say what she prefers, and I think that's where her medical decision could kind of help, but I think looking at, you know, what is your goal, like how much do you guys want to be here, you know, your factor of your lifestyle kind of can play into things too, so I mean, you know there are some studies that we're looking at as well. We're looking at right now, that may be more -- that may have an IV component. So, is that something that you would want to do? If there's an IV drug that we could give? So, we need to look at those studies and see if [he] would qualify for those."

The "you" she references should be the patient, but actually was the mother or the family as a whole: Even though the patient had experience with prior chemotherapy, radiation, and stem cell transplant, the information was not being directed to him. The evident decision makers were the mother and the doctor in the clinic. However, when the patient was asked if he had any say in the decisions that are made, he said, "She (mom) wants me to be happy, and so I do have a say. Yeah, I feel like I have a say. I do. I feel like if I say no, I don't want to do this anymore, then she will be alright with that."

Preschool to school age patients were not interviewed in the study and thus their opinions about the decision making processes were not analyzed. Importantly, these children had violations against respecting their developing autonomy by not having honest information from medical providers or their parents. Some people could argue that the children had developing autonomy and did not require the same respect as autonomous adult agents. Though patients did not yet have full competence or capacity, they could usually still understand the implications for their lives and bodies.

Though parents thought they were "protecting" their children from the information, their children became more anxious. Patients clearly knew what they were not supposed to know. Parents of one child attempted to protect the child from the word 'cancer.' However, the child saw the word cancer on the entrance to the clinic and had other children tell him that they were "sorry about his cancer." Other children learned about the prognosis based on how many fun things they were able to do, such as Make-A-Wish trips, and gifts they received. Their siblings were not receiving the same degree of special benefits or going to the doctor as much as them. Their illness was therefore very serious.

Another violation of a child's developing autonomy was not respecting a child's refusal to a procedure or intervention or obtaining assent with significant manipulation from parents. Parents of one school age child wanted investigators to deem her unable to provide assent because of her brain tumor, even though she was cognitively not delayed or impaired. They did this because she would become very emotional and say no to anything and everything without rationally considering the possibility. The parents attributed this action to the steroids. Instead of her brain tumor, they really were positing that the steroids impaired her cognition. However, a third hypothesis is that the child actually did not want to participate in the trials and was giving dissent. A different outcome may have resulted if parents and physicians took time to learn why the patient was saying, "no," instead of blaming steroids or her brain tumor.

In situations such as these, a physician has an obligation to obtain informed assent from the patient. If the patient is not willing to assent, further investigation into why the patient does not want to assent. Ideally, this would be inquired in a way that is non-threatening, non-manipulative and without the presence of those who could significantly influence the answer, such as parents. If patients continued to dissent, a physician would have a dilemma of whether

to honor the wishes of parents to have the child have the procedure or intervention. For some procedures and interventions with known greater benefit than risk of harm, it would be ethically permissible to honor the parents' desires over the child's. However, for those procedures and interventions with no benefit or concern for greater risk of harm than good, it would not be ethically permissible to honor the parent's desires' over the child's. This most often arose in the setting of clinical trials and research studies, where participation was optional, the investigational drug had unknown efficacy and known risks of harm with greater procedures. Therefore, having institutional guidelines for research studies about child assent may support physician-investigators and researchers who encounter the dilemma of conflicting desires of parents and children.

Autonomy and Shared Decision Making

Physician-patient/family relationships have shifted from paternalism to consumerism with the risk of patient and family centered medicine. (Cohn 2004) In the middle is shared decision making, which aligns closer to physician recommendations or patient and family preferences. Shared decision making swings toward physicians or patients/parents based on the competing *prima facie* duties of different decision makers. Physicians have a protected fiduciary relationship with patients (and their families), where the patients (and their families) put their trust, confidence and reliance on the physician to care for them. Physicians have professional and ethical duties to care for their patients. (American Medical Association 2001) They are to be honest, trustworthy, reliable, and present. In communicating, they are to be respectful of others, relay information in a transparent manner, and attempt to preserve hope while improving prognostic awareness. These characteristics are important in honoring autonomy or 'self-rule" of individuals with agency. Being respectful and disclosing information needed for decision

making are positive obligations that acknowledge the agency of individuals and their ability to "self-govern."

Parents have a fiduciary responsibility to care for their child, including providing a safe, loving environment, food, shelter, clothing, and healthcare. They are expected to provide emotional and spiritual support and guidance, prioritizing the best interest of the child and minimizing the harms. Parents lack professional codes like physicians their ethical and moral values are not standardized. Parents can promote the values that they see fit.

When caring for children with incurable HGGs, parents and physicians may not agree on the best plan as they balance benefits and harms differently. Thus, to make a plan, physicians, parents and patients will discuss the goals of care. Physicians have a duty to align the available and feasible options with the preferences of patients and/or families, respecting their autonomy where possible. Physicians, parents and patients have conflicting interests, with physicians attempting to uphold professional integrity and honor the autonomy of parents and the developing autonomy of pediatric patients. This is highly contextual, especially at the end-of-life.

Medical providers should probe the family's readiness for end-of-life planning when the child is still well, because waiting until the child is extremely ill "takes away the opportunity for planning, and often excludes the patient from the discussions." (Friedrichsdorf, Remke, et al. 2015) When discussing advance care planning, a medical provider may rarely be faced with different opinions from the patient and parents. (Durall, Zurakowski, and Wolfe 2012; Beecham et al. 2016; Hinds et al. 2005) In this situation, the medical provider wonders if the pediatric patient's perspective should take precedent over the parents' because he/she is going to die soon or if the parents' perspectives should be promoted because of their authority over their children.

Does the physician choose to support the opinions that align with the physician's opinion to limit aggressive interventions in this setting or the opinions that promote aggressive interventions? Medicine defaults to aggressive interventions, such as attempting cardiopulmonary resuscitation (CPR) to try to avoid death. Oftentimes, the parental authority over their children is honored and their decisions receive priority. However, when the child desires that everything be done, the child's opinion may prevail. One could argue that death will occur either way, and thus it does not matter. However, managing conflict prior to a child's death is important for bereavement following the child's death.

Finding common ground through open, honest, non-threatening communication may be possible. If a decision cannot be reached around resuscitation, a child will receive attempts at resuscitation. While harm and pain can result from resuscitation, some may wish to receive CPR for religious, cultural, or life-prolonging effect. In the setting of a terminal brain tumor, prolonging life may be a few days, hours or minutes. Parents must decide if this is care they and or their child desire.

Finally, physicians have ethical and legal obligations to honor decisions made about code status and the legal documents that justify and delineate limitations in aggressive interventions, such as advance directives, DNAR orders, or POLST forms. If no decision has been made, the decision is unknown, or the forms are not available, the default, obligatory action by the provider is to provide CPR. Thus, to honor the wishes of patients and families at the end-of-life, discussions around code status are vital to the type of care the patient receives. As one family mentioned, these discussions should be with someone the patient trusts and knows, should have all the important decision makers present (such as key family members), and should not be rushed.

Beneficence

The principle of beneficence "refers to a statement of moral obligation to act for the benefit of others. Many acts of beneficence are not obligatory, but some forms of beneficence are obligatory." (Beauchamp and Childress 2013) Actions that benefit others involve intentionally helping others by promoting a good, preventing harm, and removing or minimizing harm. (Beauchamp and Childress 2013) Beneficence obligations are requirements of action rather than prohibitions of action, as per the principle of nonmaleficence. Several of these *prima facie* rules of beneficence include "protecting and defending the rights of others, preventing harm from occurring to others, helping persons with disabilities, and rescuing persons in danger." (Beauchamp and Childress 2013)

The benefits for patients were in the forefront of decision making for patients, parents and their physicians. The benefits desired ranged from improved symptoms and quality of life to tumor stabilization, tumor regression and even cure. Decisions initially favored cancer directed benefits while later decisions favored quality of life and comfort. Over the disease course, the "best interest" of the patient shifted. Additionally, at each key decision making point, such as initial diagnosis, disease progression or end-of-life, the risk-benefit ratio shifted. Greater risks were willing to be taken earlier in the disease course than later.

At diagnosis, all patients in the study received either cancer directed therapy or were enrolled in a clinical trial. None of them had palliative care consultation at diagnosis even though studies show significant benefits of having subspecialty palliative care concurrently with cancer directed care. (Dans et al. 2017; Ferrell et al. 2017) Patients and their families were willing to be aggressive in cancer management or to participate in research from which they may not benefit. At progression, however, patients and parents would be presented with options.

Most patients attempted cancer directed care or a clinical trial again. However, this time, they may have a palliative care consultation or at least begin discussing quality of life more. If disease progression occurred again, similar options would be discussed, but patients potentially would not be eligible for clinical trials or would not be willing to undergo the intensive procedures associated with the clinical trial. For some patients, prior experiences weighed heavily on whether to enroll in clinical trials. For example, if a patient did well with an oral medication but had difficulties with intravenous therapies, parents and patients would not even consider clinical trials that involved intravenous therapy. As the end-of-life approached, some patients would still consider palliative chemotherapy or compassionate drug use but would be enrolled in hospice services or focused heavily on comfort.

While most parents hoped that they would have significant benefit from the cancer directed therapy or investigational drug, only one child had significant benefit. The mother was sincerely surprised as her child previously had significant worsening on prior study drugs. They had chosen to try this compassionate use drug as their doctor previously mentioned that it was being used in a clinical trial and it was there "only option" left. She reflected on the decision to start the compassionate use drug after talking about the MRI results that showed a "dramatic" decrease in the tumor size:

> "[I feel] great. I mean, blessed, because we, like we had no other option at that time, and it was -- like we didn't know what we were going to do next. We did radiation, and then after that it was kind of like what other medicine are we going to be able to use. There was nothing at that time except, like I said, this -- you know, this trial, so yeah, I mean, it was either use it or just you know, don't use anything, and it's great. Seeing the results right now, yeah. I think that we made a good decision."

She went on to say that her husband and the physician recommendations most influenced the decision, but foundational to the decision was first the patient's quality of life. The benefit of good quality of life was more than fulfilled with actual cancer regression. The benefit from starting the drug surpassed the family's and oncologist's expectations as this is a rare occurrence.

Though requesting a compassionate use drug is not a standard obligation, offering palliative care is. Palliative care is essential to the care of these patients, especially as it can be utilized concurrently with cancer directed care if cancer directed care. Not providing palliative care has the potential to harm the patient physically, psychologically and spiritually. Patients and families may be in despair about progression. Having an oncologist state that there are "no more options," can worsen this state. "Not having options" is a misconception and misperception, as there are many ways to care for the patient, including intensive comfort focused care.

However, oncologists did not always consult palliative care at the time of progression because they believed it would be too overwhelming to discuss palliative care in addition to 1) the "bad news" that no other options were available, or 2) the three clinical trials they were going to offer the patient and family. Rather than seeing the benefit in subspecialty palliative care and evaluating goals of care, oncologists sometimes feared that it would be harmful to the patients to discuss. Avoiding these discussions did not permit shared decision making, but rather placed patients at risk for feeling abandoned. This perceived abandonment is ethically problematic and leads to the ethical principle of nonmaleficence.

Nonmaleficence

The principle of nonmaleficence obligates one to not cause another harm and is a *prima facie* principle requiring "the justification of harmful actions. This justification may come from

showing that the harmful actions do not infringe specific obligations of nonmaleficence or that infringements are outweighed by other ethical principles and rules." (Beauchamp and Childress 2013) Physicians often cite the Hippocratic Oath when stating they are "first [to] do no harm." (Miles 2004) They have a duty to provide care that does not impose unreasonable risks of harm. Pediatric oncologists often prescribe chemotherapy that does have harms that are outweighed by the benefits of likely cure; however, for children with HGGs, there is minimal potential for cure. Thus, causing harm in providing certain treatments or investigational agents with unknown benefits can became ethically problematic. Judgments about quality of life and goals of care desired by patients and families are important in what options a physician presents in the shared decision making process.

Specific rules that include the principle of nonmaleficence include: do not kill, do not cause pain or suffering, do not incapacitate, do not cause offense, do not deprive others of the goods of life. (Beauchamp and Childress 2013) Several of these *prima facie* moral rules were important in decision making in the study. Physicians most often cited not wanting to cause pain or suffering to patients and worried about "catastrophic" adverse events that were possible with investigational or compassionate use drugs. Additionally, physicians did not want to offend parents or patients in communicating about these sensitive decisions. Physicians did not discuss the ethics around allowing the natural course of a HGG without any cancer directed intervention or removal of life sustaining treatments as they did not arise in the study.

In the study, nonmaleficence was mentioned most around CAM, compassionate use drugs, palliative care, and end-of-life care, specifically around discussing code status. When nonmaleficence was mentioned, beneficence was almost always accompanying the discussion in a way that demonstrated the ideas were competing. Nonmaleficence was not always honored,

especially if competing principles were present. Though physicians hoped that patients would have good quality of life, they often recommended clinical trials and other intensive modalities of care that could diminish quality of life. This recommendation was often because they were honoring the stated goals of patients and parents to "do everything."

A violation of nonmaleficence occurred when one physician effectively abandoned a patient. One mother revealed this violation when she discussed the decisions she made for her child and for changing oncologists. These decisions came after significant disease progression while on a third clinical trial through an outside institution, and after child's oncologist had advised against VP shunt placement a d re-irradiation, but recommended DNAR and hospice enrollment.

> "I called our doctor [at the other institution] that had that trial that we were doing. I talked to her and I said, 'you know, is there any way we could do radiation again, because they don't typically do that for what he has.' And she said, 'Yeah, actually, it isn't. It is a possibility [that] your doctor would have to agree to…' So, I called my radiation doctor from up here and she said, 'Yeah, let's definitely do it again.' So, we went in and did it again and he responded really well... So we got done with radiation, he was doing like super well. I mean, started walking again, everything. Like he was like [himself] again. So, after being off of that for – I think it was like three or four weeks, we were like, 'why don't we look at another trial, just – you know, just because he's doing so good, the tumor had to have shrank.' So, we talked with the hospice nurse and she said, 'You know, I honestly think that's a great idea.' So, she [tried to get] in touch with [his] doctor who was supposed to have like a Facetime, Face Chat so we didn't have to go into the office. [The doctor] was busy both times. The doctor said she would call us back and

she never did. We waited three weeks for her to call us back and nothing. Nothing. So that's when we decided to switch to another doctor."

This was significant as this was not the first time the mother felt abandoned. When the child had progression, she was not able to get in touch with the same oncologist who was out of the country or other oncologists the child had seen previously. The physicians were not reasonably available, even during normal business hours in the week. The parents and patient suffered from distress of not knowing what to do and not being able to make decisions when their oncologists was not available. Concerns for negligence of care are ethically impermissible, unprofessional, and unjust.

Justice

The principle of justice is based on "a group of norms for fairly distributing benefits, risks, and costs." (Beauchamp and Childress 2013) Several theories of justice include utilitarian theories that maximize the public good, libertarian theories that emphasize individual rights, communitarian theories that derive from conceptions of good from moral communities, egalitarian theories that emphasize equal access to goods in life that rational people value, capabilities theories that each person has the means to exercise capabilities to flourish in life, and well-being theories that emphasize health, personal security, reasoning, respect, attachment and self-determination. (Beauchamp and Childress 2013) Equitability and fairness are central to the distribution of burdens and benefits. Inequalities due to social determinants of health and discrimination are to be minimized utilizing the principle of justice.

During this study, physicians and other healthcare providers would ask rhetorically why some patients would be good candidates for clinical trial participation and others would not. The clinical trials did not have rigorous social criteria to participate, but some patients would have

inherent difficulties in making it to appointments and obtaining the necessary resources to participate. For one patient, a nurse explored many possibilities to help a family out. She learned that donations were available to help the family pay bills, but not to buy the family a phone, or to pay for transportation. This caused stress for the medical team as the patient missed appointments and also stress to the family as they were having pressure to fulfill the requirements.

All patients had some form of insurance and all received some form of benefit from specific foundations. This was important as they all experienced financial struggles. Those most in need received the most benefits from charitable donations. There were some differences in decision making, though, if families had higher education levels and greater financial resources. These families would often pursue second opinions or travel significant distances to receive a particular form of care or enroll in a specific clinical trial. They would do whatever it took and spend whatever money was needed to obtain these services. Those with lower education levels and less resources would not always look for other options outside of this institution. They would state that they were receiving good quality care here but would entertain looking at other institutions if their child had disease progression. They would discuss the other options of care they saw through social media but would talk about how the people who received those other options did not survive. They developed a peace about receiving care where they could.

Parents most focused on the unfairness of distribution of research dollars for children's cancer. Though there are significantly more adults with cancer than children, parents saw that there were greater losses for children with cancer. They believed that children who died lost out on living a full life while adults already had the opportunity of being a teenager and meeting other milestones, such as graduation from high school. One family stated that the child's school

participates in a specific cancer fundraising event every year. They were upset that people thought they were donating for all types of cancer for all types of people, when in fact, none of the funds went to childhood cancer research. This was unjust to the family in this misunderstanding and skewed distribution of funds for adult research.

One constraint on resources during the study was for one patient on a compassionate use drug. The company had merged and was considering stopping the production of the medication. After several petitions, the drug was continued but changed formulations. The patient's family adjusted to the new formulation and the specific manner the child needed to take it to maximize absorption.

Health policies around end-of-life care vary by state to state. Children are able to receive concurrent cancer directed care or participate in a clinical trial and still be enrolled in hospice. However, adults cannot. One young adult patient transferred care to the pediatric institution from an adult institution because she had a pediatric brain tumor (DIPG). As there was a clinical trial that was only being offered at the pediatric center, she was advised to go to the pediatric institution to increase her options. At that time, palliative care and hospice were not discussed. At the time of disease progression, the oncologists were shocked to learn that her age made her ineligible for receiving concurrent care. This ineligibility shifted the decision making for this patient, and for physicians. The types of discussions that physicians were used to having with parents and patients did not apply in this case. Clinicians were unclear about how to advise the young adult patient and then were astounded that she chose not to participate in another clinical trial. The patient went on to receive re-irradiation but lost her medical oncology home and did not have palliative care or hospice resources set up. She was left without the supports she would need as end-of-life approached. Thus, her age and diagnosis skewed her access to available

resources and deprived her of continuous medical support, leading to another effective patient abandonment. This unjust experience should lead oncologists to re-evaluate how they care for these young adult patients and consider advocacy in health policy change.

Balancing Autonomy with Justice

Justice can be in conflict with autonomy. Respecting choices of seeking out medical care or clinical trials is not wrong but can become problematic if there are depleted resources with concern about distributive justice. If the patient and family desire to pursue a clinical trial, what lengths does a medical provider go to assist that the patient is enrolled? There are limited spots on clinical trials and the physician may be caring for multiple eligible patients. Does the medical provider have preference based on disease status, likelihood of benefit, the ease of interaction, the likelihood of compliance, or first come first serve?

Does the physician have an obligation to promote research and research funding? Some would say no, as the physician is already investing resources to care for children with cancer, but others would say that physicians should invest time and effort developing more treatments which could benefit to the more people if it worked. On the other side, some physicians are also investigators in the trials they propose to patients. Physician investigators should be clear when interacting with patients and families about potential conflicts of interest. Patients and families may see that person as an expert and feel better about being in that person's care; however, that may lead to manipulation and problematic therapeutic misconception. The harm of therapeutic misconception is that it does not respect a person's rights and autonomy in the informed consent process. Without appropriate understanding, informed consent is not valid. Physicians should take care to ensure appropriate informed consent, including verbal and written materials for

people who speak different languages or who are illiterate. These participant populations could be excluded from participation and increase health disparities and discrimination.

Another area of conflict in the study was the inequitable provision of access to medical marijuana. Some medical providers were certified via state authority to certify patients with qualifying conditions. Other medical providers did not have permission or authority to do so but were willing to refer to certified providers. Still others saw this as illegal and/or unethical and were unwilling to refer patients to certified providers. Thus, there was no standard recommendation for how to approach the request for medical marijuana and some patients who requested it could be denied the request. Patients received discrepant interventions depending on which medical providers were involved in their care. Further work to ensure patients have equal access to interventions in the same clinic seems ethically reasonable and permissible.

Balancing Autonomy with Beneficence and Nonmaleficence

A prime example of balancing the competing principles of autonomy, beneficence and nonmaleficence was the use of CAM. One patient and his family openly discussed CAM, including vegan diet, herbalist recommendations, and cannabis oil. Though there are emerging studies in this area that show CAM could be beneficial psychologically and physically with potential cancer directed effect, physicians did not see these treatments as particularly beneficial. However, physicians saw that CAM was permissible if it could be safely provided and the patient agreed to it as the patient had "nothing to lose." However, if patients were enrolled in clinical trials, the use of CAM modalities was not always permitted. Clinician investigators had to address drug-herbal supplement interactions with clinical trial medications. Drug-drug interactions could lead to significant harm or prevent medications from working. Additionally, if the herbal treatment was efficacious, it may show the clinical trial in a falsely positive direction.

Patients enrolled in clinical trial had to follow the rules and regulations of the trial, or risk being removed from the trial. When a patient had disease progression, the family members inquired about the use of CAM:

"Doctor: Totally okay, and I don't -- and P11 has to be on board, right?

Grandma: Yeah, oh yeah.

Doctor: Changing his diet is going to be a challenge. (laughs)

Grandma: No, no, he's been doing really well on his vegan diet.

Mom: (laughs)

Doctor: I'm totally okay with that…I'd just like to know what. Some people choose extracts like Thistledown and different types of homeopathic remedies, and as long as I know what they are, it helps me understand other things that are going on, okay?

Mom: Okay.

Doctor: So, I have absolutely no objection to any of that. He couldn't -- it was hard for him to be on those things while he's on the study, right? But he's not on a clinical trial then that gives us a lot more freedom, and if he has nausea or discomfort, there's a good reason to try cannabis oil if that's something that your family is interested in."

The physician responded that using CAM was permissible as he was no longer on a clinical trial and had conditions. The patient had to agree to it and the family needed to transparently communicate about what remedies would be used to effectively diminish harm to the patient. The physician later said, the family had "nothing to lose" in trying CAM.

In a following visit with a palliative care physician, further discourse on the CAM and Avastin (a palliative chemotherapy) arose.

"Grandma: I mean, you know, the herbal things, they probably don't work either, but it's a closer thing to not being sick you know, while you're taking it. You're not losing your

hair. You're not, you know, getting sick, so --

Palliative Care Doctor: Well, the risk rate -- So the thing that's different about those is the risk-benefit ratio, right? Like you know, there may -- like chemo, there may actually not be much benefit, but the risk is a lot less for many patients that are doing chemo where chemo can make you feel much sicker, take away your hair, you know, a lot of those different things.

Grandma: Mhm, yeah, and it's not going to -- you're not going to make it, so you're going through this for what?

Palliative Care Doctor: Yeah. When benefit is unknown, then the amount of risk really starts to weigh in, right? In terms of what you're willing to tolerate.

Grandma: But she did tell us that now since he's not on a clinical trial that we still could try herbal things. I don't know. So, we just have to see. We're meeting with an herbalist on Friday.

Palliative Care Doctor: Okay.

Grandma: And so, then we'll know, know, you know --

Palliative Care Doctor: Yeah.

Grandma: I mean, I still want to see doctors, because I'm a nurse. I still believe that God has given doctors -- you know, you wouldn't be here if he didn't intend for you to do something, you know, but right now with this particular tumor, only God can do this, you know? So, there we are.

Palliative Care Doctor: Yeah. And I think that's where I want to make sure that you guys know that even though -- whether he goes forward with Avastin or not, whether you go forward with any therapy or not, right? To know that just because we're not giving

chemo, we're not doing that, that doesn't mean you don't have support and you don't have doctors that care about you, you know? In a way that's when we care about you the most in a sense, because when you strip away all of the chemo and all of the other stuff, right? What is left and what is supposed to be at the core of medicine, and what is, is about caring for him and you guys as a family, you know? And then what that really becomes is focusing on his quality of life and how do we help each day be as good as it possibly can be for P11 and whatever that means for him, you know?

Mom: I don't know anything. I just sit here and I listen. And I try to process.

Grandma: (laughs)"

Later, the patient and family agreed to starting Avastin and CAM. They saw the herbalist and received a long list of recommendations that ranged from yoga, water intake, and diet to herbal remedies like alkaline substances, French green clay, and several other herbs. The mother brought the list to the physician who stated that the alkaline substances would likely not impact his tumor. The theory the physician cited was that cancer grows in acidic environments, so neutralizing them with alkaline substances could decrease their growth rate. However, the physician said that the alkaline agents would not pass the blood brain barrier and his body would buffer the substances, likely making no difference to the tumor. The physician specifically looked up drug-herbal interactions and found none. Thus, the physician discussed with the patient and mother that the recommendations were safe to try but would only be recommended if the patient wanted to do them. If the patient did not like how the French green clay tasted, the physician said they should not continue it. The physician weighed in on the recommendation with an expert opinion, framed it with the patient's values, and ensured that the options that were presented were safe.

Another example where autonomy and nonmaleficence were in competition was when physicians limited activities (such as contact sports). These recommendations were meant for patient safety, but oftentimes were thought to be infringing upon liberties. Patients and were upset that they could not participate in the sports, especially as they were not going to live much longer.

Attempting to obtain compassionate use drugs or expanded access to investigational agents are included in obligations of beneficence and the duty to rescue but can compete with nonmaleficence and autonomy. One patient's family referenced the Right to Try Act several times when they discussed the options of care. A mother stated:

> "We need to find something else to help with this tumor or it is going to take [my child]. I mean, it is what it is. We all know the survival rate. We all know the history of it, and he's beating the odds. Well, you know, don't give up a child who is beating the odds. You know, we should go the next step. Okay, he made it here. He's beating the odds. Let's try something else. What else can we do? You know? And just like my husband and I were talking with the President's State of the Union [Address] that he did, he mentioned clinical trials and getting the FDA approvals and having these treatments in a safe place, and that's exactly right. And that's what I was talking with that nurse, you know, what makes you know, -- what's considered safe? Why is the FDA not approving this and how is it that so many people are going to a place like Mexico and they're okay, you know? I'm sure there's cases that aren't, but there are people coming out okay, so you know, what's the difference, and what's going on, and is it really a money thing, because so many parents say it has to do with money. It has to do with insurance. It has -- You know,

and it may, but in the meantime. I'm trying to save my child's life or improve my child's quality of life, so I -- you know, all that stuff needs to be put aside."

Briefly, the Right to Try Act of 2017 is a federal legislation proposal that has passed Senate approval (R. Johnson 2017) and is pending House approval (Biggs n.d.)(H.R.878-Right to Try Act of 2017). Bipartisan support is present and it is backed by both the Vice President and President. This legislation amends the Federal Food, Drug, and Cosmetic Act to 1) permit investigational drugs that have passed phase I clinical trials to people with life-threatening illnesses who have exhausted approved treatments and are unable to participate in clinical trials and 2) limit liability to sponsors, manufacturers, prescribers and dispensers that provides, or declines to provide, an eligible investigational drug to an eligible patient. The impact of removing the public health mission of FDA oversight in favor of patient autonomy and market forces, is an increase in potential harm to patients as the FDA already has in place "expanded access" pathways for these types of patients. (Steven Joffe and Lynch 2018) Legislation will have limited changes to the access to investigational drugs as the FDA currently has a 90% approval rate for expanded access requests and manufacturers have similar approval rates. (Steven Joffe and Lynch 2018) Additionally, the FDA's current expanded program is less laborious for physicians than prior versions, taking about 45 minutes to complete an application rather than hours. (Steven Joffe and Lynch 2018; Darrow et al. 2015)

Though the above patient has not been offered a compassionate use drug, two patients did receive compassionate use drugs. One had significant benefit with clear tumor regression. The other patient died shortly after starting the investigational agent. Though clinical outcomes varied from the compassionate use drugs, the parents felt supported by clinicians who attempted

to obtain these drugs for their children. They felt respected and felt like the goals of care were being met through provision of the drugs.

Finally, patient and parental rights to seek out care at other institutions was often respected by physicians. If parents expressed that they were considering Mexico, physicians would discuss how they were worried that Mexican healthcare providers were providing the trial to take the parents money and resources would not be available if a toxicity or severe side effect occurred there. They would discuss the risk involved going to Mexico. Most of the time, the patients and parents did not go, but were well-informed by their physician. Thus, disagreement does not necessarily mean that a physician is not respecting a patient or physician's autonomy, rather, it highlights the medical and ethical dilemmas in the spectrum of care.

Ethical Dilemmas

Throughout the HGG disease trajectory, multiple significant ethical decisions must be made. Using principlism may assist oncologists in navigating ethical dilemmas on a case by case basis. However, when conflict is serious, consideration may be made to consult the bioethics team. During this study, none of the patients had ethical dilemmas requiring an ethics consultation. However, these dilemmas do occur as in my medical practice these patients with HGG's have requested to expedite death, parents have requested to clone their child post-mortem, and more frequently, patients and parents request interventions that medical providers view as prolonging suffering, such as tracheostomy and long-term ventilation. Each dilemma is contextual and the competing principles of autonomy, beneficence, nonmaleficence, and justice will need to be uniquely applied.

Chapter 7: Conclusions and Implications for Patient/Family Care & Practice

The communication and decision making processes were investigated over the illness trajectory for children and young adults with a high grade gliomas, their parents and physicians, including oncologists and palliative care specialists. In the qualitative study, we demonstrated that decision making is complicated for children with HGGs as there are ever changing options, many decision makers, and influences on those decision makers.

Specifically, the study aimed to evaluate the decision making and informed consent processes for cancer directed therapy for patients with HGGs. The informed consent process was not evaluable by this study as no informed consent discussions were captured. Many of these conversations occurred quickly at the time of diagnosis or at progression and the principle investigator for this study was not notified or was not available for the discussion. In addition, clinical investigators frequently called patients to discuss imaging results, treatment options, and essentially review clinical trials available with a planned follow up visit in clinic. These clinic visits were truncated and often focused on completion of paperwork.

One hypothesis was that the pediatric oncology team favored phase I trials or other cancer directed therapy over palliative care and hospice. It was evident that pediatric oncologists spent more time discussing cancer directed options and briefly mentioned palliative care or hospice services. Oncologists did focus on the hope related to an intervention, believing that they were preserving hope by offering participation in a clinical trial or cancer directed therapy.

Oncologists would mention that they did not know if a clinical trial drug or compassionate use drug would have any efficacy against the tumor; however, it was evident when physicians believed that there could be a potential for efficacy. This belief in potential efficacy was greater when physicians participated in developing a particular clinical trial. Thus, conflict of interest skewed the clinician investigator's viewpoint. Patients and parents did not

see this as problematic as they viewed the clinician investigator as an expert and often sought to be under that clinician investigator's care to participate in the trial. They did not believe it prevented their voluntary participation in the trial or their understanding that the trial drug had unknown efficacy. Though the informed consent discussions were not captured, it was evident through interviews that patients and parents knew that the drugs would likely not work, but they were still hopeful. Patients and families held the hope of cure and the hope of an investigational drug being efficacious in tension with the reality of known poor prognosis. They were optimistic about treatments as many of them were often optimistic about life. For those who were not optimistic, someone else in the family often was.

Another aim was to evaluate if palliative care improves the understanding of comfort focused care and hospice services along with family-centered decision making. Palliative care involvement was in forty-six percent of the patients, which is much higher than the twenty percent who received palliative care in 2016. This increase likely reflects the initiation of an out-patient supportive care clinic in the oncology office. Though palliative care was consulted more frequently, only one visit was audio-recorded with only two palliative care specialists enrolling in the study and conflicts in scheduling. Palliative care specialists did complete questionnaires on three patients. Answers were more thorough than oncologists, which could demonstrate that they understood the family dynamics and reasoning for decision making at a deeper level than oncologists, or that they took more time to complete the questionnaires. With this limited information, the impact on the understanding of comfort focused care and hospice services was not evaluable.

Another hypothesis was that patients with HGGs received care that was concordant with their goals more frequently than those who do not have a palliative care consult. This was

partially evaluated, but no strong conclusions can be made. Eight patients without a palliative care consult mostly had out-patient management, came to clinic on days when supportive care clinic was not held, had not progressed after initial therapy (2) or were participating in a clinical trial (6). The seven patients who had a palliative care consult often did while in-patient or went to an oncologist who had clinic the same day as the supportive care clinic. Palliative care consultation did not impede patients from receiving cancer directed therapy, as all of those will palliative consultations received cancer directed care.

One patient had an in-patient consultation prior to the study. That family particularly stated that the palliative care team was unhelpful to them. The patient had been on a clinical trial, had a VP shunt placed, and at the time of progression, transitioned to out-patient hospice services. The palliative care team did not provide helpful interventions for that particular patient. None of the other patients mentioned palliative care in particular in the audio-recorded semi-structured interviews with no prompting by a question about palliative care. One patient's mother rejected palliative care and hospice when her child showed significant improvement on a compassionate use drug.

Patients who died in the hospital received intensive palliative care with the sub-specialists. Though the patients were initially planning to die at home on hospice services, they needed intensive symptom management that was not able to be provided by hospice. Additionally, they were able to have limited autopsies for research, which fulfilled goals they had. For one patient who did not have a palliative care consult and died in the preferred location of home with the aid of hospice services, was unable to have a planned limited research autopsy completed as previously desired. An earlier shift to comfort focused care did not occur when palliative care was involved. Patients who came to the center for a second opinion, desired

comfort care, or were found to be ineligible for a clinical trial did not participate in this study. Thus, the goals of care may be particular to this cohort that was studied.

The study was longitudinal in nature to evaluate how decision making, hopes and goals change over the illness trajectory fora patient with a HGG. One patient was followed over the course of ten months, while most others were followed over the course of two to four months, ending with death or the end of data collection. All patients in the study began a cancer directed therapy or clinical trial shortly after diagnosis.

During the study period, six (40%) patients had not yet had disease progression, four (27%) had disease progression, four (27%) died and one (7%) improved. Of these six who had not yet had disease progression, one was still receiving active chemotherapy, one was being observed after completing initial standard therapy, one was being observed after completing clinical trial requirements, and three were actively receiving investigational drugs on clinical trials.

Decisions for the patients receiving active chemotherapy or investigational agents were focused on coordinating schedules and finances. For patients not receiving active cancer directed care and had lived over a year without progression, decisions were more focused on future endeavors for the patient or school.

Four patients who had disease progression were faced with decisions about whether to start a new cancer directed therapy, enroll in a clinical trial, focus on quality of life, or go on trips, such as Make-A-Wish. Two patients had progression twice during the study. One of these patients chose to enroll in a clinical trial each time and have re-irradiation. The other patient enrolled in a clinical trial and started a vegan diet. At the next progression, the patient was taken off the clinical trial, continued the vegan diet, started Avastin (palliative chemotherapy),

and started herbal remedies and meditative practices as suggested by a naturopathic provider. Another patient progressed once during the study and underwent another surgical resection and enrolled in a clinical trial. A fourth patient declined clinical trial participation. For the one patient who improved, decisions were made about continuing the compassionate use drug, stopping hospice services, go on vacation, and later shifted to the sibling who was also diagnosed with a brain tumor. For those who died during the study, decisions were on memory making, legacy building, and end-of-life care.

These patients were all in different stages of their disease course and had decisions that transitioned from coordinating cancer directed care to future planning for those who do not have progression or improve. For those who had progression, decisions focused on care options and began to shift towards end-of-life care. Decisions about hospice would begin to arise for these patients. Palliative care became involved more often for patients who had disease progression, at the time when significant care decisions were being made.

Goals of care for patients and parents shifted for all enrolled patients from cure or cancer treatment at the time of diagnosis to other goals over time. These other goals depended on the trajectory. Quality of life would become an important factor at the time of disease progression and end-of-life, more so than at the time of diagnosis. Comfort focused goals became more prominent as end-of-life approached.

Parallel to the shift of decisions to be made and goals of care was a shift in the hopes of patients, parents and physicians. While patients and families discussed cures throughout the disease trajectory, they held other hopes as well. Many of these hopes focused on achievable hopes, such as going to an activity later in the day. Other hopes were less likely but achievable, such as raising money at a benefit or the patient living to a milestone. At progression, hopes

around symptom control began to emerge along with quality of life. At the end-of-life, they hoped for peace, comfort and no suffering. These findings are similar to a recent study that showed that most hopes are in the domains of quality of life, physical body, future well-being and medical care and that over time hopes increased for quality of life, future well-being and broader meaning. (Hill et al. 2018)

Physicians would mention hopes for patients to have good quality of life as long as possible at the time of diagnosis along with hopes for prolonged progression free survival. As patients progressed or approached end-of-life, the length of time mentioned in survival was shortened. Rarely a physician would mention cure. The one physician who mentioned it also hoped that the patient would avoid suffering and death, and that the family would not have to watch their child die.

The patient and parental hope for a cure may be a part of coping or purposeful ignorance and should not be discounted. It does not always mean that they do not understand the reality of the circumstances or that they lack understanding in the purpose of the clinical trial (therapeutic misconception, misestimation or optimism). However, it may reflect their positive disposition. Patients and families had functional hopes that continually shifted but promoted their ability to take "one day at a time." Inquiring about these functional and shifting hopes may foster further resilience for these patients and families.

Loci of Control Amidst Chaotic Decision Making for Children with High Grade Gliomas

Each participant in decision making had a locus of control. After life is turned upside down from a cancer diagnosis, people did what they are capable of doing. They focused on their loci of control amidst the chaos, attempting to fulfill the duties of their role in decision making.

In attempting to be a "good physician," physicians attempted to control and provide standard medical care. They may have gone above and beyond standard medical care in providing extraordinary treatment regimens. However, with patients having poor prognoses, the morale to provide supra-standard or even standard of care did decline. Though parents needed clinicians throughout the trajectory of their child's illness, good clinicians were especially needed at the end-of-life. They did not wish to feel abandoned by their oncologist.

To remediate this problem, more support is needed to improve clinicians work-life balance so that they do not develop compassion fatigue and their patient care can excel. Additionally, physicians should be trained in communication, shared decision making, and preserving hope. Physicians could also learn to interact via social media to provide guidance to patients and parents in viewing high quality information.

Parents attempted to be "good parents" by controlling and providing the basic needs for their children like food, exercise, shelter, comfort, access to knowledge for car, access to care. They cared about helping their children live as well as they could for as long as they could. They attempted to integrate their child into a community of support but also intervened when needed to protect their children's privacy. Home was a safe haven and was guarded as such. Parents worked to establish normalcy at home for the patients and their siblings. They worried about caring for their sick child and other siblings.

Patients tried to be "good patients and good children" as best as they could. They experienced many different emotions. It was hard to control their anger, fears, worries and anxieties. Patients attempted to be brave and hide their fears. They appeared to be mature beyond their years. At other times, they went back to being a normal child or regressed. Children attempted to control certain settings to feel more secure.

Communities attempted to be "good" by supporting their members, but may have felt a loss in how to support a child with HGG and the child's family. They rallied together to support patients and families, providing significant resources that enable medical care or memory making through trips like Make-A-Wish.

Acknowledging these differing loci of control is important in developing relationships, communicating ideas, and making decisions. When these roles are not honored, relationships can be damaged, communication breaks down, and distress results from conflict in the decision making process. However, when they are honored, relationships are supported, communication is transparent, and peace results from teamwork in the shared decision making process.

Implications and Communication Framework for the Longitudinal Decision Making Processes

In decision making discussions, knowledge exchange can be difficult, especially when there are many participants, opinions and emotions. Clear communication is essential in learning about the goals of care that will guide the approach to the patient's care. It is important to revisit goals of care throughout the trajectory of a child's illness, especially as the child nears the end-of-life. Figure 15 demonstrates my proposed decision making framework that has been informed by the literature and my informants (patient, parent and physician) for communication for children with HGGs.

The framework begins at diagnosis and progresses through initial discussion of treatment options, through disease progression, to end-of-life. This framework uses the SPIKES model for delivering bad news. (Baile et al. 2000) Briefly, the SPIKES model stands for the following:

1) *Set up* the interview with privacy, involving the people patients and/or parents want to be there, sit down and maintain eye contact and diminish or eliminate interruptions.
2) Assess the patient's and parent's *perception* (i.e. What have you been told so far?)

3) Obtain the patient's and/or parent's *invitation* to disclose information
4) Give *knowledg*e and information to the patient/family
5) Address the patient's *emotions* with empathic responses (observe and name the emotion, identify why the emotion is there and allow the patient/parent to express the emotion)
6) Strategy and *summary*

At diagnosis, the medical provider would provide bad news using the SPIKES model. In discussing the diagnosis, the physician should share honest, effective, compassionate knowledge in an Ask-Tell-Ask exchange with patients and their families. (Back et al. 2005) Physicians should allow time for families to process the information and ask questions. During the exchange, the physician should learn about the patient's and family's hopes. When a patient and family states that they hope for a cure or miracle, the provider should also ask what else they are hoping for as it will be important to know throughout the illness trajectory.

When discussing treatment options, the physician should be prepared to discuss the available and feasible options for cancer directed care and palliative care at a goals of care discussion. Again, the Ask-Tell-Ask strategy should be used to learn what is important to the patient and family. At this time, reveal the options that align with the stated goals of patients and families. Allow time for questions. Encourage patient and family hopes through active, empathetic listening and asking. While the patient is stable, consider discussions on advanced care planning. This discussion should be separate from discussing other treatment options as it can be overwhelming to the patient and family.

At the time of disease progression, the physician should again prepare what options are available and feasible. A goals of care discussion should ensue. At that meeting, the physician should support the family through listening and inquire about hopes. The physician should note

if the hopes begin to shift away from cure and towards comfort but should not be surprised if cure remains a hope. Again, inquire further about other hopes and more hopes may emerge that reflect comfort than cure. The physician should not abandon the patient. If the patient needs to transition to another facility or clinician, the physician should ensure the transition is as smooth as possible, providing vital information to the receiving institution for clinician.

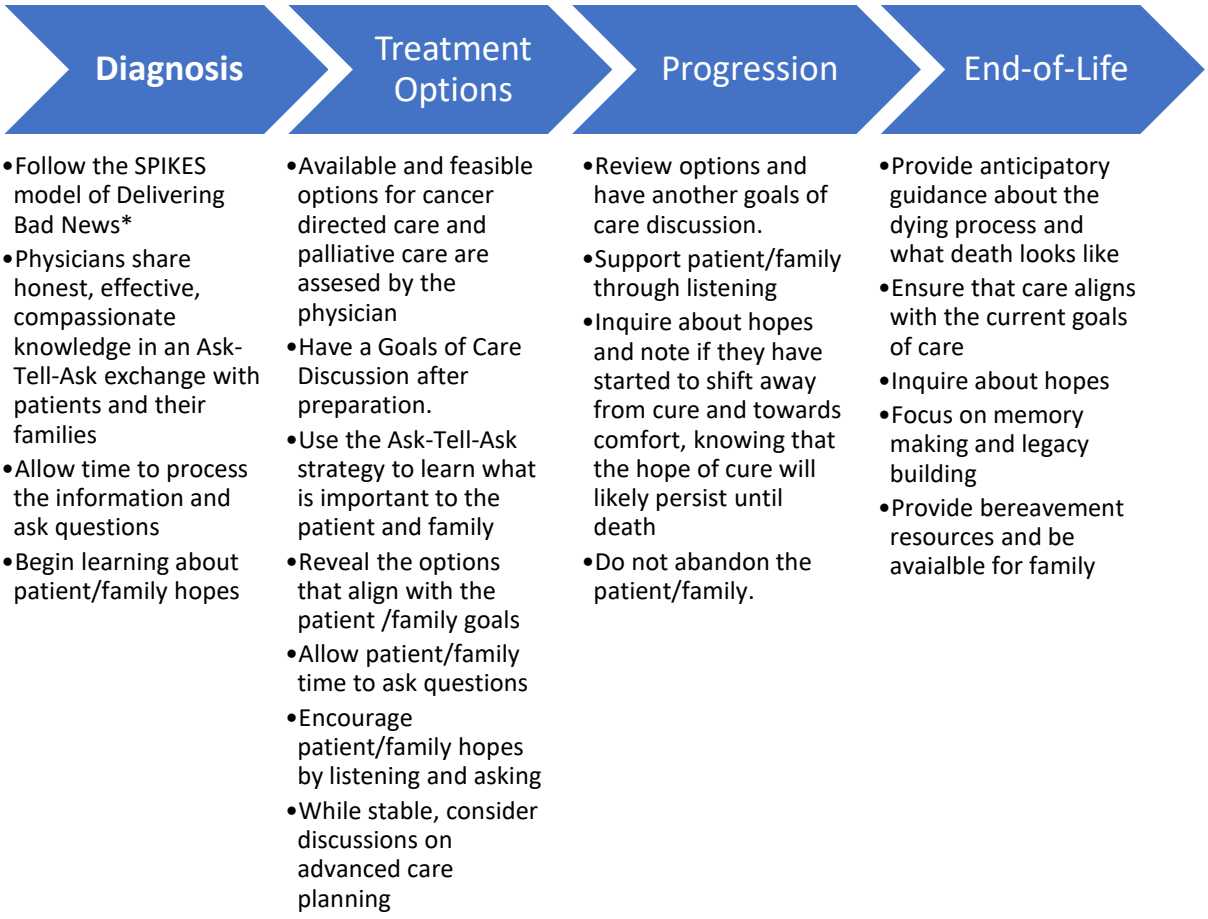
Finally, at the end-of-life, the physician should provide anticipatory guidance about the dying process and what death looks like. Ensure that care aligns with the current goals of care and continue to inquire about hopes. Focus on memory making and legacy building. Provide bereavement resources and be available for the family.

Utilizing this framework in clinical practice may facilitate clearer communication in difficult conversations. This will respect the autonomy of each participant in decision making, balancing benefits and harms, and assess the justice of the available options. The goal is to provide care that aligns with the roles of each patient and family, allowing physicians, parents, patients and communities to be good at their respective roles. When each of these participants are supported, they can more easily care for one another, share hopes with one another, and share responsibilities in shared decision making.

Future work is needed to 1) develop preference tools for pediatric patients and families to inform medical providers, 2) provide training in communication and shared decision making with pediatric oncologists, 3) further evaluate informed consent discussions for clinical trials and compassionate drugs, 4) further evaluate the impact of palliative care on decision making and compare shared decision making practices between palliative care specialists and oncologists, 5) evaluate the potential roles physicians and researchers have with assisting in decision making on social media websites, 6) determine what physicians, parents and patients determine to be ethical

in presented case studies and evaluate if there is a discrepancy, and 7) determine if physicians have moral distress or regret related to shared decision making processes.

Figure 15: Framework of Communication for Decision Making for Children with HGGs



Appendix A: Interview Guide for Patients/Families

1- Tell me all about your child's illness (Probe for: What is your understanding of your child's diagnosis and What is your understanding of your child's prognosis? When you say that, is this the facts, what you hope for or what you fear will happen?
2- Tell me about all of the options for taking care of your child are right now.
3- Did the doctor recommend one of the options? What did he or she say? Did you think this was a strong recommendation or just a suggestion? (may want to probe: What made you think that?)
4- What option did you pick and why? Tell me all about how you made the decision. (probe for influences – friends, past experiences, nurse, doctor, God) Who usually makes big decisions in your family?
5- What do you wish you could know that you have not discussed yet? How would you like to be told that?
6- What do you wish you did not know or wish that you had not been told? Is there anything you wish your child was not told?
7- What do you think is the best outcome of the choice you made? The worst?
8- Describe for me the biggest fears you have right now. What are your fears? What do you hope for right now?
9- Would you call yourself an optimist, a realist, or a pessimist?
10- How could we improve conversations like the one you had with your child's doctor? We welcome any suggestions!!!

Appendix B: Physician Questionnaires

Questionnaire for Oncologists

1- What is the patient's diagnosis?
2- Do you expect this child to live longer than 6 months?
3- Did you offer a Phase I trial?
4- Did you offer cancer directed therapy (radiation, chemo-not on trial)?
5- Did you offer palliative care?
6- What did you recommend?
7- What option did they pick and why?
8- Who do you think is the primary decision maker in their family?
9- Who do you think influenced these decisions the most?
10- What do you think is the best outcome? Why? The worst? Why?
11- Do you try to preserve hope? If so, how?
12- What are your fears for the patient? For the family? Your hopes?
13- Would you call yourself an optimist, a realist, or a pessimist?
14- If you could re-do the conversation, what would you do differently? If so, how would you change it?
15- How could we improve training for physicians to have difficult conversations like the one you had with patients and/or families?

Questionnaire for Palliative Care Specialists

1- What did the patient/family relay about the diagnosis and prognosis and treatment options offered by their primary team?
2- What options for care did you discuss with the child and/or family?
3- Did you discuss hospice?
4- What did you recommend?
5- What option did they pick and why?
6- Who do you think is the primary decision maker in their family?
7- What do you think is the best outcome? Why? The worst? Why?
8- Do you try to preserve hope? If so, how?
9- What are your fears for the patient? For the family? Your hopes?
10- Would you call yourself an optimist, a realist, or a pessimist?
11- If you could re-do the conversation, what would you do differently? If so, how would you change it?
How could we improve training for physicians to have difficult conversations like the one you had with patients and/or families?

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