Ethical Challenges in Pediatric Oncology Care and Clinical Trials

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11.1 Introduction—Why is Pediatric Ethics Different?

Clinically, the care of pediatric cancer patients is a vast departure from cancer care of adults. While the available treatment modalities—chemotherapy, radiation, and surgery—are the same, the diseases, care-delivery, and outcomes differ greatly. And just as 'children are not just little adults,' pediatric bioethics occupies a distinct place within the broader field of bioethics. In this chapter, we highlight the framework for understanding ethical issues in pediatrics and explore common ethical dilemmas pediatric oncologists encounter.

We must begin with a caveat that is important for readers of this text. We are pediatricians and pediatric hematologists/oncologists in the USA (US), where we were both born, raised, and professionally trained. The US medical and legal systems are different from those in other countries (Blake et al. 2011) and reflect unique American social and cultural values. Because ethics and law are inextricably linked, and profoundly influenced by societal and personal values, the frameworks we discuss will reflect our US-centric background and may not be completely applicable in other settings. We will denote where US laws are a major factor in our ethical analysis. But to appropriately think through ethical dilemmas in pediatric

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oncology, the reader must have a firm understanding of the value-system and legal standing in their country of practice.

Why are ethical issues in pediatrics different? Most clinical encounters for the adult patient are dyadic, involving a patient and physician jointly making decisions for the patient. But because (most) children are unable to make decisions for themselves, decisions about their medical care are made by others, usually their parents. Therefore, pediatrics involves a triadic relationship, with the child-patient and parents as independent parties in the relationship. The child's healthcare is thus subject to the views and values of both the parent and physician, and yet the child experiences the effects of decisions they had little-to-no part in making. The parent is a fiduciary of the child, with an obligation to protect and promote the health and non-health-related interests of the child. The physician is a fiduciary of the child-patient, with an obligation to protect and promote the health-related interests of their patient (McCullough 2010). At its core, 'pediatric ethics explores how to make the best choices for children […] seeks to define parental and clinician obligations to children and […] attempts to protect the interests of children' (Fleischman 2016).

Another critical layer of pediatric ethics is the concept of emerging and future autonomy. While children generally lack the ability to make decisions for themselves at the time a decision must be made, most will eventually acquire the ability to make such decisions. Most develop their own values and become autonomous adults, capable of making choices that reflect these values and preferences. Therefore, the parents and physicians, as co-fiduciaries of the child, have a duty to promote and protect the emerging and future autonomy of the child. They should promote the child's emerging autonomy by allowing the child to participate in decision-making to the extent she is developmentally capable at that time. And they should promote the child's future autonomy by making choices that optimize the chance that the child will become an autonomous adult. Often described as the child's 'right to an open future' (Feinberg 1980), this concept comes to the forefront in such decisions as performing germline sequencing in children, which we will explore further later in this chapter.

It is in this background that ethical dilemmas occur in pediatrics and pediatric cancer care. In this chapter, we will describe ethical challenges commonly encountered by pediatric oncologists, examining issues involving (a) informed consent; (b) research involving children; (c) end of life; and (d) genetic and genomic testing.

11.2 Informed Consent, Assent, and Developing Autonomy in Pediatric Cancer

11.2.1 Parental Decision-Making for Children as Incompetent Patients

Central to the discussion of informed consent especially for children is an understanding of the concepts of competence and informed consent for patients who lack capacity. While *capacity* is a medical determination, and *competence* is a legal

judgment, many argue that this difference is inconsequential in practice (Appelbaum 2007; Beauchamp and Childress 2013). For our purposes, we will use them interchangeably to indicate a person's ability to cognitively, psychologically, and legally complete the necessary tasks to make a decision. And because by law in the USA—where the age of majority is 18 years—children lack capacity, we will briefly examine informed consent for the incompetent adult prior to explicating the framework for informed consent in children. An adult who becomes incapacitated (temporarily or permanently) must have a surrogate decision-maker appointed to make decisions on her behalf. Identifying the appropriate surrogate for a patient depends on many factors, and while all 50 US states have statutes that address surrogate decision-making, there is wide variability (DeMartino et al. 2017). Accordingly, physicians should be familiar with relevant laws in their jurisdiction or should consult with ethics or legal teams at their institution.

There are two main frameworks a surrogate can use to make decisions for the patient, the *substituted judgment standard* and the *best interests standard*. Substituted judgment is the preferred framework, asking a surrogate to make the decision that the patient would if she were not incapacitated. This decision can be informed by personal conversations about specific circumstances, by knowledge of the patient's general values, or by written preferences documented in an advanced directive. While this framework strives to preserve patient autonomy by encouraging decisions that approximate the choice the incapacitated patient would make, surrogates often lack sufficient knowledge to make choices just as the patient would. When this occurs, the *best interests standard* is the more appropriate framework to use. One definition of this standard is 'acting so as to promote maximally the good of the individual' (Buchanan and Brock 1989). More simply stated, this standard asks surrogates to make the decision they believe to be in the patient's best interest.

Minor children are by definition incompetent and therefore require a surrogate to make health decisions on their behalf. The surrogate is almost always the child's parent, and with a strong moral and legal justification. Society allows parents wide leeway to make decisions for their children, including value-based decisions such as what they eat, what school they attend, and whether they practice a religion. Deference to parental choices is justified in most situations, because parents are uniquely positioned to know and understand the child's interests. Parents instill values in the child, meaning the child will share many if-not most of the parents' values. Accordingly, most of a parents' decisions are likely to reflect the decisions the child would make once they become competent. Additionally, parents almost always have the best interest of the child in mind. Lastly, parents—more than anyone else—will bear the consequences of choices that impact the child. For all of these reasons, parents are the appropriate surrogate decision-makers for children for most health decisions. At times, parents must weigh familial interests, such as the interests of other children, the parents themselves, and the family unit itself. But because familial interests usually align with the child's interests, and the child's interests often depend on the familial interests, it remains appropriate for parents to balance these interests.

There is a subtle but important distinction to make between parental autonomy and parental authority. 'Autonomy is the right of a rational person to make his or her own decisions, and provides a moral justification for … informed consent' (Unguru 2011). When parents make health decisions on behalf of someone else (the child), they do not exercise autonomy. It is more accurate to describe what they do as exercising parental authority. A corollary is that parents do not provide informed consent for medical interventions for the child, and they provide informed permission. This distinction highlights the fact that parents are surrogate decision-makers and do not have carte blanche to make whatever decision they want. Rather, they are morally obligated to use the established frameworks for surrogate decision-making outlined above.

It is inappropriate to use substituted judgment to make decisions for children. Substituted judgment is ideal for the adult who has become incompetent but at one time had the capacity to develop and express autonomous values and wishes. Because children lack capacity, application of the best interests standard is appropriate for pediatric decision-making (Kopelman 1997).

11.2.2 Participation of Children in Medical Decision-Making

Children at all stages of development will develop and express opinions relevant to their care, and children should be given choices about aspects of their care that they are developmentally capable of making. In most situations, it is appropriate to use a sliding-scale, with more weight given to a younger child's opinion about lower-stakes decisions (e.g., which arm to place an IV), but with higher-stakes decisions typically restricted to older and more mature children (Katz et al. 2016). Parents may choose to incorporate the child's values or opinion into the parents' decisions, but until a child reaches adulthood their values should rarely override parental choices, particularly about major medical decisions. In many circumstances it is appropriate to solicit the assent of the child. *Assent* refers to a child's agreement or approval to participate in the care agreed upon by the parent (Committee on Bioethics 2016). It is a way to give children a voice, respect their dignity, and promote and protect their interests (Unguru et al. 2008). There is no consensus about the age at which a child can provide assent; however, some suggest that most children are developmentally capable of giving assent at 7 years of age (Diekema 2006). Despite this ideal, it remains controversial how the minor's voice should be included in medical decisions, particularly in the setting of decisional conflict.

In the USA, there are two circumstances in which we allow minors to make autonomous healthcare decisions; that of emancipated minors and mature minors. An *emancipated minor* is granted legal status as an adult to make decisions on her behalf. A minor may become emancipated permanently if she lives independently of her parents, usually living on her own, being married, and being financially independent from her parents. A minor may also be emancipated based on predetermined health conditions, including pregnancy, sexually transmitted infections, mental health disorders, or substance use disorders. A child emancipated under

these conditions may independently consent for care only as it relates to these conditions. The rationale for these exceptions is not based on the child having capacity for these decisions. Historically, adolescents have not sought care for these conditions when parental permission was required, and society's public health interests—that adolescents seek and secure treatment for these conditions—generally outweigh concerns over minors' incomplete capacity to make these decisions (Katz et al. 2016). A *mature minor* is a child who is determined by a judge to have sufficient capacity to give informed consent or refusal for a particular medical decision. Not all US states have mature minor statutes (Coleman and Rosoff 2013). Furthermore, when a child successfully petitions for status as a mature minor, her decision-making authority is limited to the specific decision approved by the court.

11.2.3 Ethical Dilemmas Involving Informed Consent

11.2.3.1 Parental Refusal of Cancer Treatment

While most parents agree to recommended cancer treatment, some families resist or refuse curative cancer therapy, and the oncologist must decide whether to support the refusal, or attempt to persuade the parents. In general, when the prognosis is extremely poor, or the morbidity of treatment extremely high, it may be appropriate to allow parental refusal. In contrast, when the prognosis is good, or the morbidity of treatment is low, persuasion should be attempted. These deliberations can be contentious, can lead to significant distress for the oncologist (Rosenberg 2015), and some even draw widespread media attention (Goldschmidt 2015). If attempts to persuade a family are unsuccessful, the oncologist may request court-ordered treatment, claiming that failure to treat would constitute medical neglect. There is no consensus about how to decide when to request court-ordered treatment. Some believe the best interests standard should guide this decision (Pope 2011), while others have proposed alternative ethical frameworks for these decisions, including the *Harm Principle* (Diekema 2004), *Constrained Parental Autonomy* (Ross 1998), and the *Zone of Parental Discretion* (Gillam 2016). Requests for compelled treatment are not always granted, as some judges defer to parents' wishes or find the child to be a 'mature minor' (In re EG 1989). Other judges may compel chemotherapy, even for children just under the age of majority (In re Cassandra C 2015).

Pediatric oncologists should be familiar with the relevant medical neglect laws in their jurisdiction, as well as their obligations as mandated reporters of abuse and neglect. Most agree that legal involvement should be a last resort. To avoid this, it may be appropriate for oncologists to consider alternative treatment options, compromises or making alterations to the treatment that would be acceptable to the family without significantly reducing the chances of cure and/or risk of toxicity. Consultation with experts in other disciplines may help navigate these cases, including social work, psychology, child life, chaplaincy, ethics, palliative care, legal or risk management, and child abuse. Despite persuasion or legal involvement, some patients abscond to avoid treatment (Caruso Brown and Slutzky 2017).

11.2.3.2 Child Refusal of Treatment

Children, particularly adolescents, may object to aspects of their cancer care when they experience or worry about side effects. In some circumstances, this may be easily overcome by good communication from the child's parents and the oncology team. Psychosocial team members (e.g., child life specialists, psychologists, social workers, etc.) may be helpful, particularly if there are concerns about depression, or when refusal occurs shortly after a child's diagnosis, such as a teenager refusing chemotherapy due to not wanting to lose her hair. In other situations, a child's refusal can pose significant challenges, as adolescents can be difficult to convince to do something against their will, and may even run away to avoid being forced to comply with treatment (Ross 2009).

11.2.3.3 Parental Requests for Non-recommended Treatments

When a child develops refractory and progressive cancer, parents may ask oncologists for treatment options that have no meaningful chance of benefiting the child. Sometimes these options include early-phase clinic trials, which despite a low likelihood of clinical benefit (explored in greater detail below), advance scientific knowledge and may provide psychological benefits from hope and from making a contribution to science. At other times, however, parents may request treatment without evidence of efficacy, and not available through a clinical trial. Physicians are not obligated to provide care they believe to be inappropriate (Bosslet et al. 2015). Historically such requests were labeled as 'futile'; however, the term 'futility' is controversial, and its use is falling out of favor (Burns and Truog 2007). Most scholarly attention to this problem centers around requests for care in intensive care unit settings and has resulted in a series of policies—e.g., the Texas Advance Directives Act of 1999 (Texas Health and Safety Code 1999)—or procedural approaches for resolving conflicts (Truog 2009). Some criticize the approach of 'exclusively leaning on policy, [as it] underplays the ethical significance of the decision and insufficiently recognizes the singular role of the parent' (Marron 2018). Because technological and scientific advances continue to expand the range of treatment options available to pediatric cancer patients, future work is needed to develop an ethical framework for how to best consider and navigate these requests.

11.2.3.4 Minors as Hematopoietic Stem Cell Donors

Some children with aggressive or refractory cancers require allogeneic stem cell transplants to maximize their chance of being cured. HLA-matched, biologically related donors are preferred due to lower risks of transplant-related complications, and siblings are the most likely family members to be an HLA match. Because siblings are often children—and therefore unable to provide autonomous consent to the procedure—there are unique ethical issues and arguments to consider (Kesselheim et al. 2009). Most agree that minors may ethically serve as donors, however due to rare cases of significant psychological harms to donors (Opel and Diekema 2006), the American Academy of Pediatrics recommends a risk/benefit calculation

that takes into account both the physical and psychological well-being of the donor, including how this relates to the recipient's survival (Committee on Bioethics 2010).

11.3 Research Involving Children

Around the world, the efforts of cooperative groups dedicated to pediatric cancer research receive significant funding and have resulted in an increase in cure rates from approximately 10% in 1950 to greater than 80% today (O'Leary et al. 2008). Despite the overwhelming success of this research model, there are numerous ethical issues that must be considered and addressed when conducting research involving children.

11.3.1 Children as a Vulnerable Population

Children have long been recognized as a vulnerable population that could be subjected to unethical research (Grodin and Glantz 1994), and stringent protections exist to minimize their exposure to harm, yet also to ensure they aren't excluded from the benefits of research (Office for Protection from Research Risks 1983). Because children require surrogate decision-makers, parental permission is required for a child's participation in research. This process of permission should be identical to informed consent for an adult research participant (Diekema 2006). Assent may be required depending on a child's age, maturity, psychological state, and the determination of the research ethics board [e.g. Institutional Review Board (IRB)]. Assent holds more weight in research deliberations than in routine clinical care, and a child's dissent (i.e., refusal to assent) ought to be respected for nearly all research, except where research participation offers prospect of direct benefit, and is unavailable outside of the research context (Office for Protection from Research Risks 1983).

11.3.2 Therapeutic Misconception

The *therapeutic misconception* is 'the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge' (National Bioethics Advisory Commission 2001). This misconception occurs 'when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled… may potentially benefit from the intervention under study or other aspects of the clinical trial' (Henderson et al. 2007). This belief is problematic for the conduct of clinical research, as it calls into question and undermines the validity of subjects' informed consent. Other types of

misunderstandings can similarly undercut and compromise research consent, including *therapeutic misestimation, therapeutic optimism* (Horng and Grady 2003), and *unrealistic optimism* (Crites and Kodish 2013), and these misunderstandings may sit on a continuum (Sisk and Kodish 2018). Evidence of these misunderstandings has prompted calls for new approaches to clinical trial enrollment. While some have suggested that clinicians ought not present study details or offer enrollment (Flory and Emanuel 2004; Eder et al. 2007), this would be a significant challenge in pediatric oncology, where most physicians also serve as investigators on clinical trials.

The two best-studied examples of misunderstandings during clinic trial consent revolve around understanding of randomization, and consent to phase I clinical trials.

11.3.2.1 Randomization

In audiotaping informed consent conferences (ICCs) between pediatric oncologists and parents of children with Acute Lymphoblastic Leukemia, Kodish et al. found that a significant percentage of parents offered enrollment on a randomized controlled trial mistakenly believed that enrolled children would receive the treatment arm that the clinician felt was the best fit for the child (Kodish et al. 2004). Many of these children (84%) were ultimately enrolled on the trial, and while not statistically significant, parents who did not understand randomization were more likely to consent to the study than those who understood it. This raises the question of whether parents, were they to understand randomization, would not enroll their children in randomized clinical trials.

11.3.2.2 Phase I Research Consent

Phase I trials are a critical part of clinical research, particularly in the emerging era of 'targeted therapies.' The goal of a phase I trial is to explore the safety of a new drug, by determining the dose-limiting toxicities and maximum tolerated dose of the agent, with hopes of finding a safe dose for subsequent trials to examine efficacy. These early-phase trials are limited to small numbers of subjects, and while the hope is that novel agents will prove to be safe and efficacious, there is no therapeutic intent to the phase I trial. This lack of therapeutic intent is a source of confusion for parents. Daugherty et al. found that barely one third of adults enrolling in phase I trials understood the purpose of the trial to include 'dose/toxicity determination.' The vast majority reported 'seeking anticancer response' such as remission or cure as the main reason for participation (Daugherty et al. 2000). Cousino et al. found that parents of children with cancer who participated in ICCs had poor understanding of the safety and dose-finding purposes of phase I trials (Cousino et al. 2012). While the cause of misunderstandings is unclear, efforts are underway to improve pediatric oncologists' communication skills for ICCs (Cousino et al. 2011, Johnson et al. 2015).

11.3.3 Is There a Prospect of Direct Benefit in Phase I Clinical Trials?

Whether phase I trials offer the prospect of direct benefit to subjects is a critical question to decide whether it is permissible to enroll children with cancer on these studies (Kodish 2003; Ross 2006; Weber et al. 2015; Kimmelman 2017). A recent meta-analysis of phase I pediatric oncology trials from 2004 to 2015 found that 10% of participants had an objective response (Waligora et al. 2018). In addition to citing tumor response rates as direct benefits, others insist that participants benefit from maintaining hope, and making scientific contributions that benefit future children with cancer (Kodish et al. 1992). An added layer of complexity is that parents, who are not the research subjects and yet provide informed permission, may derive these benefits (e.g., hope) from the child's trial enrollment.

11.3.4 Randomized Clinical Trials and the Challenge of Equipoise

Randomized controlled trials (RCTs) compare the efficacy of two treatments by randomly assigning participants to the treatment arms. It would not be ethically justifiable to subject study participants to less efficacious treatment if one of the options were known to be superior. *Equipoise*—the 'state of professional uncertainty about [the] relative therapeutic merits' of the two treatments being studied—is an important justification for the conduct of RCTs (Miller and Joffe 2011); however, there are many criticisms and challenges to the concept.

First, while this theoretic 'state of uncertainty' is conceptually appealing, oncologists may have a preference for a novel treatment, given the level of evidence of efficacy required for an investigational therapy to make it to a RCT. Promising preliminary data may be sufficient to move expert opinion even before validation in a RCT. Secondly, most patients expect their physician to recommend the best therapeutic option based on their experience, knowledge of existing data, and of the patient. Equipoise requires that patients accept having their treatment chosen randomly, without their physician's input. Thirdly, equipoise ignores the fact that patients may have preferences between treatment arms, even if the oncology community does not. Lastly, even if equipoise exists at the onset of a study, there may reach a point when study data favors one treatment over the other. At this point, equipoise is disturbed, and continuing the trial—if justified by equipoise alone—would be considered unethical. This last concern led to the formation of Data Safety Monitoring Committees, whose role is to evaluate interim data and determine whether to halt a trial. When interim data are equivocal, equipoise remains intact, and a trial continues until completion or until another interim analysis triggers early stopping rules.

11.3.5 Timely Access to Novel Therapies

The clinical research pathway to drug approval is a formal and highly regulated path to enabling access to new medical therapies that are safe and efficacious. Testing new therapies for children with cancer takes far longer than for adults, delaying approval and access to potentially efficacious treatments (Neel et al. 2019). Of the 126 drugs approved by the FDA for oncology indications from 1997 to 2017, only 6 had a pediatric indication with the approval. The fact that childhood cancer is rare, combined with the additional regulations on pediatric research, prompted the passage of laws to promote the development and approval of drugs for children, including the Best Pharmaceuticals for Children Act (US Food and Drug Administration 2002), Pediatric Research Equity Act (United States Congress 2003), and Research to Accelerate Cures and Equity for Children Act (Schmidt 2017). Many hope these measures, along with age-agnostic development of targeted drugs (Drilon et al. 2018), will help expedite the delivery of new therapies to children with cancer (Shulman and DuBois 2019).

11.3.6 'Right to Try' and Compassionate Access

Historically, access to unapproved and unproven therapies has been restricted to 'compassionate use' or 'expanded access' programs, which are intended to provide the rare patient who cannot participate in a clinical trial with a mechanism to seek a novel therapy that *may* benefit her (US Food and Drug Administration (FDA)). In 2018, the US congress passed a controversial 'right-to-try' law that attempts to expand and streamline access to non-FDA-approved therapies (United States Congress 2018). Supporters argue that patients' right to self-determination and self-preservation means they ought to be able to choose to accept the unknown side effects of investigational drugs for the chance the drug will benefit them. But in the USA, physicians are not required to give patients anything they want, and courts have found that 'there is no fundamental right… to experimental drugs for the terminally ill' (Abigail Alliance For Better Access v Von Eschenbach 2007).

Right-to-try opponents worry that terminally ill patients' desperation makes them vulnerable and in need protection, a fact recognized by the US Congress when drafting the Pure Food and Drug Act (Piel 2016). Children with incurable cancer are particularly vulnerable, as there is little parents wouldn't do for any perceived chance to save their child's life. And yet harms may occur from untested drugs, or from the consequences of such laws. Some state right-to-try laws prevent patients from obtaining hospice care or home health care for a period of time after receiving the experimental treatment (Kearns and Bateman-House 2017). For children with progressive cancer, these services are critical to alleviate suffering, and help achieve high-quality end-of-life care. A final concern is that expansion of right-to-try laws may undermine the existing research enterprise and impede approval of medications. At the time of this writing, it is too soon to know what consequences, intended or otherwise, right-to-try legislation will have on pediatric cancer patients.

11.4 Additional Ethical Issues in Pediatric Oncology Care

11.4.1 Drug Shortages

There are between 170 and 200 drug shortages each year in the USA, and these shortages are becoming more frequent and lasting longer (Council on Science and Public Health 2018). Over the past decade, there have been severe shortages in vasopressors, intravenous fluids, neurologic agents, chemotherapeutics, among others. Unfortunately, children with cancer are not immune to the effects of such shortages. One study found that 50% of pediatric patient-subjects enrolled on a clinical trial were impacted by drug shortages, and two-thirds had their clinical care impacted by shortages (Salazar et al. 2015). In recent years, the USA has experienced shortages in chemotherapeutics commonly used in pediatric oncology, including vincristine, methotrexate, etoposide, daunorubicin, and asparaginase. While an equivalent alternative drug may be available, replacing medications of proven efficacy with alternatives can have dire consequences. When the shortage of mechlorethamine necessitated its replacement with cyclophosphamide for children with Hodgkin lymphoma, this substitution resulted in a significant decrement in event-free survival for children with this otherwise highly curable cancer (Metzger et al. 2012).

Drug shortages are not unique to pediatric oncology, but they are particularly impactful in this field given the central role of generic injectable medications (those most commonly affected by drug shortages) in the treatment of children with cancer. It is best to avoid making rationing/allocation decisions being made by the treating clinician at the patient bedside, as this presents a conflict of interest for the clinician, who must both consider how to allocate the drug in scarce supply and simultaneously vouch for the best interests of their patient. It is advisable to have procedures in place for managing drug shortages and to minimize conflicts of interest and maintain public trust, and the allocation strategies should be transparent to physicians, patients/families and to the general public and should involve just application of allocation principles (Decamp et al. 2014; Drug Shortages Task Force 2019).

11.4.2 Requests to Withhold a Cancer Diagnosis

Parents occasionally ask that the oncology team hide a cancer diagnosis from a child. Clinicians who encounter this request should explore the parents' motivation for the request. Some families come from cultures that believe in withholding cancer diagnoses from all patients, including autonomous adults. More commonly, however, parents want to protect their child, and worry about causing additional distress or anxiety at a time when they are already sick and undergoing medical procedures and treatments. Despite this natural parental desire to protect their child, it is important to be transparent with the child about their diagnosis. Disclosing this

information exemplifies respect for the child's emerging autonomy, so that she understands why she is sick and the nature of the tests and treatments she will undergo. Often it is appropriate to disclose a cancer diagnosis to the parents and child at the same time, particular when the patient is an adolescent. Other times, the cancer diagnosis may be disclosed to the parents separately, and the oncologist should seek the parents' input into the best way to inform the child. Soliciting this information recognizes and respects parents' unique understanding of their child's psychological needs (Mack and Grier 2004) and ensures that disclosure is done in age and developmentally appropriate language, and with appropriate social and psychological support surrounding the child. Most children take the news of a cancer diagnosis better than parents fear, as the word 'cancer' is less likely to trigger the same negative stigma that it does for adults.

The second, practical reason not to honor parents' request for non-disclosure is that it will be impossible to hide this information from a child who is likely to visit a 'cancer center' for appointments, interact with providers whose badges or clothing refer to cancer, receive chemotherapy, and meet or see other children with alopecia due to chemotherapy. An observant child is likely to put the pieces together and deduce that she has cancer. Additionally, even if an oncologist agreed to withhold this information from a child, the child will interact with dozens of healthcare providers each hospital day or visit to the clinic. It would be impractical to expect everyone else not to use the word 'cancer,' and accidental disclosure is inevitable. Withholding this information may have negative consequences for a child, including fear or anxiety knowing that their parents and doctor are keeping a secret from them. Some may interpret this to mean that the situation is worse than it really is; for example, a child may think she is dying when in fact she has a highly curable cancer. Other children will have difficulty trusting their parents and physicians, with negative consequences on their cancer treatment experience or adherence (Mack et al. 2018; Lin et al. 2019).

11.5 Ethical Issues at or Near the End of Life

Many ethical challenges arising in the care of children with cancer at or near the end of life are similar to those encountered in the care of adults; however given the unique nature of pediatric bioethics, some features of pediatric end-of-life (EOL) care are particularly noteworthy.

11.5.1 Requests not to Tell a Child They Are Dying

When a child is not expected to survive, parents may wish to not tell their child that they are dying. This is challenging for all involved, and similar principles and considerations apply as above, when a parent wishes to not tell a child about their cancer diagnosis. In this case, however, the stakes are even greater and most would

agree that the telling the truth to the child is imperative. Doing so can support the dying child's burgeoning autonomy, allowing them to participate in their EOL care plans and express what they would like to do with their remaining time. The level of involvement will depend on the child's age, developmental status, and clinical scenario, but most minors express a strong desire to be told of their prognosis and expected treatment course (Mack et al. 2018).

Openly speaking about prognosis and death in both children and adults with cancer is a relatively recent phenomenon. As recently as 1961, 90% of physicians reported not telling patients that they had cancer (Oken 1961). Today, nearly all oncologists believe they have an 'ethical imperative' to disclose a cancer diagnosis (Daugherty and Hlubocky 2008), yet it is not universal. Complicating these prognostic discussions are cultural differences in how this truth-telling about prognosis is perceived (Rosenberg et al. 2017). Whether to tell a child about their prognosis when a parent requests to withhold this information, represents a unique conflict between the rights of the child and the authority of the parent. With limited data on how to navigate this dilemma, oncologists should explore and thoughtfully address parents' reasons for wishing to withhold this information and explore ways to deliver the truth that are acceptable to all involved.

11.5.2 Refusal of Life-Sustaining Therapies

While typically the goal of treatment is to prolong the child's life and/or enhance their quality of life, sometimes the decision is made to forgo life-sustaining therapies (LST) when a child appears to be nearing the end of their life. Adults have the legal and ethical right to refuse medical treatment, and in most circumstances, parents have the authority to refuse treatment on behalf of their minor children, including all types of EOL care, be it palliative chemotherapy, mechanical ventilatory support, or other therapies (Katz et al. 2016). In 1983, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research developed a framework for considering both the perspectives of the medical team and the preferences of the parents when faced with a decision whether to continue or forgo a particular LST for a child (President's Commission 1983). Communication and collaboration among clinicians, parents, and the patient are of particular importance in such scenarios, and legal and/or ethics support may be advisable, particularly if there is disagreement about the decision (Weise et al. 2017).

Pediatric oncologists occasionally encounter the challenging question: can parents refuse all therapies in all scenarios for their children at or near the end of life? Factors such as the child's prognosis, risks and benefits of treatment, quality of life, and patient/family preferences should be considered. Decisional frameworks discussed above—such as the *Best Interest Standard*, *Harm Principle, Zone of Parental Discretion*, and *Constrained Parental Autonomy*—can aid clinicians in deciding whether to attempt to override refusal of EOL therapies, or to respect the refusal. The clinical and ethical considerations for a minor child at the end of life

are quite different than those at other points in the care continuum. For example, while a child with incurable cancer may derive some measurable benefit from palliative, oral chemotherapy, the harms from legal involvement and conflict would almost certainly exceed those benefits if the child's parents did not wish to provide such therapy. As a result, parents should generally be given wide discretion regarding EOL treatment decisions, with attempts to override these decisions made only in unique (and rare) circumstances.

11.5.3 Withholding and Withdrawing Life-Sustaining Therapies

Although withholding and withdrawing medical interventions are generally considered to be ethically equivalent, many clinicians report these to be psychologically quite distinct. It is often stated that it feels more difficult to withdraw a LST (e.g., mechanical ventilation) than to choose not to initiate such a therapy. There are further differences in how it feels to withdraw different types of medical therapies. For example, it is less controversial to withdraw intensive, invasive, or burdensome interventions (e.g., surgery, chemotherapy, mechanical ventilation), sometimes referred to as 'extraordinary' measures. But the same cannot always be said for more 'ordinary' measures such as artificial nutrition and hydration (via intravenous fluids, nasogastric feeds, etc.). While most agree that it is ethically permissible to withdraw life-sustaining artificial hydration and/or fluids for a child at the end of life, many experts recommend consultation with local experts from ethics, legal, and/or other support services given the complexity of and emotional response to such withdrawals (Diekema and Botkin 2009).

11.5.4 Palliative Care and Palliative Sedation

The field of pediatric palliative care has grown substantially since early work identified that children who die of cancer often experience significant symptom burden as they approach the end of life (Wolfe et al. 2000). Some also experience existential distress about their pending death. Given the great improvements in supportive care and palliative care in the inpatient and outpatient settings, most symptoms can be controlled for children dying of cancer. Rarely, symptoms cannot be adequately controlled despite maximal supportive therapies, and palliative sedation is an important consideration for such uncommon scenarios. The purpose of palliative sedation is to alleviate the dying child's symptoms, while acknowledging that doing so may unintentionally hasten the child's death (American Academy of Pediatrics 2000). The doctrine of double effect (DDE), a guiding principle first developed by Catholic clerics in the Middle Ages, provides justification for palliative sedation in children and adults (Quill et al. 1997; McIntyre 2018). According to the DDE, a given intervention is ethically permissible as long as it meets each of four conditions:

1 The act itself is morally neutral or good. In the case of palliative sedation, the act is the administration of a medication such as morphine.
2 The provider intends for the 'good' effect of this intervention but not for a possible 'bad' effect (though the bad effect may be foreseen). In this case, the good (intended) effect is relief of the child's pain/suffering and the bad (unintended) effect is hastening of the child's death.
3 The bad effect cannot be the means by which the good affect is achieved. In palliative sedation, pain relief is due to the primary effect of the morphine, not to death itself (contrast this with administration of a very large dose of intravenous potassium chloride: Potassium has no pain-relieving properties, the child's pain relief would result solely from her death).
4 Finally, the benefits of the good effect must outweigh the harms of the bad effect. While this assessment is subjective and may be debated, given the degree of uncontrollable pain that would warrant consideration of palliative sedation, relief of pain and suffering outweighs even the possibility of hastened death.

In addition to the ethical support the DDE provides for the practice of palliative sedation, this practice also has legal support. In 1997, the US Supreme Court invoked the DDE in stating that it is legal to provide medication to alleviate suffering to a dying patient 'even to the point of causing unconsciousness and hastening death' (Vacco v Quill 1997). There are ethical and legal distinctions, however, between palliative sedation, physician aid in dying (sometimes referred to as medical aid in dying, physician-assisted suicide, etc.) and euthanasia. A full review of these practices is outside of the scope of this chapter, but at the time of writing, neither are legal for minor children in the USA, though they are legal for children in Switzerland, the Netherlands (for children over age 12) and Belgium (for children with terminal illnesses). These legal standards may change, so clinicians should consult with both ethics and legal consultants regarding such practices in their home country.

11.6 Ethical Issues in Genetics, Genomics, and Precision Cancer Medicine

Recent advances in genetics, genomics, and personalized medicine have ushered in a new era in medical and pediatric oncology. Paradigm-shifting success with imatinib first highlighted the potential for the use of genomically targeted therapies in cancer. In pediatric oncology, molecular profiling of tumors demonstrates great promise (Mody et al. 2015; Harris et al. 2016; Parsons et al. 2016) and genomically-targeted therapies are rapidly moving from the laboratory to the pediatric oncology clinic (Laetsch et al. 2018; Donadieu et al. 2019). Ongoing worldwide efforts are underway to better understand the genomic landscape of pediatric cancers and identify how to harness genomics to improve care of children with cancer.

With the hope brought by these advances come new ethical considerations. How can pediatric oncologists balance the hope (or, possibly, hype) surrounding genomic technologies with the limitations of the current state of clinical pediatric cancer genomics? How should clinicians communicate with patients and parents about the subtleties in this growing field? It can be difficult to explain nuances like differences between clinical sequencing and research sequencing, differences between germline and somatic alterations, and the uncertainty inherent in much of clinical cancer genomics.

11.6.1 Somatic (Tumor) Sequencing

A great amount of research aims to identify actionable mutations in pediatric cancers, particularly driver mutations. The hope is that identification of a driver mutation will lead to development of a targeted drug, and that this drug might prove more efficacious and less toxic than the non-specific cytotoxic agents presently used to treat pediatric cancers. Numerous studies have performed widescale sequencing of pediatric tumors, including iCat, the GAIN Consortium, BASIC3, Genomes4Kids, MOSCATO-01, the LEAP Consortium, and Pediatric MATCH. Despite significant hope behind these efforts, under 20% of pediatric patients appear to experience direct benefit from receiving targeted therapy, and even fewer demonstrate an improvement in overall survival (Mody et al. 2015; Chang et al. 2016; Harris et al. 2016; Parsons et al. 2016; Harttrampf et al. 2017).

The hopes of young adults and parents of children with cancer outpace the present state of this technology, as most hope genomic sequencing will provide more treatment options and/or a greater chance of cure (Marron et al. 2016). As the lines between clinical and research testing become blurred—tumor sequencing initially performed only through a research study is now often sent as a clinical test (Marron et al. 2019)—pediatric oncologists face the challenge of communicating these nuances, and managing patient/parent hopes for tumor sequencing with the realities of what it can provide. This communication is particularly challenging given that genomics depends on statistical probabilities, heritability, and other complex concepts. At present, these complexities mean that many pediatric oncologists lack confidence in their ability to incorporate tumor genomic findings into their practice and/or counsel patients and parents about genomic findings (Cohen et al. 2016).

11.6.2 Germline Sequencing

Approximately 10–15% of children diagnosed with cancer have an underlying cancer predisposition syndrome (Zhang et al. 2015; Chang et al. 2016; Harris et al. 2016). Most patients and parents in the pediatric oncology setting want this information, even if no screening or prevention is available (Marron et al. 2016). These findings mirror data from outside of pediatric oncology (Gray et al. 2012).

Despite the importance of identifying such syndromes, and desire for this information, there are numerous ethical challenges inherent in germline sequencing of children with cancer.

Notably, not all patients and families want data about cancer risk (Gray et al. 2012; Marron et al. 2016), and anecdotally, some report this information adds worry and stress at a time when they want to focus their energy on the patient with cancer. It remains controversial whether learning information about an underlying cancer predisposition should be mandated as part of tumor genomic sequencing. Further, some have raised the question of whether the minor child should have a say in whether or not to learn about their risk of cancer and/or other disorders. This so-called right to not know is closely related to arguments made regarding a child's right to an open future (Feinberg 1980). In this line of thinking, children's future prospects should not be limited whenever possible, so that they can make informed choices for themselves at a future date, once they have the capacity to do so. Applied to this type of testing, the debate is whether cancer predisposition testing should be delayed until children reach the age of majority (age 18 in the USA) so that they can make the decision to undergo the testing for themselves. The argument in favor of delaying testing is stronger if it is expected that the child will not benefit from the testing until they are an adult. Testing for *BRCA1* is one example of such an ethical quandary, since cancers linked to *BRCA1* mutations do not present in most patients until adulthood. Many adults who are known to be at risk of inheriting BRCA1 mutations choose not to undergo diagnostic testing, raising the concern that some children who undergo testing without a say in the decision may grow to regret the knowledge.

11.6.3 Incidental Findings

Incidental findings are results discovered as part of a genomic test but not the intended or expected result of that test. While incidental findings are not unique to genomics—'incidentalomas' are sometimes found on imaging studies such as MRI or CT—they are more frequent, more controversial, and potentially more ethically treacherous in genomic medicine. In 2016, the American College of Medical Genetics and Genomics (ACMG) published a list of 56 germline genomic alterations it felt should always be reported when found through clinical genomic sequencing, regardless of the clinical indication (Green et al. 2013). The ACMG argued that the value of knowledge about these alterations outweighs any potential drawbacks, even if the individual tested is a child and/or the patient does not desire these results. Many took issue with these recommendations, particularly regarding genomic testing for children (Burke et al. 2013), leading the ACMG to slightly change its recommendations (ACMG Board of Directors 2015). Because many tumor sequencing methodologies include germline sequencing, this controversy is of great relevance to pediatric oncology.

Incidental findings also raise concerns about genetic discrimination. Legal protections against such discrimination vary greatly by jurisdiction, though in the

USA, the Genetic Information Nondiscrimination Act of 2008 provides protection against discrimination for health insurance and employment based on genetic findings (United States Congress 2008). This bill does not, however, prevent discrimination in other forms of insurance (e.g., life, disability, long-term care) or for some subgroups (e.g., government employees). Though negative effects on insurance and employment are a common concern about genetic testing among the public (Gollust et al. 2012), these concerns appear to be less prevalent in the pediatric oncology population (Marron et al. 2016). To date, it is reassuring that few reports of such discrimination have been uncovered (Hall and Rich 2000).

11.6.4 Additional Ethical Challenges in Pediatric Cancer Genomics

Because genomics is rapidly being integrated into standard clinical practice in pediatric oncology, the consequences of this paradigm shift are only beginning to be fully understood, and other areas of ethical complexity are emerging.

11.6.4.1 Big Data in Cancer Genomics

Because of the vast amounts and specificity of genomic data, there are concerns about privacy and confidentiality regarding collection and publication of this so-called big data. When a patient's laboratory results or clinical data are gathered in clinical or research contexts, there is a reasonable assurance that these data will remain de-identified, and the patient's or subject's identity will remain confidential. Because genomic data are more detailed and more identifiable, confidentiality is less certain. Studies of the genetic basis of diabetes in Havasupai Native Americans demonstrate the hazard of big data, when, given the small population studied and specificity of genomic data, it was discovered that published genomic data could be linked to particular individuals (Drabiak-Syed 2010). Without adequate protections, similar problems could arise with genomic data in pediatric oncology. That said, these concerns must be balanced with the importance of sharing these data to maximize its utility and the efficiency of clinical investigation. There is growing recognition of the importance of collaborative research and open access to genomic repositories, with efforts underway through the National Cancer Institute's Genomic Data Commons, CBioPortal, and other similar resources, to pool data and optimize investments of patient-subjects and society at large.

11.6.4.2 Direct-To-Consumer Genetic Testing

Developments in genomic technologies have been commercialized through direct-to-consumer (DTC) genetic testing, and numerous companies offer and advertise such testing. Many of the ethical challenges described above are augmented in their magnitude due to the absence of clinician involvement with such testing. If a child with cancer has a cancer predisposition syndrome identified on a sequencing panel performed at their oncologist's office, the physician, genetic counselor, and other trained professional are available to help interpret the results

and discuss their clinical implications. This is not available with DTC testing, and many worry about misinterpretation of results and inadequate support for patients and families. Further, while most companies report not allowing minor children to get sequenced, enforcement of such policies is difficult. There are additional concerns about the accuracy/reliability of this testing (Covolo et al. 2015; Gill et al. 2018) and the growing recognition that data from such testing are sold to large tech conglomerates, pharmaceutical companies, governments, and law enforcement agencies (Martin 2018). Despite concerns, supporters of DTC argue that there is a 'right to know,' and that testing enables patients and families to take ownership over their health. Because DTC genetic testing will continue to be part of the clinical landscape for the foreseeable future, further work is needed to understand the ethical challenges it presents to pediatric oncology and more broadly.

11.6.4.3 Future Advances

Just thirty years after the Human Genome Project began, genomic science has become a core feature of pediatric oncology practice. Progress in this area continues at a rapid pace, and gene therapy, CRISPR-Cas9, proteomics, epigenomics, and immunotherapy represent but a small portion of the genetic/genomic advances likely to impact the care of children with cancer in coming years. While it is exciting to consider the role of future advances in pediatric oncology, it is paramount that we consider the potential ethical hazards and unintended consequences of these technologies. Discussions about germline gene editing in the wake of the CCR5 scandal can serve as a guide for how scientific advancement can be balanced with conscientious discourse (Regalado 2018), with the goal of ensuring the safe and effective application of these advances to patients.

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