Ethical Issues in Pediatric Hematology/ Oncology

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Preface

Pediatric hematology and oncology is plagued with ethical dilemmas from the time of diagnosis through end-of-life care. Although adult and pediatric hematology/oncology share the same core ethical principles of respect, beneficence, nonmaleficence, and justice, pediatrics contains its own unique challenges. Our goals in presenting this book are to provide a uniquely targeted overview of the principles of ethical pediatric decision-making, the unique difficulties in enrolling children as research subjects, the common ethical conundrums involved in providing end-of-life care, and the general moralities of pediatric hematology/oncology practice.

Pediatric hematologists and oncologists must understand these issues and face these challenges in order to provide ethically sound clinical care. Children's decision-making capacity evolves along a developmental continuum, while minors are not able to provide legally effective informed consent. Thus, in a model of shared decision-making, the physician provides information to the caregiver and the child, the caregiver provides permission to treat the child, and the child, to the extent their capacity permits, gives assent. However, considerable controversy remains about how to assess a child's understanding of the information provided, how seriously dissent should be taken, and when the child's wishes should take precedence over those of the caregivers.

Furthermore, in contrast to adults, children with cancer and blood disorders are often enrolled onto clinical trials and are nearly universally treated with protocol-based therapy. Despite the importance of conducting this research to improve patient outcomes, there remain significant ethical challenges that are unique to the pediatric population. As with clinical treatment, permission and assent for research participation require complex shared decision-making. Nontherapeutic interventions, such as research-related blood draws, or research with uncertain direct benefit, such as early phase clinical trials, may further complicate the ethical challenges in this vulnerable population.

Every pediatric hematologist and oncologist is confronted with these frequent challenges in daily practice and clinical research. We aim in this textbook to highlight the interaction between ethical principles and clinical and research issues in a systematic manner that will enhance providers' understanding of this interaction

and offer guidance to help untangle difficult problems and suggest a path forward that is both ethical and practical. We hope to expand and strengthen providers' knowledge and experience in pediatric hematology/oncology ethical issues, positioning providers to be a beneficial resource to other faculty, staff, patients, and families within their institution. We include the multidisciplinary approach to sound ethical practices that is necessary to effectively care for these patients and their families.

We would like to thank the many colleagues and collaborators who have increased our understanding of ethical issues in clinical care and research. Most importantly, we acknowledge and thank the countless patients and families without whom this text would not exist, and who inspire and teach us every day.

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Part I
Introduction to Ethics in Pediatrics

Chapter 1
Ethics: A Historical Perspective

Tessy A. Thomas and Perry Ann Reed

Since the beginning of time, human civilization has been influenced by culture, religion, science, politics, and philosophy. In the quest for reason, ancient Greek society encouraged the pursuit of higher knowledge to understand the complex relationships and behaviors of humans to self, others, God, and/or gods. The Greek physician and teacher, Hippocrates of Kos (460–370 B.C.), is universally regarded by historians to be the "father of Western medicine" [1]. Though not much is specifically known about Hippocrates' life, his philosophical and clinical tenets have been widely accepted as the foundation for the way Western medicine is practiced today. Hippocrates advocated for examining the patient, observing for clinical signs, and making rational conclusions that guide both diagnosis and treatment of the patient [1, 2]. Over 60 essays and texts are attributed to him and comprise what is called the *Hippocratic Corpus* [1]. The literary source of the *Hippocratic Corpus* writings remains debated, with some arguing that many of the works were written and published after Hippocrates' lifetime [2]. Within this collection of works, Hippocrates is credited with being the first to conceptualize medicine as a profession; in so doing, he identified the unique relationship physicians have with the patient, other physicians, and society at large. What is documented includes not only specific observations on various clinical diseases but also perspectives and reflections on the conduct and duties of the physician [2]. The famous maxim "First, do no harm" (a phrase translated into Latin as *Primum non nocere*) is often mistakenly believed to be written by Hippocrates himself [1–3]. The actual origin of this renowned phrase remains unknown [3].

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Nevertheless, the closest text highlighting this moral principle, authored by Hippocrates, advises physicians: "As to diseases, make a habit of two things—to help, or at least to do no harm" [2, 3].

The most famous work included in the Hippocratic Corpus is the *Hippocratic Oath.* Though historians argue that the oath was probably written hundreds of years after Hippocrates time, it still remains a classical declaration of the standard moral code of conduct for medical physicians [2, 3]. The basic tenets of the oath are integrated within its four parts: (1) preamble, the invocation of gods as witnesses for the oath; (2) covenant, the declaration of one's duties to the profession; (3) code, the statement of one's duties to patients; and (4) peroration, which affirms one's status after abiding by the oath [3, 4]. Additionally, evoked within the oath is the moral vision for physicians: (1) of beneficence (to do good) to patients, (2) to maintain confidentiality, (3) to teach the art of medicine, (4) not to assist suicide, and (5) to know one's limitations [3, 4]. This oath is the first evidence of any ethical and legal medical writings regarding euthanasia, patient confidentiality, abortion, code of practice as an entity, physician competence, individual responsibilities, clinical ability, and reasonable judgment in the best interest of patients [5, 6].

Historically, the first recorded administration of the Hippocratic Oath in a medical school setting was at the University of Wittenberg in Germany in 1508, and the oath did not become a standard part of a formal medical school graduation until 1804, when it was incorporated into the commencement ceremony at Montpellier, France [7]. The Hippocratic Oath continues to be pledged by medical students 2,500 years later, but the classical account has been modernized into different versions to reflect changing values and practices within an evolving complex society.

The Hippocratic Oath

I swear by Apollo Physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath and this covenant:

- To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art—if they desire to learn it—without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but no one else.

I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.

I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.

Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.

What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself, holding such things shameful to be spoken about.

If I fulfill this oath and do not violate it, may it be granted to me to enjoy life and art, being honored with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.

Translation from Greek by Ludwig Edelstein [3].

Hippocrates was not the only ancient Greek thinker of his time to philosophize about morals and values. Socrates (469–399 B.C.), Plato (427–347 B.C.), and Aristotle (384–322 B.C.) are considered the leading founders of the science of virtue-based ethics [8]. Aristotle was the first to use and then apply the term *ethics.* He included this word in the title of his works: *Nicomachean Ethics* and the *Eudemian Ethics* [9, 10]. *Ethics originated from* Greek and later Latin contexts of the word *ethos*, which denotes moral philosophy and appeal to moral character or custom [11]. Socrates, Plato, and Aristotle elucidated the concept of moral virtue and defined social versus individual good and which principles should govern a person's behavior, character, or activity [8]. Aristotle argued in Book II of the *Nicomachean Ethics* that the purpose of ethics is not to merely know what is good but to become good. Aristotle envisioned a virtuous moral agent, such as a physician, as someone who has ideal character traits [8, 12]. He believed a virtue was a characteristic between two opposing vices, "the mean by reference to two vices: the one of excess and the other of deficiency" [8, 13]. For example, "Courage—lies between foolhardiness and cowardice. Compassion—lies between callousness and indulgence" [13]. The ancient Greek philosophers did not explicitly provide an all-inclusive list of ideal virtues for which someone to strive. However, in Book IV of the *Republic*, Plato discussed four virtues that hold both the ideal state and the ideal moral agent together, prudence, justice, temperance, and courage, which are now considered the cardinal virtues [12, 14, 15]. These virtues are also often translated in contemporary times to mean wisdom, fairness, restraint, and fortitude, respectively [12].

Virtue-based ethics, defining the kind of moral agent/person one should be, dominated Eastern and Western ethics tradition up until the early eighteenth century [14]. In the late 1700s, two British physicians—John Gregory and Thomas Percival—advocated for surgeons and medical physicians to be considered under one profession. As one profession, physicians and surgeons could advocate and

uphold common goals. Gregory and Percival identified three shared moral and scientific obligations:

> First, physicians and surgeons should commit to becoming and remaining scientifically and clinically competent, by practicing, doing research, and teaching on the basis of Baconian "experience"-based medicine. Second, physicians and surgeons should protect and promote the patient's health-related interests as their primary concern and keep their economic and other forms of self-interest systematically secondary. Finally, physicians and surgeons should maintain and strengthen medicine as a public trust that exists for the benefit of future patients and not as a merchant guild that exists to protect the economic, political, and social interests of its privileged members [16].

In 1794, Percival was the first person to introduce the term "medical ethics." In his book entitled *Medical Ethics*, he centered on the behavior of doctors with each other and on the professionalism of the vocation within the context of society at large [15]. This early code of interactive behavior among clinicians was a key step in differentiating between the professional and personal belief systems that guided physician ethics. While Percival's code was not well received in his home country of Great Britain, it was fundamental to the creation of the first American Medical Association (AMA) Code of Ethics in 1847 [15].

During the eighteenth and nineteenth century, two main universal theories—*deontology and utilitarianism*—began to framework the discourse of ethical reasoning when faced with any ethical conflict. These theories focused on identifying the one rule of right moral action. Immanuel Kant is the philosopher credited with being the father of deontology (*deon* meaning duty or obligation) [15]. Deontology focuses on the moral dimensions of an action and not merely on the consequences. The decisions of deontology may be appropriate for an individual but not necessarily for the greater good of society. For Kant, understanding the motivations for action or inaction was of primary concern. Through his *Categorical Imperative*, Kant argued that regardless of the consequences (ends), actions should be guided by moral obligation to duties. Commonly phrased, this means "the end can never justify the means" [15]. Therefore, harm is always unacceptable irrespective of its consequences [17]. The physician-patient relationship is by nature deontological since the medical profession's oaths and traditions place duty to patient first with the primary goal of strengthening the fiduciary relationship between physician and patient [17, 18]. When this deontological practice is broken, the risk for medical negligence arises [17]. Similarly, the utilitarian philosophy also attempted to universalize ethical reasoning when faced with any ethical conflict. Instead of focusing on the motivations of actions and moral obligation to duties, however, utilitarianism claims that an action is right if it maximizes the greatest possible good for the larger whole and not just the individual [18–19]. English philosophers Jeremy Bentham and John Stuart Mill theorized that consequences of an action justified the means of the action [18–19]. Thus, utilitarianism is a form of consequentialism. The right or wrongness of an action is solely dependent upon the ends. Thus, it may be said that in utilitarianism, "the ends do justify the means" [17–19]. Within medicine, an example of utilitarianism is allocation and rationing of resources for all patients—i.e., short-

ened length of appointment times—when the resources (physicians) are finite and the patients in need are many [18]. One criticism of utilitarianism is that what creates the greatest happiness for the greatest number of people is not necessarily morally right [17–19].

In 1927, the term "bioethics" was coined by Fritz Jahr to mean the ethics of medical and biological research. Jahr proposed a "bioethical imperative" which "extended Kant's moral imperative to all forms of life" [20]. Current scholars have broadened Jahr's initial conception of bioethics to encompass the further study of its intersections with medical, legal, research, technological, political, social, religious, cultural, philosophical, economical, and historical perspectives. The true birthplace of bioethics as a field is hard to pinpoint, however. Prominent bioethicist Arthur Caplan, PhD, states that in his view, bioethics "began in response to scandal and uncertainty" [21]. Some argue that the 1932 Tuskegee Study, which continued until the 1970s—involving the study of untreated poor rural black men with syphilis—was the first major medical scandal [21]. Other scholars attribute bioethics' origin to the end of WWII when the Nuremberg war tribunals were conducted [21]. The trials included judgments against Nazi physicians who participated in the tragic war crimes of the Holocaust. In 1947, the Nuremberg Code, a set of judicial documents that emerged from the trials, set forth basic principles for ethical medical human experimentation [15]. In 1948, the Declaration of Geneva further outlined physicians' ethical duties regarding clinical research [21]. Modified from the Nuremberg Code, the World Medical Association in 1964 issued the Declaration of Helsinki, which is now considered the keystone for ethical principles regarding human medical research and protection of human rights adopted by the medical community at large [15].

Other scholars suggest that bioethics as a field fully emerged in the 1960s when advancements in life-sustaining technologies and allocation of limited resources such as heart-lung machines, kidney dialysis machines, ventilators, organ transplantation surgeries, and dedicated intensive care units became possible [15, 21]. The interface of technology, public policy, research, clinical medicine, and societal values thus demanded scholarly discourse. The common language for medical ethics and bioethics discourse has always been rooted in philosophy. As philosophers, theologians, lawyers, physicians, scientists, and lay members of society negotiated medical ethical dilemmas and challenges, the need for practical guidance and commonly shared ethical frameworks evolved. Additionally, since people are rarely pure theorists, American philosophers Tom Beauchamp, PhD, and James Childress, PhD, advocated in the late 1970s for a pragmatic principle-based approach (principlism) to moral reasoning and reflection. In their updated book, *Principles of Biomedical Ethics*, Beauchamp and Childress list respect for autonomy (self-determination), beneficence (doing good), non-maleficence (avoiding harm), and justice (fair distribution) as the four main principles of bioethics and the foundations for ethical assessments and evaluations for current-day ethical dilemmas [22]. It is important to note that the four principles are non-hierarchical; nevertheless, it is crucial to consider each principle and determine which one may carry more weight when reasoning through a particular situation.

Respect for Autonomy

Autonomy stems from its Greek definition to mean "self-rule" and "self-determination" [22]. The principle of autonomy assumes that an individual is free from the control of others and has cognitive capacity to make decisions for him- or herself. This self-rule applies to body and mind. Respect for the principle of autonomy refers to healthcare providers having a duty to protect the patient's ability to make informed decisions about care and to honor decisions made by the patient or the patient's representative. It is the principle supporting the practice of the tort doctrine of informed consent. Key considerations associated with informed consent include legal competency to give consent, ability to apply free power of choice, and adequate understanding of risks and benefits of treatment options.

Informed consent requires that the patient clearly understands the decision he or she is making and the potential risks and benefits of the decision. A patient who does not demonstrate the ability to understand the issue may be unable to exercise autonomy, and a substitute decision-maker may need to be identified. The practical reality for healthcare professionals is that some patients make decisions that contradict the judgment of the physician. For example, patients of free will and decision-making capacity may elect to leave the hospital against medical advice. Nonetheless, physicians are obliged to create the necessary conditions to promote autonomous choice. Physicians then educate and counsel patients when their choices seem harmful to their overall well-being. In addition, respect for autonomy, according to Beauchamp and Childress, includes respect for confidentiality and privacy. In essence, the respect for autonomy also extends to the privacy of information regarding a person's identity, family, health status, and medical treatments. When a person chooses to disclose some of his personal private information, he expects that what is said and done will be kept confidential [23].

Beneficence and Non-maleficence

Beneficence is the principle that healthcare professionals have a duty to (1) do good, (2) act in the best interest of their patient, and (3) act in the best interest of the society overall. A physician is obliged by the principle of beneficence to provide and promote the highest standard of medical care to his or her patients. Non-maleficence is the negative-obligation-related principle referring to the healthcare professional's intentional duty to (1) do no harm to his patient and (2) do no harm to society overall. Non-maleficence is the overriding principle for any healthcare professional who accepts the responsibility of caring for a patient. The two principles focus on maximizing potential benefit while minimizing harm and risk to the patient. Essentially, the two principles establish the foundation for the risk/benefit analysis [22].

Justice

Justice usually signifies fairness or equality [22]. Considerations regarding justice involve distributing scarce resources, identifying competing needs, evaluating rights and obligations, and avoiding potential conflicts of interest. In bioethics, the ethical principle of justice encompasses concepts such as equal access to healthcare, provision of treatment and resources according to need, fair distribution of healthcare benefits and burdens, good stewardship of organizational and societal resources, and accountability [22]. National Medicaid and Medicare programs were borne out of the application of this principle. Respect for justice also demands that benefits and burdens of research participation be distributed equitably. For example, institutional review boards (IRBs) play a key role in ensuring that research subject selection is equitable.

In 1979, the Belmont Report published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research summarized key ethical principles applicable to research involving people. In accordance with the principles outlined by Beauchamp and Childress, the Belmont Report's three basic principles are (1) respect for persons (autonomy), (2) beneficence, and (3) justice [24]. These principles underscore the practices of informed consent, analysis of risk and benefits, and selecting human research subjects [24]. While many believe informed consent is essential and necessary to ensuring that research is ethical, scholars continue to ask the question, what makes clinical research ethical? [25] Renowned ethicist Ezekiel Emanuel, MD, PhD, and colleagues proposed seven requirements that are both necessary and sufficient to make clinical research ethical. The seven specific requirements for research ethics are outlined in Table 1.1:

Table 1.1 Seven specific requirements for research ethics

Seven specific requirements for research ethics	Definitions
Social value	Value enhancements of health or knowledge must be derived from the research
Scientific validity	The research must be methodologically rigorous
Fair subject selection	Scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits should determine communities selected as study sites and the inclusion criteria for individual subjects
Favorable risk/benefit ratio	Within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits must be enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks
Independent review	Unaffiliated individuals must review the research and approve, amend, or terminate it
Informed consent	Individuals should be informed about the research and provide their voluntary consent
Respect for enrolled subjects	Subjects should have their privacy protected, the opportunity to withdraw, and their Well-being monitored

Table adapted from reference Emanuel et al. [25]

The State of Medical Ethics Today: Practical Applications

The field of bioethics is ever-evolving, reflecting the complex changes within medicine, law, research, technology, and society. How do we then reason the right course of action? There is no absolute algorithm to follow, and a right answer or choice may not always be clear. Should we prioritize the needs of society or the individual? Should we framework decisions applying virtue-based ethics as the Greek philosophers before our time, or employ principlism as suggested by Beauchamp and Childress? It is not uncommon to have well-intentioned and reasonable people differ in their judgments even when considering various known principles and virtues [26]. In the clinical setting, two basic tools are exercised when an ethical issue arises: ethical analysis and argument.

> Ethical analysis requires us to be clear about concepts that we invoke and to use those concepts with a consistent meaning to give reasons for our judgments and behavior based on them. Ethical argument requires us to identify the implications of clear ethical concepts for how we should proceed. Simply listing disconnected ethical considerations does not count as argument. Nor does starting with conclusions and then going in search of supportive ethical considerations. Ethical arguments must use deliberative (evidence-based, rigorous, transparent, and accountable) clinical judgment [26].

Each healthcare organization may have its own paradigm for ethical analysis that adapts to the institutional specific culture, resources, legal precedents, and relevant ethical dilemmas. When faced with an ethical dilemma, consulting with institutional bioethics committees and medical ethicists may provide guidance for reframing the case and performing the subsequent ethical analysis and argument in a structured format. Additionally, referencing major professional and legal policies, oaths, codes, declarations, standards, and appeals may provide the initial framework to ground ethical analysis and initiate discourse to achieve consensus.

Pediatric-Related Ethics

Pediatricians face many ethical challenges that are similar to other specialties in medicine. Broadly, ethical issues relating to professionalism, application of justice to public health needs, use of life-sustaining technologies, and upholding fiduciary responsibilities within the physician-patient relationship are equally shared. However, the field of pediatrics is unique in that the shared decision-making and delivery of healthcare involves the intertwining relationship of three main stakeholders: the clinician, the patient (infant/child/adolescent), and the parents/family members. Therefore, the ethics of everyday pediatric clinical care encounters, the informed consent processes, end-of-life discussions and processes, pediatric research ethics, and pediatric-specific professionalism issues require additional considerations for balancing benefits and burdens, especially related to decision-making and determination of the patient's best interests.

Key controversies that brought attention to the need for understanding pediatric-specific ethical issues include the 1960s Willowbrook, NY, hepatitis experiments on children with intellectual challenges and the 1980s passage of the Baby Doe Law regarding the treatment of neonates and children [15, 21]. Unlike adult-focused bioethics, which highly values the respect for autonomy, pediatric-focused bioethics operates under the ethical belief that the neonatal and pediatric populations need additional protections due to their inherent vulnerable states. As ongoing changes occur in healthcare technologies, legal precedents, and research innovations, pediatric-specific decision-making also continues to evolve. The greater impetus to protect pediatric patients from harm is based on the fact that neonates and children do not have the decision-making capacity and developmental capability to make autonomous choices and decisions for themselves [27]. Thus, the decision-making process in pediatrics involves someone else other than the patient giving consent. The usual legal assumption is that parents have primary decision-making for their child and should be primarily providing medical consent [28, 29]. Parents have an inherent responsibility to protect their children, impart familial values, and foster familial bonds that develop a child's moral character [28]. And unlike adults, children cannot express their autonomy. Therefore, traditionally, a parent is expected to make decisions for his/her child in the child's best interest. Given the complexities of caring for the pediatric patient, three core concepts of pediatric ethics—(1) The Best Interest Standard of a Child, (2) Parental Surrogate Decision-Making, and (3) Informed Consent/Pediatric Assent—may comprise an ethical framework to guide pediatric healthcare professionals with clinical decision-making [29].

Best Interest Standard of a Child

According to the United Nations Rights of the Child Convention held in 1989, the Best Interest Standard of a Child was conceptualized as, "in all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration" [30]. Applying this standard promotes thoughtful risk assessment: maximizing benefit for the child and minimizing burden with the initialization or continuation of any medical interventions and courses of therapy. In 1995, the American Academy of Pediatrics (AAP) first recognized the Best Interest Standard of a Child as a core concept of pediatric ethics that should be prioritized in medical decision-making for children [29, 31]. Both healthcare professionals and parents have "beneficence-principle based prima facie obligations to protect and uphold the health-related interests of the child who is the patient" [29]. Therefore, "a child's health-related interests should be viewed independently of the child's relationship to others" [29]. Scholars have debated what specific explicit and implicit perspectives foster judgments upholding best interest standard given its highly subjective nature. Subsequently, it has been identified that the integration of biological, psychological, and social perspectives should be the primary drivers for

Table 1.2 Rights, needs, and capabilities of a child which should be promoted

Rights, needs, and capabilities of a child which should be promoted	Descriptive analysis content
1. Life	Have the right to a normal length of life
2. Health and healthcare	Have access to healthcare and protection from pain, injury, and illness
3. Basic needs	Be adequately nourished and sheltered
4. Protection from abuse and neglect	Be in a safe environment and protected from exploitation and physical/mental abuse
5. Emotional development	Be able to experience emotions
6. Play and pleasure	Play, rest, and enjoy recreational activities
7. Education and cognitive development	Have a diverse education with the ability to think, learn, imagine, and reason
8. Expression and communication	Develop and express thoughts and feelings
9. Interaction	Interact with and care for others and the world around them; develop consistent caregiver relationships
10. Parental relationship	Be able to interact and know their parents
11. Identity formation	Be protected from discrimination and have a connection to their culture
12. Sense of self	Have a sense of self and self-respect
13. Autonomy	To act intentionally with self-discipline, reflect on the meaning of life, and influence course of life

these judgments [29, 32]. Explicit viewpoints include those of the physicians, parents, and at times, the patients themselves. Influential implicit viewpoints include religion, finances, culture, extended family, and education. Recently, other scholars have advocated for a more precise picture of children's interests to broaden the framework away from a "single" best interest standard. For example, Janet Malek, PhD, proposed a series of 13 major interests of children and specific descriptive content that should guide and promote "best interest of child" clinical judgments. These equal priority rights, needs, and capabilities include the following elements outlined in Table 1.2 adapted from Malek's qualitative literature synthesis of a Best Interest Standard of a Child [33]:

This list proposes core elements that should be considered by healthcare professionals when making clinical judgments about the overall well-being of children. Promotion of this descriptive analysis of the basic rights, needs, and capabilities of a child may decrease the subjective aspects of defining the best interest for the child [33].

Informed Consent Process and Assent in Pediatrics

The current model for the informed consent process originates from ethical and legal theory. The legal aspects have roots in battery and medical malpractice case law [34]. The ethical foundation for the informed consent process is to protect,

promote, and incorporate the patient and/or family in medical decision-making based on the ethical principles of beneficence, justice, and respect for autonomy [34]. Obtaining informed consent or patient assent is not a one-time discrete event, but rather a process that requires ongoing communication, sharing of information, and education exchange with the physician and patient/family [31, 34]. In 1976, the American Academy of Pediatrics Committee on Bioethics first published policy statements regarding medical decision-making in pediatrics. Since that time, the standard of the medical and legal culture within the United States is to obtain informed permission from parents or legal guardians before any medical procedures and therapies are started on pediatric patients. Three different yet mutually linked major obligations that should be included in the informed consent decision-making process encompass the ethical concerns for truth-telling: (1) disclosing information about the nature of the illness, probability of success of proposed diagnostic steps/treatment, and potential risks/benefits/uncertainties with an option of no treatment, (2) assessing the patient's or surrogate's decision-making capacity, and (3) obtaining voluntary agreement with the plans before starting any interventions [34].

Only patients who have appropriate decisional capacity and meet legal requirements can give their informed consent for medical procedures and treatments [34]. The AAP policy statements acknowledge that the doctrine of "informed consent" has only limited *direct* application in pediatrics [31, 34]. Since many pediatric patients are not legally able to provide consent, parents or other surrogate decision-makers provide informed permission for diagnosis and treatment of children and assent of the child is obtained whenever appropriate [29, 31, 34]. Updated in 2016, the AAP policy statement on *Informed Consent in Decision-Making in Pediatric Practice* specifically addresses the following issues: (1) informed consent, (2) right to refuse treatment, (3) proxy consent, (4) parental permission and child assent, and (5) informed consent of adolescents [34]. The revised policy statement continues to endorse that pediatric patients should actively participate in decision-making appropriate with their development and encourages obtaining assent from children as young as 7 years of age to foster the moral growth and development of autonomy [34–38]. As children are increasingly capable of expressing mature judgments and decisions regarding their willingness to accept proposed medical care, they should be increasingly involved in decision-making [29, 31, 34]. The more "adult-like the child's decision-making process is, the greater ethical weight should be given to their preferences" per McCullough et al. [29]. Thus, healthcare professionals have an ethical obligation to advocate for the child's best interests *and* the child's preferences at this stage [29].

When parental surrogate decision-making is made by a person authorized by law for a child who does not have capacity to express their values and preferences and participate in the informed consent process, the ethical norm of the best interest standard alone should guide parental and surrogate decision-making [29]. Four main standards for the surrogate decision-making process in pediatrics have emerged within the literature and are recognized by the AAP Committee on Bioethics to encompass the pediatric patient's overall emotional, medical,

Table 1.3 The four standards and adapted definitions for surrogate decision-making

Best interest standard of surrogate decision-making
The surrogate makes decisions from medically reasonable options presented by physicians which maximize benefits and minimize harms to the patient, at the same time as keeping the holistic view of the patient's biopsychosocial interests a priority [29, 34].
Harm principle
Identify a harm threshold beyond which parental decisions will not be accepted, and outside intervention is necessary to protect the child [29]. Physicians have legal and moral obligations to ensure the child is not in significant risk for serious harm and have the responsibility to contest surrogate decision-making if beneficence of the child is jeopardized [29, 34].
Constrained parental autonomy
As long as the child's basic biopsychosocial needs are being met, parents have the right, though not absolute, to balance the best interests of the child with the family's overall reliable best interest, values, beliefs, and preferences [29, 34].
Shared, family-centered decision-making
A process for pediatric decision-making that values active collaboration among families, patients, and healthcare professionals [29, 34]. Evoking the ethical duties of veracity and fidelity, physicians have the responsibility to share "complete, honest and unbiased information with patient and their families on an ongoing basis and in ways they find useful and affirming" [39].

psychological, and social concerns in conjunction with the child's family goals, values, and religious and cultural beliefs [34]. The four standards and adapted definitions for surrogate decision-making outlined by the AAP are highlighted in Table 1.3:

Past, Present, and Future Pediatric Ethical Challenges and Controversies

Living at the interface of medical uncertainty, life-sustaining technological advances, research endeavors, varying legal/policy declarations, and changing societal values and family compositions requires healthcare professionals to adapt and evolve in response. What emerges during this time is a pervasiveness of ethical quandaries, a complex multitude of *ought* versus *should* inquiries. End-of-life decisions present especially complex pediatric medical ethical issues. In 1975, pediatrician Karen Teel appealed for "a system of advocacy which ensures that a child's rights are observed" [40]. On August 12, 1976, the *New England Journal of Medicine* published a "statement to guide a hospital in the process of decision making regarding the use of cardiopulmonary resuscitation" [41]. In subsequent years, the physician and parental role in decision-making and advocating for the child's right regarding the "code status" and appropriate medical interventions for critically and/or chronically ill pediatric patients became the central point of ethical debates [42]. Navigating end-of-life issues and reframing discussions regarding the appropriate and reasonable ways to care for the dying child or the child with a serious

life-limiting illness became the primary focus of medical ethicists and those who specialized in palliative care medicine [43]. These crucial medical and social paradigm shifts in the late 1970s and early 1980s stimulated the development of pediatric ethics consultation services across hospitals within the United States to support healthcare professionals in managing various clinical and research-based ethical issues within the pediatric population [44].

Communicating the reality about the death and dying process, particularly of and to a child, requires a robust skillset and specific training and continues to be a struggle for many healthcare professionals and parents today [43, 45]. Maximizing the effectiveness of prognostic communication requires "motivation […] and attention to the process of communication, where purpose represents the will and process the ability to communication" [45]. The American Academy of Pediatrics policy "Guidance on Forgoing Life-Sustaining Medical Treatment," updated in 2018, states that despite the prevailing notion that the best interest of the child is usually in favor of sustaining life, "in some circumstances, the balance of benefits and burdens to the child leads to an assessment that forgoing life-sustaining medical treatment is ethically supportable or advisable" [46]. The AAP promotes and advocates for multidisciplinary collaborative decision-making with families and patients in the context of applicable legal frameworks with specific institutional, regional, and national regulations and considerations [46]. The known untoward consequence of poor physician prognostic communication and failure to discuss the active death and dying process with patients and families has been associated with moral distress among various healthcare professionals including pediatric hematology/oncology nursing staff [47, 48]. As a result, experts in both palliative care and medical ethics can help foster a collaborative multidisciplinary approach for a shared decision-making process, improved communication skills, and illuminating the various perspectives of multiple stakeholders involved in the medical care and coordination of a child [43, 44, 46, 47].

Additionally, despite the ethical obligation for physicians to maintain truth-telling as a top priority virtue, some families, based on their cultural or religious values, may request physician nondisclosure of a serious illness to their child in order to limit the child's psychological or emotional distress. This predicament needs to be cautiously managed. Experts advise, "sometimes it is ethically permissible to defer to family values regarding nondisclosure of health information" [49]. To mitigate this conflict, "early setting of expectations and boundaries, as well as ongoing exploration of family and healthcare professional concerns," [49] is warranted. Additionally, given the difficulties and uncertainties with medical prognostication and the need of many families "to do everything possible" and have "more time" with their loved one, a *time-limited therapeutic trial* of medical interventions is sometimes offered. Time-limited trials explicitly set forth a timeframe in which the intervention's success will be judged, with the goal of the intervention determined and agreed upon between the healthcare professional team and the patient or surrogate decision-maker ahead of time [50]. The time-limited trial also provides the healthcare teams and family members involved an opportunity to adjust to the natural realities of the illness. This trial potentially provides a better understanding

of the benefits and harm of continuing the medical interventions for the patient and potential appropriateness of disclosure and may help establish new goals of care for the patient [49, 50].

In the future, we will continue to see the historical moral obligations be tested by everyday nuanced ethical challenges. Currently, shortages of life-saving medications, use and withdrawal of life-sustaining technologies, allocation of limited resources, inequality based on limited access to care, use of complementary medicines and therapies, etc. all raise serious ethical quandaries about fair allocation, risk/benefit ratio, beneficence, the best interest standard, and the collaborative decision-making process and demand sound ethical reasoning and shared consensus frameworks within pediatrics [51, 52]. For instance, in response to chemotherapy drug shortages, experts in the field of pediatric hematology/oncology integrated various ethical models and frameworks (such as justice principle and utilitarianism) for decision-making that explicitly prioritized "maximizing lives rather than life-years saved" for pediatric patients by (1) maximizing efficiency and minimizing waste, (2) identifying stakeholder responsibilities during a drug shortage, and (3) outlining specific allocation considerations [51]. This multi-institution collaborative publication illustrates one systematic ethically conscientious way healthcare professionals can continue to address the ethical challenges at the bedside today. Ethical principles and professional statements guiding the current practice of medicine will always be rooted in historical perspectives, philosophies, and frameworks which are built upon a rich tradition of prioritizing professional obligations to relieve suffering and promote well-being in a fiduciary relationship with the patient. The ongoing challenge for many hospital ethics committees, professional organizations, and social policies is to maintain a balance between offering general guidance and prescriptive recommendations, while respecting the individual professional judgments of healthcare professionals at the bedside and the requests of patients or surrogate decision-makers within the context of generalized ethical, legal, religious, and cultural frameworks. However, the unchanging variable for the pediatrician today, amidst all these challenges, is the intrinsic need to protect the child's rights and act in accord for the child's best interest. Thus, going forward, it is reasonable to expect that the ethical issues specific to pediatrics will remain especially valuable in the advancement, study, and practice of bioethics.

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Chapter 2
Ethical Principles in the Practice of Medicine

Ryan R. Nash and Mark J. Wells

Introduction

In approaching children with cancer and their caregivers, healthcare practitioners face numerous scenarios in which those involved in a child's care come into conflict. When and how should a diagnosis of cancer be revealed to adolescents and their families and should adolescents be free to deny their parents this knowledge at certain levels of capacity? Who should have the say regarding the distribution of scarce resources? To what extent should healthcare practitioners accommodate traditional, complementary, and alternative medicines within their treatment plans?

Each of these queries falls under the domain of medical ethics, a field which has attempted to provide frameworks and principles for guiding medical care in ethically dubious scenarios. This chapter will consider the challenges of defining ethics, the different frameworks of considering ethics, and the challenges of living in a pluralistic society. It will also discuss the most commonly cited principles in medical ethics and how to approach medical ethics at levels of law, professional standards, and moral foundations and will introduce a tool for use by clinicians in facilitating ethics discussions with patients and families. Throughout the chapter, these considerations will be correlated with ethical challenges faced in the field of pediatric oncology, which may be developed further in later chapters of this text.

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Defining Ethics

Before addressing principles that might guide ethical practice, the broader question of the definition of ethics poses itself. According to Merriam Webster, the term may be defined as "the discipline dealing with what is good and bad and with moral duty and obligation," "the principles of conduct governing an individual or a group," and/or "a consciousness of moral importance" [1]. However, is it simply the distinguishing of good from evil, right from wrong? Often more applicable for bedside decision-making, it can be viewed as a search for the better, or "less bad," in each scenario into which clinicians (and, subsequently, ethicists) are thrust. Ethics does not consistently deal in absolutes, but instead, frequently entails finding the better option on a moral gradient. Decisions at the bedside are often made when no options are truly "good" or "right" to stakeholders in cases, e.g., families and caregivers, care teams, etc., leaving what some ethicists have called a "devil's choice" in care – called such simply because no "good" or "right" choice is evident [2]. Furthermore, distress arises in making these decisions from making decisions contrary to one's moral philosophy or code, or from perceptions of oppression by systems or patterns of practice, leading to a sense of helplessness among practitioners. Most of all, persons involved in patient care encounter some of the most harrowing scenarios of suffering and death without significant ability to remedy their patients' pains. Healthcare professionals are left facing the finitude of their patients, their abilities, and themselves.

For our purposes, ethics will encompass the whole of these questions and tensions that pose themselves to each stakeholder in a medical case differently. Admittedly, in some scenarios, only some parties involved in a patient's care will feel this tension, leading to confusion when one party voices their concerns. For example, a traditional Amish family refusing life-saving chemotherapy on grounds of religion causes frustration to the hospital staff. Medical ethicists and clinicians themselves may not be experts at discerning the correct path forward among these differing viewpoints. However, at the least, they examine parties' assumptions, ask clarifying questions, and identify and raise attention to relevant pieces of information that might guide cases toward appropriate resolutions, all the while aspiring to approximate the good and the right.

Approaches to Medical Ethics

The field of medical ethics has represented and continues to constitute an essential portion of medical decision-making and medical practice. Although approaches to ethics are not separate from cultures in which they surface, medical ethics in the West has its own unique history. For the last 2500 years, the Hippocratic Oath was considered a foundational text for clinicians, albeit inconsistently applied. In 1847 the American Medical Association promoted a formal ethics code that established

physicians' moral obligations to their patients [3]. Challenges arising from human experimentation and new technologies during the nineteenth and twentieth century led to further shifts in approaches to medical ethics. Experiences of compulsory sterilization and involuntary experimentation on human subjects for the sake of eugenics in the United States and Nazi Germany prompted greater reflection on how ethics ought to be enforced in medical research and practice. Such reflections became embodied in documents such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report.

These texts and other societal movements formed a number of approaches to contemporary medical ethics (Table 2.1). These methods have been informed by a number of academic fields as well, including but not limited to anthropology, legal studies, philosophy, theology, biomedical sciences, and women's studies. Each of these methods serves its purpose in developing solutions to ethical quandaries

Table 2.1 Approaches to contemporary medical ethics

Principle based Beneficence – promote patient well-being Autonomy – respect patient self-determination Nonmaleficence – do no harm Justice – protect vulnerable populations; fair allocation of resources
Professionalism Determined qualities that make a "good" professional physician Practitioner true to standard by honoring established principles and oaths
Virtue based Good physician defined by virtues 1. Fidelity – honoring the trust of the patient-physician relationship 2. Disregard for self-interest – protect the patient from exploitation and refrain from using the patient as a means for self-advancement or benefit 3. Empathy – exhibit compassion and caring 4. Intellectual honesty – knowing limits of knowledge and capability 5. Prudence – identifying alternatives and demonstrating strength in times of uncertainty and stress
Caring based Serving others through a common connection of personhood Develop a relationship based on empathy and compassion
Respect for personhood Treatment of patients reflects the inherent dignity of every human regardless of race, gender, socioeconomic status, etc. Medical decision-making values the needs of the patient above all else
Humanities Use of literature, art, and history to arrive at sentiment of right and wrong
Religious and cultural Application of religious or philosophical belief systems to medical decision-making
Gender based Feminist ethics address gender conceptions shaping perception of the world including moral reasoning and medical decision-making

Adapted from Nash and Rink [28]

through identifying critical questions within these quandaries and posing potential courses of action.

The most common method employed in bioethics today involves the application of principles initially considered in the Belmont Report for research ethics. After Belmont, the publication of Beauchamp and Childress' [4] *Principles of Biomedical Ethics* furthered making the four principles relevant to clinical encounters. The four principles – autonomy, beneficence, nonmaleficence, and justice – differ from the Belmont Report's initial three principles of respect for persons, beneficence, and justice, but nonetheless take similar approaches to ethical situations [5]. These four principles have come to be taught in clinical education across the world, to the extent that they are often considered testable material on medical licensure examinations. However, clinicians may wrestle with how best to weigh these principles within their clinical practice, though they do provide a language by which people may frame their concerns within a patient's care. Further consideration of these principles will be made later in this chapter.

Additional perspectives that have developed encompass how a clinician can develop qualities and/or behaviors that create ethical persons and lead to ethical actions. For example, professionalism assists clinicians in determining what makes a professional "good." The profession in which one practices establishes guidelines and principles to assist clinicians in cultivating attitudes that would produce ethical behavior. The American Academy of Pediatrics upholds the following principles in practicing professionally as a pediatrician or pediatric specialist: honesty and integrity, respect for others, reliability and responsibility, compassion and empathy, self-improvement, self-awareness and knowledge of limits, communication and collaboration, and altruism and advocacy [6]. Adherence to these principles within one's clinical interactions would thus produce ethical actions. Similarly, virtue-based ethics endeavors to cultivate particular virtues within clinicians to ensure that clinicians become good. Rather than being concerned with specific principles and clinical ethics cases, virtue ethics encompasses the clinician inside and outside the patient encounter in cultivating virtues to form a virtuous pattern of living [7]. The particular virtues themselves may vary among different virtue ethicists, but may involve fidelity within the physician-patient relationship, empathy toward patients and their families, and recognition of one's own limits in knowledge and abilities.

Other ethics systems focus on persons' relationships with one another and forces that influence them. Feminist ethics addresses how people conceive the world and highlights power structures at play in medical decision-making. Care ethics focuses instead on the commonality of personhood among humans, which prompts development of relationships based on empathy and respect. Similar attitudes are constructed through systems that respect personhood, which focus on how each patient is deserving of human dignity irrespective of ethnicity, sex, race, etc. The decision-making instead focuses on how to respect the person before a clinician, valuing their needs and desires more than other elements in therapeutic decisions.

"Respect for persons" as a form of ethics may be considered duty-based or deontological, which considers actions as intrinsically good or evil in essence. In this case, an action would be considered good or evil based on treatment of the human

person. Kantian ethics employs deontological approaches as well, holding that persons must be pursued as ends, rather than as merely means to ends. Such ethical forms stand against consequentialist forms of ethics, which consider only the consequences of actions. These consequences may be considered by different metrics, such as the extent to which pleasure is increased and pain decreased, whether higher or lower pleasures are increased, and net social increase or decrease in pleasure. However, the duty to avoid specific actions in clinical care based on an intrinsic belief about that action is removed.

Lastly, ethics systems function within a variety of religious and cultural traditions that inform people's behavior either actively or subconsciously. Persons of different religious backgrounds may hold to beliefs that narrow their scope of available therapeutic options based on their beliefs regarding what is permitted by a deity or transcendent power, e.g., limited use of porcine products in surgery among Muslims, limited use of blood products among Jehovah's Witnesses, among others [8, 9]. Different views of quality of life may also lead to differences regarding how care is approached, such as Orthodox Jews refusing to remove ventilators in cases of brain death [10]. Additionally, cultural norms may inform patients regarding preferred care environments as well as methods of administering therapies, e.g., an intramuscular injection holding greater potency than an oral ingestion. Even for those who do not actively hold to a religious or cultural tradition may be influenced by the prevailing norms of a given society. As such, awareness of the common traditions that inform patients' care in a locale proves helpful to clinicians, even if they themselves do not belong to the traditions.

The Problem of Pluralism

In considering the multiple approaches to ethics described above, questions arise regarding how one ought to reach resolutions to ethical questions. Should a virtuous person make a choice that a person from another culture finds reprehensible? When should the care for a person overrule decisions based on a utilitarian calculus? These conflicts of visions arise from the problem of pluralism. Pluralism arises from the differences in ethical approaches held among various groups within a society, including but not limited to assumptions regarding what the good and the valuable are, the origins or foundations of the good, and the methods by which one reaches the good and the valuable. Based on these differences, difficulty arises in coming to consensus regarding how ethics ought to operate in a society in which no shared vision exists. For example, all may hope for the good of a patient, i.e., beneficence, in a clinical encounter, but what that good entails would vary from practitioner to practitioner – representing competing visions of health [11].

Attempts at creating homogenous views of principles are also met with great difficulty. Social theorists such as John Rawls have considered how one might secure a just society rationally by considering how one might mentally conceive of such a society [12]. In considering what an ideal society would look like, one could

consider a thought experiment in which one's identity and status, e.g., occupation, religion, economic well-being, etc., were concealed, and one subsequently attempted to determine how society ought to function. However, creation of such a veil of ignorance is futile, as one can never take an objective, neutral stance apart from one's identity, for even one's unconscious biases would influence how such a society would be structured.

H. Tristram Engelhardt [13] critiques approaches that attempt to provide commonalities in content within ethics from a secular standpoint and instead advocates for a position based on permission (what some have considered an autonomy-centric ethic) in the context of pluralistic societies. Namely, he recognizes that Western philosophy, in attempting to ground ethics in the rational faculties, has failed to secure a common secular basis for ethics upon which different groups may rely in order to reach similar conclusions. From considering ethical theories as diverse as utilitarianism, game theory, and casuistry, he critiques each system as not only incompatible with one another but also failing to provide a secular basis that justifies any moral content they provide [13]. Instead, he proposes that regardless of which system one chooses, persons ought to receive permission from one another to act within the medical profession. He proposes this model not as a manner of securing a shared ethical conclusion in all cases nor to claim that each system is even valid, but to allow individuals and groups with specific and differing moral visions to live at peace with one another. Importantly, in this vision permission is not merely needed from the patient – a willing clinician within a profession with certain standards, a willing facility, and an allowing state in the particular jurisdiction are all required. Many, like Engelhardt himself, long for their particular moral vision beyond this basic ethic of permission to become accepted and the norm for ethical decision-making. Simple observation, however, reveals the problem of pluralism – agreement can be elusive.

The Four Principles of Biomedical Ethics

While recognizing the problems posed by pluralism of different systems of ethics, special attention should nonetheless be paid to the most common ethical system used in clinical practice at the time of this publication: principlism. The four principles – beneficence, nonmaleficence, autonomy, and justice – serve clinicians by prompting consideration of different factors in a patient's case that may deserve attention in reaching an ethical decision. Beneficence assists them in reflecting on a patient's well-being. Nonmaleficence considers how to avoid harming the patient. Autonomy promotes the patient's ability to determine for himself the proper course of action. Justice contemplates what would be fair in a given scenario. Again, these principles unto themselves fail to provide solutions to ethical puzzles, but rather serve to provide a shared understanding of how actions may be considered. According to the principlistic model, no one principle can stand as an absolute, creating complex ethical scenarios when clinicians are faced with conflicting principles.

Considering beneficence, the principle is grounded in promoting both the well-being of the patient and producing good generally, prompting physicians to act in accordance with those actions which would promote both under ideal circumstances. Promoting this well-being is often described in conjunction with the principle of nonmaleficence, i.e., the obligation not to cause harm or injury, *primum non nocere* ("first, do no harm"). These principles must be considered in evaluating pediatric oncology patients, as interventions may pose differing levels of help or harm that each may be of different value to managing clinical care and to ensuring patients' and parents' wishes are respected. What constitutes the "good" for the patient becomes more complicated in scenarios in which adolescent patients and their parents differ on what would be considered a desirable state or outcome.

Although historically beneficence has been the most considered and influential of the principles, significant attention has been paid to the principle of autonomy given the increasingly competing visions of what "good" and "health" constitute. The principle of autonomy poses specific questions for pediatric patients and their families due to questions concerning the extent to which children and adolescents ought to have voice in their healthcare decisions. Autonomy, also known as self-determination, advocates for the decision-making capacity of persons based on their cultural, religious, philosophical, and personal beliefs, as well as their plans and experiences. These decisional preferences may stand against those preferred by family members, by clinicians, and/or by society. Furthermore, respecting autonomy grounds the provision of informed consent, which establishes that a patient with sufficient information and capacity to make a decision can elect to receive or decline an intervention. However, autonomy does not extend to a positive right in which a patient may demand that a treatment be received, irrespective of benefit or cost to himself or others. Likewise, autonomy does not force healthcare teams to administer therapies considered to be harmful or futile. Within a pediatric case, where parents will provide consent for their children, difficulties arise when parents disagree on the decision to be made for their child. Additionally, children and adolescents themselves have been regarded by some as able to make their own healthcare decisions in certain domains, such as regarding birth control, thus raising questions regarding the extent to which their preferences ought to govern other healthcare decisions.

The final principle, justice, considers how best to distribute the provisions of healthcare equitably. This principle stands as most scrutinized due to increasing costs of healthcare, leading to its application not solely to protect vulnerable populations but how to distribute scarce resources broadly within communities and societies. As a principle, justice considers how patients ought to be treated equally unless evidence suggests that other criteria should apply in a particular scenario to change treatment. The obligation of the clinician then becomes serving in the role of advocate for their patients' good, whether in determining various criteria for how scarce resources ought to be distributed or in approaching patients without sufficient insurance coverage in their clinics and hospitals.

"Doing Ethics": A Modest Approach

In recognition of the above principles, how ought the clinician translate them to the ethical challenges at the bedside? How does one, if one will, "do ethics"? These principles end up being recognized at different levels of ethical understanding developed within the medical system. Procedural ethics then provides insight into how to approach each clinical encounter, while retaining awareness of the underlying foundational questions and concerns within ethics.

This modest approach to procedural ethics may be considered three-tiered: (1) legal and policy statements, (2) professional and community standards, and (3) the aforementioned foundations. Regarding the first tier, legal and policy statements enable clinicians to assess whether an action taken has been deemed acceptable by the government under which one practices. Different governments may enact different standards within their laws and policies, but awareness of these standards within practice enables one to either abide by them out of agreement with the state's policies, to strive to improve upon them or otherwise change them, or to violate them as an act of protest against the governing body, risking potential criminal indictments. They do not necessarily represent the good, right, or valuable as understood by all stakeholders within a clinical case but should be known to help frame the decision.

The second tier, professional and community standards, assists practitioners in evaluating what colleagues in their field, professional societies, and hospital systems consider acceptable practices. Notably, however, professional societies may differ among and within themselves regarding which practices are ideal, which practices are acceptable alternatives, and which practices are unacceptable. Although majority and minority opinions may not be resolvable with dialogue within these societies, the statements do provide guidance regarding the ranges of views deemed acceptable within one's practice setting and among one's colleagues. However, healthcare providers should not believe or assume that these professional statements or the previously considered legal and public policy statements signify the ultimate source of right and wrong, good and evil. Competing visions of health, life, illness, birth, and death create ongoing challenges in the way medicine is practiced.

The third and final tier, the foundational tier, concerns itself with the personal and/or group beliefs that ground one's practice. Within this tier may be found a general philosophy of life, belief structure, and/or religious tradition that centers an individual's own convictions, reasons for practicing medicine, and particular biases when considering treatment decisions. Many of these possible perspectives were addressed earlier in the approaches to ethics (Table 2.1) and help form levels of adherence to laws and public policy and to hospital and professional statements.

By considering these three tiers of belief, one may achieve a kind of *modus vivendi*, a pattern of practicing by which persons of disparate foundational beliefs might serve together as colleagues in benefiting the health of the patient by operating in accordance with the first two tiers. Again, such practice does not undermine these foundational beliefs, but rather permits peaceful practice within a pluralistic ethical landscape.

Legal and Professional Considerations in Ethics

To further understand how to operate in accordance with this *modus vivendi* in the field of pediatric oncology, the ethical challenges within pediatric oncology and the policies that shape practice will here be examined. Some of these challenges arise from end-of-life care of the pediatric oncology patient, while others concern issues relevant to pediatric ethics more broadly, such as adolescent decision-making. Box 2.1 lists a number of ethically challenging situations encountered by pediatric oncologists, which will be addressed in part below.

Pediatric ethics stands as a unique field based on the typical assumption that one must look to someone other than the child for a decision in medical care, namely, a parent or other caregiver. In the United States, parents have the legal right to make decisions regarding how their child ought to be cared for within medical contexts. A set of parents would be able to consent for their 18-month-old for a bone marrow biopsy to help establishment of a cancer diagnosis. They are entrusted with this right based on the presumption that they typically have the best interests of the child in mind as expressed through their roles in raising the child. This standard of "best interests" (beneficence) may be considered the bedrock of pediatric ethical decisions, in comparison with ethics in adult medicine, which typically focuses on the patient's wishes (autonomy). However, limitations exist regarding the scope of parents' rights to decide what these best interests are. For example, a father who does not possess decision-making capacity himself would not be able to make decisions on behalf of his child. Similarly, decision-making may fall to a court-established

Box 2.1 Examples of ethical issues encountered in pediatric oncology

- Gamete banking and fertility preservation
  - Objections to masturbation
  - Objections to artificial reproductive technologies
  - Gamete harvesting risks
- Public health disparities and access to care
- Adolescent decision-making
- Genetic screening and testing
  - Siblings
  - Children of pediatric oncology patients
- End-of-life care
  - Medical futility
  - Pain management
  - Euthanasia and physician aid-in-dying

guardian in cases of abuse or neglect. The kinds of choices that can be made by parents also are limited at law. The *Prince v. Massachusetts* [14] United States Supreme Court decision ruled that parental authority was not absolute and that the state could prevent parents from making their children "martyrs." Furthermore, the US Department of Health and Human Services considers inadequate provision of medical care for a child to constitute neglect [8]. As such, this case has been foundational in addressing parents who refuse to consent to life-saving therapies for their children [15].

Another area unique to pediatric ethics concerns the adolescent patient with respect to decision-making. Ideally, children should still be involved in the decision-making process, even though they are not able to give legal consent in most cases. This inability is due in part to distinguishing between decision-making capacity and decision-making competence. Capacity involves a patient's cognitive ability to make decisions based on presentation of relevant information and to express their wishes in their medical care. However, even if patients have this capacity, their competence is determined by the law rather than by their physical or cognitive abilities. Patient assent, i.e., agreement to an intervention from an individual unable to give consent, should be acquired whenever possible. For those who are able to provide informed consent for patients, physicians should "explain their opinion about the nature of the patient's problem, recommend a course of treatment, give the reasons for the recommendation, propose options for alternative treatment, and explain the benefits and risks of all options" [16].

In specific circumstances, however, minors are able to give consent for their own medical decisions at law. For example, a legally emancipated minor would have the ability to consent for their own medical treatment rather than have their parents stand in for their best interests. Some ethicists advocate for the promotion of a "mature minor rule," i.e., the promotion of minor decision-making capacity more broadly based on cognitive similarities between young adults and adolescents [17]. Such a rule has been adopted at law to a limited degree in some states, e.g., Delaware, which allows minors to consent to treatment after reasonable attempts to contact parents have been made [17]. Other common contexts in which states grant minors special ability to provide consent authorization without parental permission include contraception, care for substance abuse, and mental illness. Care for substance abuse may be of specific concern for the pediatric oncologist in cases of adolescent patients at risk for substance abuse alongside use of narcotics for treatment of cancer-related pain.

Critics of the mature minor rule argue that pediatric patients do not gain more autonomy from such legislation but may become unduly swayed by clinicians. To critics, parents act as a buffer to protect their children from procedures that may not be in their best interests that may be offered in appealing terms by clinicians. The less mature the child, the greater the possibility of power dynamics of the clinical encounter influencing the decisions for treatment rather than the true wishes of the child. Furthermore, the very movement toward a mature minor ruling may be understood as a general distrust of the family unit to respect the best interests of their children at all stages of development, leading to questions of whether the family

unit itself has been medicalized as pathologic at certain stages of children's and adolescents' lives. Therefore, while the mature minor rule may be advanced based on the intent to aid minors in developing their decision-making capacities, significant caution should be used before advancing them at law to prevent inadvertent limitation of this very capacity.

Religious objection by patients and families can lead to complications in caring for patients depending on the scope of care in which the tradition objects. As an example, members of the Followers of Christ tradition opt out of all medical care in favor of anointing with oil and laying on of hands [8]. However, other traditions may have exceptions to such refusal of care, e.g., Church of Christ, Scientist allows for physical procedures, such as bone setting, to merit medical attention [8]. For the pediatric oncologist, potential concerns may arise in extreme views within these traditions, which may prompt parents and/or their children to refuse any kind of chemotherapy or radiotherapy out of belief that a deity or higher power will provide partial or complete remission of the cancer. Religious exemptions to child neglect do exist if no harm or substantial risk of harm exists in deferring procedures; however, the American Academy of Pediatrics object to these exemptions due to lack of clarity regarding what falls under such categories of harms that would justify deferrals [8].

On the other side of the question of religion stand the concerns from physicians who may object to procedures that contravene their own foundational beliefs. Such clinicians may be attempting to protect the patient from an action they believe may be harmful. Pediatric oncologists caring for children with terminal cancers may be faced with questions and concerns posed by physician aid-in-dying, i.e., means by which doctors can assist patients in choosing how to die. The two forms of physician aid-in-dying – euthanasia and physician-assisted suicide – are distinguished from one another by who ultimately acts to terminate the patient's life: the physician (euthanasia) or the patient (physician-assisted suicide) [18]. In the Netherlands and Belgium, euthanasia has been legalized for minors with some restrictions. Pediatric euthanasia has been legally available since the Netherlands enacted the Termination of Life on Request and Assisted Suicide (Review Procedures) Act in April 2002 [19]. The Dutch law allowed for minors between the ages of 12 and 16 to request euthanasia with parental reconciliation to the request, so long as other criteria were also met, including voluntariness of request and "lasting and unbearable" [19, p., 263] suffering, among others. Voluntary pediatric euthanasia did not become available until Belgium passed an amendment in 2014 to their original euthanasia ruling removing the age limit [20]. However, the child must explicitly request the procedure, demonstrate the intellectual capacity to make a decision of this magnitude as assessed by a multidisciplinary team, and receive parental consent for proceeding [20].

At the time of this publication, physician aid-in-dying is not legally permissible within the United States, although recent commentary in the journal *Pediatrics* has advocated for it [21]. Additionally, a survey of 223 pediatric oncologists who were members of the American Society of Clinical Oncology noted that 13.7% of them supported euthanasia for patients in excruciating pain (9.5% of the 223 reported

performing it during their careers) and that 30.9% supported physician-assisted suicide for patients in excruciating pain (4.5% of the 223 reported performing it during their careers) [22]. As a professional recommendation, American Academy of Hospice and Palliative Medicine promotes an air of neutrality on the issue of physician aid-in-dying in general, but comments that it should not be legalized without significant consideration of the social ramifications and protection for physicians who object to the practice [23]. Were such legalization to occur, and objecting physicians fear they would be forced to perform the procedure, Section 1553 of the Patient Protection and Affordable Care Act [24] prohibits discrimination against providers who elect not to participate in assisted suicide services, which presumably would apply to pediatric aid-in-dying were the practice legalized in the United States.

Additional end-of-life challenges arise from concerns regarding medical futility. The rapidly rising costs of healthcare in the United States have led to enormous pressure on physicians to withhold or withdraw treatments that do not offer clear benefit to patients. At present, there is no standard definition of medical futility, although attempts have been made to quantify it, e.g., an intervention that would not provide benefit to one patient in 100 cases, or to qualitatively assess whether a treatment's benefits outweigh its burdens [25, 26]. Most physicians simply acknowledge that "I can't define it but would know it when I see it" [27].

Many important factors should be considered in assessing whether an intervention ought to be deemed medically futile. First of all, simply because a therapy exists does not mean that it must be used. For example, advanced therapies in terminal cancer patients may simply prolong the suffering of patients or even risk inadvertent hastening of death. Additionally, the mantra of "doing everything possible" may include interventions beyond what "everything helpful" entails. When patients request that "everything possible" be provided in their care, further assessment of that statement should determine what patients and families expect from "everything possible," e.g., all therapeutics determined to be life-saving, all therapeutics determined to prevent unnecessary suffering, etc. Lastly, clinicians' opinions regarding medical futility are inevitably shaped by their personal experiences, their medical knowledge, and understanding of resources at their disposal. Such experiences should be used in shaping recommendations for patients and their families but should be clarified as such rather than proclaimed as a rigid ruling.

A multidisciplinary team should be included in the decision to rule a therapeutic intervention as medically futile. The physician, patient, family, and other healthcare providers should come to a consensus with regard to both the disease process affecting the patient and the prognosis of the patient. To ensure families understand the terminal nature of the disease process, articulations of the prognosis should be at once sensitive and straightforward. The physician and other members of the healthcare team should review expected outcomes of different treatments and their benefits and burdens relative to the patient's condition and values. While doing so, the physician can identify and address any misconceptions held by the patient or the family regarding goals or expected outcomes of therapies that could prevent medical decision-making from occurring in an appropriate manner.

To consider the laws and standards outlined above in practice, one might consider the specific case of gamete banking for preservation of fertility in pediatric oncology patients. Typically, such a procedure involves prompting an adolescent to provide a semen sample through masturbation in order to produce sperm quantities sufficient for cryopreservation. In most states, the decision to consent to cryopreservation would be performed by the parents, although the adolescent would have to give assent in order to produce the specimen for preservation. However, further considerations would be raised if the patient or the parent refused to provide the sample based on beliefs in the wrongness of the action of masturbation or in future use of assistive reproductive technologies. As failure to undergo this preservation does not constitute significant risk to the patient, the objection should be able to stand at law. Alternative experimental procedures, such as testicular sampling, may be offered with description of associated risks and benefits. If an objection exists for the pediatric oncologist on similar grounds, consultation with professional bodies may be necessary to determine if professional bodies advocate offering this therapy, or referral to providers willing to provide this procedure is warranted.

In addressing each of the potential concerns above, one must recognize again that this approach remains a *modus vivendi*. Simply because these laws and professional policies exist do not make them normative, foundational ethical authorities. These policies should inform healthcare professionals, patients, families, and all other stakeholders in what should be taken into account when coming to a decision in clinical care.

The Four Boxes of Clinical Ethics

The above legal and policy considerations help inform clinicians as they practice at the bedside and facilitate agreement among disparate parties. Physicians assist their patients and families in understanding options available to them and help clarify questions that arise. While physicians may be hesitant to share their own recommendations to patients due to historical recent discouragement of medical paternalism, failure to share their opinions may inadvertently deprive patients of their clinical expertise that may in fact be desired by families. Recommendations should take into consideration patients' and families' values, with the physician inviting to families to comment on whether their backgrounds are sufficiently understood by the physician. This understanding coupled with medical knowledge should guide recommendations in clinical care. To make a recommendation with regard to a problem of ethics, the Four Box-Model provides a standard pattern for organizing information pertinent to the ethical concern.

The Four Box-Model provides a method of organizing ethically relevant information to assist healthcare providers in making informed decisions. First, it assists in ensuring that relevant information is gathered by highlighting four domains of ethical concern: medical indications and facts, patient and family preferences, quality of life, and contextual features (Table 2.2) [16]. Additionally, the boxes are orga-

Table 2.2 The Four Box-Model

I. *Medical information*	II. *Patient and professional preferences*
What is the patient's diagnosis and prognosis? How has the patient's condition changed? Are symptoms adequately treated? What is the proposed intervention? How effective is the intervention likely to be for this patient? What is the intention of the proposed intervention? What are possible alternatives?	What is known about the patient's wishes and values? What is known about the wishes of surrogates, family members, and other involved parties? Does the patient have the capacity to make decisions about medical treatments? Who is involved in making the decision and what is his or her involvement? What is the recommendation of the physician and interdisciplinary team?
III. *Benefits and burdens*	IV. *Contextual features*
What are the potential benefits and burdens/risks of the treatment in question? How does the patient describe his or her quality of life or burden of life? What brings meaning or sustains the patient? How has the patient made treatment decisions in the past? What types of treatments would provide a satisfactory outcome for this patient's life? What is achievable with regard to the patient's preferences?	Who is this patient? What are the patient's life story and primary values? What is the patient's relationship with family members and significant others? What are the patient's cultural, religious, and spiritual beliefs, and values? What are the potential benefits and burdens of each alternative for the patient and family, including financial and emotional costs? What are the legal considerations? How will the decision affect the patient and family physically, emotionally, spiritually, socially, and economically?

Adapted from Jonsen et al. [15]

nized with a hierarchy of information gathered, with preferences of patients and their families taking precedence over cultural facts, for example. This hierarchical structure should not undermine the relevance of quality of life or contextual features, but rather properly order them with respect to other information in making an ethical decision. Furthermore, the very procedural nature of the Four Box-Model does not necessarily address the nature of an action as ethical but provides a practical construct by which approaches may be made to reach a well-informed decision. Finally, it creates a language by which patients, physicians, and other stakeholders might discuss a case, leading to an agreed upon outcome and increased likelihood of conflict resolution. Granted, the conflict resolution itself may not necessarily be ethical by some standards of ethics, but in dialoguing across the systems of ethics employed by clinicians, patients, families, and other stakeholders, an agreement may be made regarding the best step forward that would respect to the extent feasible each respective system.

The Four Box-Model itself incorporates elements of the principlistic method employed earlier. Questions concerning the medically relevant facts and indications provide insight into what would help or prevent harm to a patient, reflecting the principles of beneficence and nonmaleficence, respectively. Patient and family preferences emphasize the autonomy of persons capable of making decisions in particular

cases. Quality of life considerations account for both beneficence and nonmaleficence in considering patients' outcomes, while also accounting for autonomy by focusing on patients' goals and personal standards for quality of life. The principle of justice may be accounted for through contextual features, which may inform how providers make decisions with respect to the communities impacted by the decision.

Ethics Consultation

At times, even when the above methods have been employed by the clinical team, difficulty arises in arriving at an ethical resolution to a case. Such situations may merit a formal clinical ethics consultation, not necessarily because the methods above have been improperly used but potentially from a desire for a perspective from outside the immediate care team. The clinical ethicist allows stakeholders from each involved party to voice their concerns to someone not directly involved in the medical management of the patient, which may allow greater freedom to share perspectives and, thus, a greater range of stakeholder responses. Their expertise stems not solely from this outsider perspective but from their ability to clarify relevant values within respective parties; articulate legal, public policy, and hospital standards; and assist in providing options that would resolve conflicts or confusion over those values among case stakeholders. Additionally, their familiarity with the healthcare systems and legal matters surrounding common ethical scenarios, such as informed consent and decision-making capacity, would allow more efficient determinations of possible steps than clinicians less familiar with them.

While resolutions may take place among other parties within a healthcare system, clinical ethicists can provide more expedient solutions that would hold potential for saving healthcare expenditures associated with unresolved conflicts. Delays in resolving these conflicts can lead to lengthier stays with increased costs of care, disharmony among clinical staff, and lower patient and family satisfaction scores. Their services can be structured to meet the needs of the institution, whether by individual consultants to increase efficiency or a committee to encourage greater interdisciplinary collaboration. By facilitating ethical solutions to care questions, clinical ethicists help foster harmony among staff members, reduce unnecessary expenditures from unresolved concerns, and increase the sense of satisfaction among patients and families.

Conclusion

The above discussion of the ethical principles in the practice of medicine has highlighted the challenges of living in a pluralistic world. While beneficence, nonmaleficence, justice, and autonomy provide a common language in which people may

frame ethical issues, they do not necessarily imply the same views for each individual. Considerations should be made in making ethical decisions within medicine of the moral and ethical foundations of each individual within a case to determine how they approach questions. Awareness of what legal, public policy, professional, and hospital standards should inform the stakeholders approaching a case regarding the ramifications of abiding by or violating these standards. Lastly, models that encompass these principles and ethical tiers of consideration can be used effectively within clinical settings to facilitate understanding of what is ethically at stake in a given scenario. Together, these principles and approaches to medical ethics may effectively inform and assist pediatric oncologists in caring for children and families facing pediatric cancer diagnoses.

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Part II
The Ethics of Everyday Clinical Encounters

Chapter 3
Communicating Prognosis at Diagnosis and Relapse or Progression

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Evidence for Honest Communication

Why Is Honest Communication Difficult?

The importance of honest communication in medicine, specifically oncology, has emerged over the past several decades. Prior to the late 1970s, the norm was not to tell patients the truth regarding their diagnosis [1], following the Hippocratic dictum to "first do no harm." Studies in the 1950s–1960s began to look at physicians' attitudes toward truth telling and found the norm was a strong and general tendency to withhold information regarding a cancer diagnosis [2]. Standards have certainly changed over the past several decades, and at present, it is routine practice in Western medicine to inform patients and their families of a cancer diagnosis. In the late 1970s, the shift toward increased disclosure practices was driven by bioethics and legal emphasis on patient autonomy rather than scientific data [1]. In more recent decades, scientific evidence has shown the practice is preferred by patients and leads to better patient outcomes [3].

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At the same time, advances in oncology have made conversations regarding bad news, prognosis, and end-of-life care more difficult. First, treatment options make the future less certain and clinicians report difficulty in talking about uncertainty. Second, the proliferation of options has forced clinicians to consider whether the balance between risks and benefits of a therapy is favorable for a particular patient. These decisions are often very patient dependent and require a clinician to be able to talk about values with patients. Finally, talking about how to change goals when more chemotherapy may not help is difficult for both clinicians and patients who have come to expect that other options will always be present. Oncologists surveyed at the 1999 Annual Meeting of the American Society of Clinical Oncology noted an average of 35 bad news discussions per month [4]. They felt that discussing the cancer diagnosis was the least difficult task when giving bad news and found that discussing cancer recurrence, failure of a treatment to produce an intended result, and the lack of further curative treatment options were more difficult [4].

Despite the common occurrence of these discussions, particularly in oncology, clinicians have struggled for decades with these conversations, due to worry about how they will affect their patients and families. Communicating difficult news is sometimes seen as counterintuitive to clinicians' inclination to "do no harm," as they worry about the psychological welfare of their patients and their families when they are informed of a poor prognosis, progressive disease, or cancer relapse [5, 6]. Thus, refraining from prognostic communication may stem from clinicians' compassionate inclinations [7]. Clinicians may desire to shield their patients and their families from the undeniable anguish, fear, sadness, and anger that breaking bad news can invoke. These tendencies persist despite data, discussed in section "Why Is Honest Communication Important?", indicating that patients welcome these conversations. Perhaps, then, clinicians run the risk of projecting their own negative emotions regarding prognostic discussion onto their patients.

Comfort level and confidence in any task in medicine is typically built through formal medical training. Ironically, although these conversations are difficult, many physicians have had little to no formal training in how to conduct these conversations. For example, a survey of adult oncology fellows found that they were more likely to have received formal training and feedback on routine procedures than end-of-life communication [8, 9]. An informal survey that assessed attitudes and practices regarding breaking bad news, defined as "any information which adversely and seriously affects an individual's view of his or her future," [10] was conducted at the 1998 Annual Meeting of the American Society of Clinical Oncology and found that the minority of respondents had received any formal training in breaking bad news and only slightly over half rated their own ability to break bad news as good or very good [11].

Why Is Honest Communication Important?

These conversations are important for two reasons. First, as bioethics has emphasized, we have an ethical responsibility to the child and his or her parents. Second, the empirical data suggests that parents desire prognostic information. Finally,

despite fear that distressing conversations will cause lasting emotional damage to patients and their families, there is ample evidence to support the beneficial impact of these conversations.

Parents and their children have an ethical right to know their medical information, regardless of its nature. Respect for autonomy requires honest disclosure of the child's medical condition, its prognosis, and treatment options, or lack thereof. Stemming from this, the parent's ethical responsibility to make medical decisions in the best interest of the child requires receipt of honest counsel from the physician [12].

Beyond the parental right to know is the fact that they also want to know. In a pediatric study of 194 parents of children with cancer, 87% of parents desired as much information about prognosis as possible. Although 36% of these parents found information about prognosis to be extremely or very upsetting, those parents were more likely to want additional prognostic information than those who were less upset [13]. Thus, despite the distress of bad news, parents still desire an honest discussion that does not seem to be associated with higher rates of overall distress. In another study that evaluated parents' ability to find peace of mind in the first year of their child's cancer treatment, peace of mind was not found to be associated with prognosis. Rather, parents noted greater peace of mind when the oncologist disclosed detailed prognostic information and provided high-quality information about the cancer and when parents reported greater trust in the oncologist's judgment [14].

Recent studies have underscored the beneficial nature of sharing this information to both the parent and the physician. In the adult oncology setting, it has been shown that there are no higher rates of depression or worry in patients with advanced cancer that had discussed end-of-life care planning with their physician than compared to those who had not [15]. Additionally, in the same study the caregivers of patients who had discussed end-of-life care with their loved one's physician had lower rates of depression in the bereavement period [15]. In a study conducted with 144 parents of children who died of cancer and 52 pediatric oncologists to ascertain both parents' and physicians' assessments of the quality of end-of-life care for children with cancer, parents were especially likely to rate physician care positively when they believed that communication with physicians had gone well. Specifically, parents were more satisfied when they received clear anticipatory guidance during the end-of-life period, news was delivered with sensitivity and caring, and doctors communicated directly with the child when appropriate [16]. In contrast, medical outcomes such as pain control and time spent in the hospital in the last month of the child's life were not important determinants of parental ratings of care. These findings emphasize that when a cure is not possible, the physician's care of the child and family remains highly valued and that the relationship itself can be a therapeutic agent [16].

Why Is Honest Communication Vital to Decision Making?

Parents of children with cancer are faced with countless decisions that must be made regarding their child's care. The choices that they are confronted with regarding their child's life when faced with poor prognosis, relapse, or progression of

disease are understandably some of the most difficult decisions a parent will ever have to make [17]. Parental expectations of outcomes often guide their decision making; however, parental hopes and expectations regarding the outcome of their child's medical care are often incongruent. Physician disclosure of information, therefore, is important in shaping these hopes and expectations and thus the parental choices regarding care that follows.

The link between uncertainty and fear is strong and hinders decision making. Families require clear and honest information about their child's medical condition in order to make good decisions for their children. There is a temptation, however, for clinicians to base the depth of their communication on the family's emotional reaction, as opposed to recognizing and acknowledging a strong reaction as normal. While it is imperative to respond to emotion, it is equally important to ensure the family receives all of the relevant medical information. Clinicians who withhold medical information for fear of harming the family or child risk increasing parental uncertainty and thus impairing decision making. The desire to receive detailed prognostic information despite emotional upset was nicely demonstrated in a survey of 194 parents of children with cancer and their children's physicians. In this sample, the degree to which parents found prognostic information to be upsetting was directly correlated to the parent wanting more detailed information [13]. Parents who found information about prognosis very or extremely upsetting were no less likely to believe that prognostic information had helped them with decision making than other parents. Interestingly, parents who were upset were more likely to report that the oncologist had never discussed prognosis. The authors concluded that the tendency to tailor information on the basis of the reaction of the parent, whether consciously or unconsciously, may leave parents who display greater emotional distress less informed [13]. This should be kept in mind, as prognostic discussions often need to be re-reviewed once the acute stress of the initial conversation has passed. This evidence suggests that subsequent conversations regarding prognosis should not be tailored based on the emotional reaction to the initial conversation.

Studies have shown that parents make better decisions if they are aware of the doctors' knowledge of the medical situation. In one study, parents of children who died of cancer as well as their primary oncologists were interviewed to determine whether an understanding of the child's prognosis alters parents' treatment goals [18]. The time from realization that there was no realistic possibility of cure to the time of death was measured in both groups. For parents, the first recognition of this occurred at a mean of 106 days prior to death; for physicians it occurred much earlier with documentation that the child had entered the end-of-life period at a mean of 206 days prior to the child's death [18]. The outcomes for the group of children in which both the physician and the parent recognition occurred more than 50 days prior to death revealed that there were statistically significant earlier documentation of hospice, better parental ratings of the quality of care delivered by the home care team, earlier institution of do-not-resuscitate orders, less use of cancer-directed treatment in the last month of life, and higher likelihood that both physician and parent identified the primary goal of cancer-directed therapy to be to lessen suffering [18]. These findings underpin the importance of high-quality, accurate clinician communication with parents of children with terminal cancer for improved decision making regarding end-of-life care.

Are We Taking Away Hope?

Hope is central to the practice of oncology and oncologists have faith in this concept. It can be defined as a feeling of expectation and desire for a certain thing to happen. In the medical setting, most clinicians assume that the definition of hope as it relates to disease is the belief that cure is possible. Hope and cure may not coincide in every situation, however, and even if the initial hope was for a cure, patients with realistic perceptions of their disease can transform hope into other reasonable and equally meaningful possibilities [19–22]. In other words, hope does not need to end with the recognition that death is likely. Similarly, while a physician's initial hope may be for a cure, when that is not possible, oncologists may hope for lack of suffering, a sense of fulfillment, and a dignified death for their patients.

One of the most commonly cited reasons to avoid detailed prognostic conversations when the outcome is suspected to be poor is the clinician's concern for the disruption of patient and family hope when faced with bad news [11], that when faced with a poor prognosis, for example, patients and their families may "give up." Thus, clinicians may limit prognostic information based on their belief of its effect on patient/family's hope.

However, patients and families do not believe that clinicians should withhold information in order to preserve hope. Among adult patients with incurable metastatic cancer who were surveyed to identify preferences for the process of prognostic discussion, almost all (98%) wanted their doctor to be realistic, and most (82%) noted that the use of euphemisms would not facilitate hope, but rather foster hopelessness [23]. These patients defined hope as being "that you can still enjoy a good quality of life even if life expectancy is uncertain" [23]. In other words, disclosure of bad news is not incongruent with hope. The clinician has to decide what information to give and how to give it. There is a need to deliver clear and compassionate information regarding prognosis and goals of treatment while creating realistic hopes and expectations. The idea that optimism for a prolonged life is a prerequisite for patient hope often leads to the use of euphemisms rather than clear honest disclosure of bad news.

Interestingly, the data suggests that better communication, even of bad news, promotes hope. In a single-center survey of 194 parents of children with cancer in their first year of treatment and the children's physicians, the relationship between parental recall of prognostic disclosure by the physician and outcomes of hope, trust, and emotional distress was evaluated. Parents were more likely to report communication-related hope when they also recalled increased prognostic disclosure, and this increased recall of prognostic disclosure was associated with communication-related hope even when the child's likelihood of a cure was less than 25% [24]. Not only does this finding dispute the notion that diminution of hope follows disclosure of poor prognosis, but it also indicates that communication of prognostic information, regardless of likelihood of cure, supports the hope that parents of children with cancer derive from high-quality communication with their child's physician.

A subsequent study collected prospective data among parents of children with advanced cancer [25]. In this qualitative study, conversations between 32 pairs of

parents and clinicians of children with relapsed or refractory cancer were audiotaped, followed by interviews with the parents about their experiences with prognostic communication [25]. When these parents were asked to reflect on prognostic statements, most (69%) described feeling upset and used statements such as being "hit over the head" and "crushing" to describe their reaction [25]. Although this may seem to confirm fears of taking away hope, most parents (69%) also noted that they valued honest and straightforward communication about prognosis and that a potential threat to parental hope is actually excessive clinician optimism. One family said, for example, "[Clinician] has always from day one said, 'I will never try to hide anything from you. I will be 100% honest with you the whole time.' And that is all I ever asked her to do is, 'Don't try to cover the sky with your hands. Don't try to cloud this up for us.' I want the nitty-gritty down to the bottom line" [25]. For these parents, honest communication was a component of hope because it led to making the best decisions for the child and the family [25].

Finally, while it may be tempting to misinterpret parental maintenance of hope in the face of a poor prognosis as denial or ignorance, data indicates that parents of children with incurable cancer find many different things to hope for, including cure, while acknowledging the reality of the situation. In the same cohort described above [25], parents were asked specifically about their hopes and expectations for their children in order to understand the extent to which parents can feel hopeful when faced with their child's impending death [26]. Statements the parents made in the interviews indicated a high degree of understanding of the incurable nature of the child's disease. In fact, the statements the parents made often mirrored the recorded statements of the physician during the prognostic discussion [26]. Despite acknowledgment of a poor prognosis, parents were able to express hopes, which ranged from prognosis/treatment-related (cure, treatment response, a long life, etc.) to non-treatment focused (quality of life, normalcy, and minimal suffering). Further, the majority of parents (72%) were able to acknowledge that their hopes differed from their expectations [26], indicating that their choice to speak in a language of hope did not mean they failed to understand the terminal nature of their child's disease. Probing for a parent's hopes and expectations not only increases the physician's understanding of how a family or patient is handling prognostic information but also may enhance the therapeutic patient-parent-physician alliance.

Parental Decision Making: Other Considerations for the Clinician

Parents of children with cancer are responsible for making a number of difficult decisions regarding their child's care, the majority of which are made late in the course of treatment [27]. In a study where 39 parent participants of children with cancer responded about factors that were important when making the decision to continue care, the most frequently reported difficult decisions were choosing

between a phase 1 study drug, conventional chemotherapy, maintaining or withdrawing life support, or no further cancer-directed treatment [27].

Studies have shown that parental decision making is guided by more than prognostic information and assessment of risks and benefits. A central concept that comes up in the literature is the sense of whether the decision is consistent with the parents' identity – e.g., is it something that shows that they are a good parent? In a study of families who had to make decisions regarding phase 1 trials, adoption of a do-not-resuscitate order, or initiation of terminal care [28], the families were questioned about what helped them make a decision. Considering the facts, explanations, opinions, and preferences of experts and others (e.g., family members, ill child, and other bereaved parents) and then choosing the option most consonant with an internal definition of a caring, competent protector of their child was a driving influential factor for 84% of participating parents [28]. In another study, feeling like they made a decision consistent with being a good parent helped parents cope emotionally after the loss of their child [27].

Understanding what exactly "being a good parent" means in the context of a parent of a child with incurable cancer may allow the clinician to address these ideas and communicate strategies to help parents achieve this important goal. This was investigated in a cohort of 62 parents, who had made one of these difficult non-curative treatment decisions for 58 patients, by collecting responses to open-ended questions about the definition of a good parent and about how clinicians could help them fulfill this role [29]. The theme that was most common among these parents was that of "doing right by my child," with 89% of parents reporting this definition [29]. Parents said, for instance, "We tried as much as we could to get her the best treatment," and "This is simple – doing what is best for your child" [29].

This study also explored which clinician behaviors reinforce the parent's view that they were "good parents." Overwhelmingly, parents (>80%) indicated that they wanted medical personnel to continue to treat their child with the same level of dedicated and compassionate care they had become accustomed to. In other words, they did not want to be treated differently based on the decision they had made, whether it was to continue cancer-directed therapy or not. Further, acknowledgments that their child would not be forgotten, that the family would be given time to consider all options, that honest communication would continue, and that staff would not "give up" on their child were extremely important in the maintenance of the "good parent" role [29].

Consideration of Cultural Variations

Within the context of communication of poor prognosis, we would be remiss not to mention the importance of the consideration of cultural differences that exist in terms of preferences for receipt of bad news. In a previously mentioned cohort of patients, English speakers were more likely to prefer realism as compared to those who spoke another language at home [23]. It is possible that this latter group is

influenced by a culture where avoidance and paternalism are more common. Additionally, in some cultures, communication of poor prognosis is viewed as harmful and brutal [30].

Likewise, cultural differences in methods of clinician communication surrounding disclosure of unfavorable medical information to cancer patients exist. For example, oncologists in non-Western countries are more likely to avoid direct disclosure of a grave prognosis to the patient, use euphemisms, withhold information from the patient at the family's request, and offer patients treatment that they knew was unlikely to work so as to maintain hope [4]. These behaviors are less prevalent in Western countries, which may explain why Western physicians report having more discussions about treatment failure and resuscitation with patients as well as more difficulty in handling patients' emotions after giving bad news [4]. Despite these findings, the practice of selective conveyance of information still occurs in Western countries. Among the physicians in Western cultures, 33% said that they occasionally, and 19% frequently, used euphemisms in discussing grave prognosis; 24% occasionally administered treatment that was not likely to work in order to maintain hope in the patient [4].

It should be emphasized that although cultural differences are present and clinicians should be aware of this possibility, the need to explore individual patient and family preferences, regardless of cultural background, is never obviated.

Nuts and Bolts of Honest Communication

Conveying Prognostic Information

While the value of honest communication between medical providers, children with cancer, and their families cannot be overstated, many physicians find it extremely difficult to have these conversations [5, 31]. Inherent to any prognostic discussion in pediatric oncology is acknowledgment that the proposed treatment plan may be unsuccessful, even when the diagnosis is associated with a very high cure rate. Clinicians may also find themselves giving information to families they have just met, such as during the "day one talk," or to families with whom they have become emotionally invested during discussions at a time of relapse or progression. While the dynamics of these conversations are different, a protocol for delivering prognostic information can be extremely helpful in allowing physicians to navigate emotionally charged conversations.

In outlining their SPIKES method (Table 3.1), Baile and colleagues identified four essential goals of difficult conversations: gauging the patient/family's understanding of the situation, transmitting medical information, providing support to the family, and establishing a collaborative relationship to plan for the future [11]. Achievement of these goals begins with preparation. Arranging for a quiet space free of interruptions, making sure the parents and child have appropriate support, and sitting down are all vital components to these conversations [32, 33].

Table 3.1 The "SPIKES" framework

S	Setting	Arrange for privacy Manage interruptions (e.g., pager, phone) Review chart & clarify medical facts Discuss goals of meeting with team & who will lead Involve others (i.e., family, staff) Sit down & introduce everyone
P	Perception	Always *get* information before *giving* information "What have the doctors told you?" "What is your understanding of…?"
I	Invitation	Ask how patient/family likes to receive information (i.e., "big picture" or details) Ask who else should be present
K	Knowledge	Consider giving "warning shot" of bad news No jargon Give information in chunks Check understanding frequently
E	Empathy/ emotion	Let them know you have connected with the emotion Use "NURSE" statements (see Table 3.2) STOP TALKING
S	Summary/ strategy	Check overall understanding & recap goals Ask permission to move forward (e.g., treatment plan, support services) Probe for questions Document discussion

A six-step framework for delivering bad news and conducting family meetings. The method is designed to help the clinician gauge understanding, transmit medical information, provide support, and establish a collaborative relationship. (From Baile et al. [11])

Prior to conveying any information, it is extremely important to understand the family's perception of the disease up to the point of the conversation. Beginning the conversation with a statement such as "What have the doctors told you so far?" allows the interviewer to ascertain the level of understanding and any misconceptions from the start. Importantly, starting a conversation with a question also gives the family control over the pace and direction of an otherwise intimidating meeting and indicates to the family that they are collaborating in the effort. Asking a child or their parents how much they want to know or how detailed they want the information to be furthers this perception. Acknowledging that difficult conversations may need to occur in more than one sitting relieves the stress of trying to address issues the child or family may not be ready for and also allows for the fact that much of the medical information conveyed will not be retained [34]. In a situation where the family or child is not receptive or ready to receive detailed prognostic information, it may be best to focus first on building a relationship with the family and to give the information later when they are emotionally ready to receive it.

Sharing medical information with a child and his or her family is complicated by the technical nature of the information, the natural tendency of clinicians to use medical terminology, and the desire to share all information at one time [3]. Firing a warning shot is often a good way to begin the process of sharing diagnostic or

prognostic information. A statement such as "I've had the opportunity to look at your child's blood under the microscope, and I'd like to take some time to talk with you" alerts the parent and child to the gravity of the discussion but also gives them a moment to focus their attention on what is about to be said. This statement could be followed by "based on what I've seen, Landen has leukemia, which is a form of cancer." It is important to avoid the natural tendency to hedge or to obscure the headline of the conversation with a lot of supporting information. Hearing the word "cancer" is likely to cause strong emotions such that continuing at this point would inundate the child and family with a tsunami of information which will not be heard or remembered [35], while hedging will only serve to cast doubt or confuse the information being shared. Even though it may be uncomfortable, a better strategy is to pause after giving distressing information and allow the family and patient time to process the information.

Receipt of diagnostic and prognostic information is obviously distressing, and responding to the emotions of both the child and the parents is challenging [11]. Displaying empathy, however, further engages the medical provider with the family and sets the stage for collaboration and goal setting [16, 36]. The NURSE method (Table 3.2) is helpful in constructing responses to strong emotions [37]. Naming the emotion is the first step in conveying that you are feeling the parent or child's emotion. "This news is very shocking" can be followed by a statement of understanding such as "although you knew something was wrong, nothing could have prepared you for this." An acknowledgment that the parent or child's disbelief is valid and normal humanizes the response and shows respect for their role as either a good parent or a good patient in the disease-fighting process. Offering support through the process with a statement such as "although this isn't the news we wanted to hear, I am in this with you, and we will face this together" reinforces the idea that the child is not alone and will not be abandoned by the medical provider whatever the outcome. "Is there more information you need, or should we just take a minute to think right now?" further explores the direction of the conversation and also gives control back to the child or family.

The final goal of prognostic conversations is to talk about options for the child and how best to move forward. Key to this process is the establishment of clear treatment goals because they will define the approach to therapy. At the beginning of cancer-directed therapy, the goal of cure is almost always the focus of the child,

Table 3.2 The "NURSE" pneumonic

N	Name	"It sounds like you are angry."
U	Understand	"I can't imagine what you're going through."
R	Respect	"I see how hard you have been fighting for her."
S	Support	"I'm here for you."
E	Explore	"Tell me more about what you're thinking."

This pneumonic provides guidance for constructing responses to strong emotion in difficult conversations. (From Medical Oncology Communication Skills Training, Fundamental Communication Skills, Learning Module 1 2002)

family, and physician. These conversations tend to focus on disease eradication. When a poor prognosis is given (e.g., relapsed or progressive cancer), goals may become focused on life prolongation or quality of life [38]. Patients and families who successfully navigate transitions in goals tend to move their focus from a need to continue therapy to fighting for quality of life, time, and ease of suffering [39]. Helping children and their families view the treatments they choose through the lens of their goal of care encourages decisions that lead patients closer to their goal and shifts focus away from the false perception of deciding between life and death.

Complications in Communication

Even the most skilled communicators experience roadblocks to effective communication. Prognostic uncertainty and parental disagreement are common areas that cause clinicians difficulty.

Conveying prognostic information can be complicated by medical uncertainty. Pediatric cancer-directed therapy is unique in that patients often have an undulating course marked by periods of good health and low points of severe or even critical illness. Further, despite advances in basic and clinical science, it remains difficult to predict which children will or will not respond to therapy from the outset, especially when certain prognostic details, like cytogenetic information, are not available until after the beginning of therapy. Up to this point, we have focused on situations where the information is clear (e.g., "your cancer is back"). More commonly, particularly when discussing the future (e.g., prognosis), the information being discussed is tinged with uncertainty. Predictions of the future are, by their very nature, probabilistic and thus uncertain. How, then, do we discuss this information with parents? We know that parents who recognized no chance for cure earlier were more likely to rate high quality of care by the medical team and choose less cancer-directed therapy while focusing on lessening suffering, rather than curative measures [18]. On the other hand, we often don't know when there is "no chance." Such uncertainties can lead to vague, overly optimistic discussions about possible outcomes [40, 41]. Encouraging optimism rather than helping parents understand that uncertainty exists is problematic because it may encourage parents to shape their decisions based on unrealistic expectations.

The first step in addressing prognostic uncertainty is to acknowledge its existence, for example, "we are not sure what the future will bring." Doing so signals to the family that the clinician is considering all potential outcomes and increases transparency. It also creates an opportunity for the clinician to address treatment options or poor outcomes prior to crisis situations [42] and to ask about hopes and expectations throughout the treatment process [43]. A communication technique that has been used to talk about an uncertain prognosis is to describe the best, worst, and most likely outcomes. This strategy clearly lays out the possible future and can lead to a discussion of how we will know which outcome is most likely and what is "worth" going through given these options [44].

In addition to attending cognitively to uncertainty, it is important to acknowledge its emotional impact. It is hard for parents to be unsure what is going to happen to their child and to worry about whether they are making the right decisions [45]. Acknowledging the emotional worry brought on by uncertainty (e.g., "it is so hard to not know how this is going to turn out") and discussing parents' coping strategies (e.g., "how are you dealing with the uncertainty?") can help build a therapeutic alliance.

Another difficult situation is when parents disagree with each other regarding the care of their children. The majority of subjects in the existing data on communicating prognosis with parents in pediatric oncology have been mothers. Fathers, however, often approach setting goals of care for their seriously ill child differently than mothers [46] and may have a more dichotomous view of treatment decisions [47] even when consensus on the meaning of prognostic information exists. Additionally, a study comparing the views of mothers and fathers of children with cancer [48] found a great deal of agreement in the understanding of prognostic information and treatment goals at the beginning of cancer-directed therapy. Differences emerged, however, when the child was felt to have incurable cancer. In this scenario, fathers, both as a group and within matched couples, were more likely to focus on continued cancer-directed therapy. While many of these differences resolved in the last month of life, continued parental disagreement with regard to focusing on comfort was associated with an increased parental perception that the child suffered at the end of life.

Typically when one parent perceives a need to continue with cancer-directed therapy, such therapy is sought even if the other parent does not completely agree. Unfortunately, such decisions often lead to regret in retrospect [49, 50]. Further, greater parent-physician agreement in children with incurable cancer is associated with improved end-of-life care [18]. Thus, helping parents confront and resolve differences in opinion is important for both the care of the patient and of the parents in the bereavement period.

When such differences exist, it is helpful to not only name the disagreement (e.g., "I can see you have different views on the next steps") but also to assure both parents that you will continue to provide support regardless of their decision. It is important for the clinician to recognize that disagreements among parents are both common and normal. Understanding that both parents are making decisions out of love, or as a "good parent" would, is important not only for the clinician but also for each parent. One could say, "Having walked this journey with other families, it is not uncommon for parents to feel differently about what is best for their child. What's clear to me is that you are both good parents trying to do right by and love your child." Beyond helping disagreeing parents identify their common ground, it may also be helpful to ask them to think about how they have dealt with other disagreements or to reflect on other times during the child's therapy when they worked through an uncertain circumstance. In some cases it may be very hard to find agreement, and at that point it may be helpful to involve other professionals with more expertise in family dynamics. Regardless of the situation, it is important for the clinician not to be perceived as

taking sides. While offering a medical opinion is always warranted, remaining neutral in such disagreements allows the oncologist to support both parents moving forward.

Communicating with Children

Pediatric oncologists also must decide when and how much information to convey when they talk to their patients about their cancer. Protecting children from harm is a natural instinct for both parents and physicians, and non-disclosure is often falsely justified by beliefs that difficult information will either depress or confuse the child [3]. Feelings of failure, sadness, or anticipatory grief over the loss of a patient are also deterrents to the oncologist caring for the child [51]. Regardless, establishing open and honest communication with the child is important and can be rewarding.

Generally, children, and especially adolescents, want to know and understand their prognosis [52] even if the news is grim [53]. As such, they deserve the ability to understand their disease, prognosis, and treatment and to participate in shared decision making to the extent they desire [54]. Even very young children are capable of understanding the concept of death [55] and are often aware of the potential terminal nature of their cancer diagnosis simply by being in the milieu of the pediatric cancer ward and clinic. Involvement of the child in these conversations engenders trust between the oncologist and the child [32] and allows them to better express their wishes with regard to treatment, end-of-life preferences, and code status [28]. Although not every patient desires to know their prognosis [56, 57], avoidance of addressing these questions with children may result in significant behavioral issues including anxiety, anger, poor school performance, and fear [58]. Concurrently, helping parents discuss prognostic issues, like death, with their child reduces decisional regret in bereaved parents [59], and physician participation in this process relieves the parent of the burden of telling the child about their illness alone.

Beale and colleagues [60] have outlined an effective strategy for communicating prognostic information with children (Table 3.3). The first step is to establish permission from the parent to approach the child with this information. Parents may find it difficult to accept the need to share distressing information with their child, and some may indicate a desire to avoid the conversation with the child. The physician should explore these feelings with the parent, express the importance of open communication, and set guidelines early on in the therapeutic relationship regarding honesty [42]. It may help the parents if the clinician emphasizes they are going to offer information to the child and that if the child does not want to talk, the clinician will not push.

Parental refusal to grant such permission can be distressing to the healthcare team, but in these circumstances maintaining trust and communication with the parent is important, as many will change their feelings on this over time. In this situation, a physician may agree to comply with the parental request so long as the parent understands that the issue will be revisited and that the physician will reply truthfully to questions directly asked by the child [56].

Table 3.3 The "six Es" for communication with children

*E*stablish	Establish an agreement with parents, children, and caregivers early on in the relationship with them concerning open communication.
*E*ngage	Engage the child at the opportune time. Signs of significant behavior change can suggest that the child is struggling with emotions and will provide an opening for discussing the illness.
*E*xplore	Explore what the child already knows and wants to know about the illness.
*E*xplain	Explain medical information according to the child's needs and age. "What would you like to know?" and "what have you been worrying about?" allow for identification of specific information needs.
*E*mpathize	Empathize with the child's emotional reactions. "I can see that you've really been worried about this."
*E*ncourage	Encourage the child by reassuring him or her that you will be there to listen and to be supportive.

The "six Es" provide guidance for communicating prognostic information with children. (From Beale et al. [60])

Prognostic discussions should occur on the child's timeline. A child may open the door to conversation at any point, and so it is helpful for the provider to look for opportunities to talk. Instead of having an agenda for the conversation, exploring what the child knows or wants to know about their condition is a good way to open the door. If a child expresses anxiety about their disease course, a question such as "what is giving you the most worry?" essentially tells the child that you are willing to listen to their concerns if they want to talk about them. Allowing the child to direct the course of the conversation gives the clinician the opportunity to identify the patient's major concerns and correct any misconceptions about the illness.

Answering the questions of a seriously ill child can be emotionally difficult, especially in the case of a terminal prognosis. If a child asks, "am I going to die?," the clinician is faced with the prospect of being too blunt versus being overly optimistic or evasive. One strategy for addressing this question is to answer it with a question such as "sometimes we don't have the medicines we need to make kids better. Is that something you are worried about?" Doing so allows the child an opportunity to decide if the statement applies to their situation while the answer gives the clinician clues as to how deep the child wants the explanation to be. As with any difficult conversation, addressing the emotions of the child is of paramount importance. Validating and empathizing with a child's feelings toward his or her illness experience solidifies the notion that the provider will help the child moving forward. In the end, simply demonstrating that the clinician will not abandon the child opens the door to communication along the spectrum of the illness experience.

Conclusion

Communicating diagnostic and prognostic information to children with cancer and their parents is an important yet daunting task for pediatric oncologists. Honest and well-timed sharing of information is the cornerstone of a healthy

physician-parent-child relationship. Rather than destroying hope, honesty between providers and their patients increases trust and expands the definition of hope even when sharing poor prognostic information. Children have a right to know and understand their disease process and trajectory, and navigating disagreements between parents and their thoughts on disclosure to the child requires patience and a willingness to allow both parents and children the time they require to fully process and hear this information. Communication based on understanding, respect, empathy, and non-abandonment can transform the provider-patient relationship into a therapeutic agent, even in dire circumstances.

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Chapter 4
Managing Conflict When There's Disagreement in Care Between Medical Providers, Caregivers, and Patient

Ernest Frugé, Michael Sprehe, Laura Loftis, Melody Brown-Hellsten, and Courtenay Bruce

Introduction

> One of the secrets of cooperation is that it results in a great deal of conflict.
>
> Conflicts are especially frequent whenever individuals have goals that they care about and are involved in relationships they value.
>
> D.W. Johnson. *Constructive Controversy: Theory, Research, Practice*. 2015 [1]

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The medical care of children with life-threatening and life-limiting illness is a crucible containing many volatile issues and complicated circumstances that predictably provoke conflict between well-meaning people. This chapter will review the prototypical types of conflicts that occur in the practice of pediatric hematology/oncology and propose methods of managing these conflicts that hinge on established ethical principles and disciplined reasoning. We draw on the broader field of conflict management for an empirically grounded understanding of conflict and conflict resolution strategies.

Wall and Callister, in a comprehensive review of conflict and its management across a variety of settings, point out that only a small percentage of conflicts can be accounted for by personality factors or character "traits" (e.g., "the disruptive physician") [2]. However, there are certainly personal factors or "states" of mind and experience (e.g., strong emotional reactions) that are associated with an increased likelihood of conflict. For example, research indicates that conflict is more likely when individuals have high goals and high commitment and when negative emotions such as stress and fatigue are present. There are also interpersonal and organizational factors that contribute to conflict. Examples here are situations where there is high task interdependence, that is, work that requires intricate coordination among multiple agents. Lack of clarity among important roles (e.g., ambiguity in responsibility and authority for decisions) is a similar factor. Conflict is also more likely if the issues at hand are complex and involve high stakes or core values. These factors should all sound very familiar to professionals working with pediatric hematology/oncology patients – conjuring up memories of contentious exchanges involving family members or colleagues, particularly in acute care and end-of-life scenarios.

In 1949, Morton Deutsch proposed a unifying theory of conflict and cooperation [3]. The basic premise is that conflict ultimately results from a problem in achieving alignment between the goals of stakeholders. Our working hypothesis is that the most frequent, fundamental, and influential source of conflict in pediatric hematology/oncology is a problem of achieving alignment of goals among the multiple, key stakeholders that are typically involved in caring for the patient. Ironically, if this hypothesis is correct, then conflict in pediatric hematology/oncology will likely increase as advances in the field lead to greater technical complexity of care. Determining a plan of care is a common, complicated, and primary task in pediatric hematology/oncology – a task that should reflect an alignment of goals but often must be done under conditions, as noted above, that predictably promote conflict. Disagreement over the plan of care has been shown to be a significant point of conflict within families, between families and professionals, and between professionals in both acute care and end-of-life settings [4–6].

If our perspective is correct, then all the manifestations of conflict that are not actually attributable to difficult (and difficult to alter) personality structures may be addressed by procedures that promote the identification and alignment of primary goals. This is not to say that the negotiation of such goals is an easy task, but we propose that if the reasonable and ethically justified alignment of goals is a guiding principle in methods of conflict resolution, then the outcomes should be better rather than worse. The literature on conflicts due to disagreement over medical care can be

placed in three categories according to the relationship between the particular roles involved and the rights/authorities and responsibilities pertaining to each type of role (patient/families, disciplines on the hematology/oncology team, and different specialties). The following sections will describe the prototypical sources of conflict in the practice of pediatric hematology/oncology, relevant ethical appeals, and suggested strategies for resolution of conflict between patient/families and providers, between providers on the same inter-disciplinary specialty team, and between different medical specialists.

Conflict Between Patients/Families and Professionals

The diagnosis of a malignancy in a child threatens not only the individual patient but the whole family unit. Creating a trusting relationship between the patient, parent, and the care team is crucial to optimizing goals of care and creating effective treatment plans. Creating and maintaining such trusting relationships when disclosing a threatening diagnosis or a downward trajectory is a complex task. When there is a lack of trust in providers or the family is unable to accept the diagnosis or prognosis, there will inevitably be conflicts that will challenge professional integrity and potentially compromise professionals' ability to carry out their responsibilities. Conflicts between professionals and patients or parents can be broadly separated into three main categories – conflicts over decisional authority and the best interest standard, the decisional and non-decisional rights of adolescent patients, and problems in alignment and communication among professionals.

Source of Conflict #1: Decisional Authority and the Best Interest Standard

The first broad category of ethical conflict in pediatric hematology/oncology centers on the authority to make decisions. In Western societies, respect for autonomy of the individual patient is paramount and shared decision making is recommended as a way to maintain autonomy yet not deprive the patient of the expertise of the physician. Shared decision making is endorsed by the American College of Critical Care Medicine and the American Academy of Pediatrics [7, 8]. In this model, the physician and the patient agree upfront on how they would like to make decisions together [9]. This model is also recommended in circumstances where adults are in the role of surrogate decision makers for their spouses, parents, friends, or adult children. As such, they must abide by surrogate decision-making rules – they must give priority to what the patient would have wanted, based on their life experiences and values, were they able to voice their opinion. The main shortcoming of shared decision making is that it does not specifically address how decisions should be made for children who legally have no decisional authority and whose life experiences often

cannot help inform the decision-making process (e.g., the infant patient). In this situation, with no legally binding wishes for the surrogate, how are decisions to be made for children? There is conflict in today's culture regarding the extent of parental authority. Should a parent be able to demand any potentially life-prolonging therapy even if it is not possible to save the patient's life and such therapy will likely lead only to more suffering? This situation is, unfortunately, not uncommon, especially when parents have unrealistic expectations.

Ethical Considerations

According to the American Academy of Pediatrics, the best interest standard is currently the criterion by which parents and physicians should make decisions for children [10]. In pediatrics, parents are typically given the right and responsibility of determining what is in their child's best interest, but clinicians also have a beneficence-based obligation to confirm, as much as they are able, that parents' decisions align with the best interest standard. However, there is no single accepted definition of best interest. Article 3 of the UN Convention on the Rights of the Child states that "in all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration." Assessing the best interests of a child is defined as balancing and evaluating "all the elements necessary to make a decision in a specific situation for a specific individual child or group of children" [11]. These statements are not explicit, allow for much value-laden interpretation, and therefore are not very helpful at the bedside.

In 2009, Malek sought to clarify the definition of the best interest by comparing the UN Convention on the Rights of the Child, the book *The Irreducible Needs of Children*, and a list of human capabilities to provide content of what should be considered when determining what is in a child's best interest [12]. From the overlap of these statements, she found that the concept of best interest covered 12 domains that were considered universal (see Table 4.1).

This model allows and requires clinicians and parents to take a broad view of a child's well-being. Further, it limits overemphasizing physical well-being and puts appropriate weight on the effects of a condition or treatment(s) on a child's other interests in a holistic fashion. The author notes that the lack of any one of the interests can severely compromise a child's overall quality of life and that there is a

Table 4.1 Children's interests

Life	Education and cognitive development
Health and healthcare	Expression and communication
Basic needs	Parental relationship
Protection from neglect and abuse	Identity
Emotional development	Sense of self
Play and pleasure	Autonomy

diminishing marginal utility in furthering a single interest. Of particular note is the assertion that interests are not interchangeable – the promotion of one interest is unlikely to compensate for a deficit in another. The advantage of such a catalogue is that it requires clinicians to take a broader view of a child's well-being than the purely medical and provides an understanding of relative importance – only 4 of the 12 interests are physical, while the other 8 are cognitive, emotional, and social. However, physicians should be considered the content experts within the biological realm. As such, physicians must be as clear as possible about what is medically appropriate, the strength of the biomedical evidence behind their recommendations, and the interaction between the health interests and the child's other interests. Patients and parents must then factor this biological component with psychological and social aspects to make a decision that will uphold the child's best interest.

Requests for non-beneficial therapies conflict with the fiduciary obligation of the physician and the virtue of professional integrity. Healthcare professionals have a fiduciary obligation to protect and promote the health-related interests of the patient. This obligation can be expressed in terms of the ethical principles of the non-decisional rights of beneficence and non-maleficence. In the clinical setting, these principles obligate the healthcare professional to seek the greater balance of clinical goods over clinical harms in the management of the patient [13]. It is important to remember that the goals of medicine, for over 2000 years, are to heal when possible, to comfort always, and not to prolong the dying process [14]. The artificial prolongation of dying is termed dysthanasia and can lead to excessive and needless suffering [15]. In addition, using patient or parent autonomy to justify acquiescence to patient's requests for non-beneficial services violates professional integrity. Professional integrity requires physicians to adhere to standards of intellectual and moral excellence. For physicians, intellectual excellence is achieved by submitting clinical judgment to disciplined, evidence-based reasoning, rather than simply acquiescing to requests for non-beneficial therapies.

Although "parental autonomy" should not be used to justify acquiescing to parent's requests for non-beneficial therapies, parents are owed, at the very least, transparent and complete communication of relevant information in a manner they can comprehend in order to enhance their autonomy and role in decision making. They serve as the ultimate decision maker in cases where there is a range of reasonable and evidence-based options. Only in a circumstance where there is one clearly superior option should clinicians exercise more authority than parents in the decision-making process.

Source of Conflict #2: Decisional and Non-decisional Rights of Adolescent Patients

Parents, often wanting to shield their child from harms, will occasionally resist telling their children about a cancer diagnosis or informing their children when the prognosis has changed for the worse. In addition, there are occasions where the child does know the diagnosis and prognosis, but there is conflict between

providers and parents about how much say the child should have in determining plan of care. Should the child, in line with his developmental capacity, have a say in continuing therapies, especially when they are unlikely to be of significant clinical benefit? It is of note that parents themselves are often not in agreement about continuing therapies of marginal potential benefit, and in these situations the child is usually not brought into the treatment decisions.

Ethical Considerations

Legally, adolescent patients do not have competence and thus have no decisional rights. Morally and ethically, however, the adolescent should be given their healthcare information to the degree that they are capable of understanding [10]. Requests to not inform the adolescent patient, if agreed to, infringe upon professional integrity in that they impede the non-decisional right to the truth and honest communication. In addition, while in some instances it may seem counter-intuitive, being open and honest is compassionate. Without the knowledge of one's own impending death, the ability to craft a good death is impaired. While the concept of a good death is highly individual, important attributes found in the literature include being in control, being comfortable, having a sense of closure, affirmation/value of the dying person, trust in care providers, recognition of impending death, beliefs and values honored, burden minimized, relationships optimized, appropriateness of death, leaving a legacy, and family care [16].

Source of Conflict #3: Problems in Alignment and Communication Among Professionals

Another source of conflict between patient/families and professionals derives from actual or perceived erroneous, incoherent, and/or contradictory communication among professionals and between professionals and the patient/family regarding diagnostic, prognostic, or treatment information. The field of pediatric hematology/oncology has a long tradition of providing comprehensive care to children and families with complex needs through multi-disciplinary teams (hereafter "teams") and collaboration with a wide range of other pediatric specialties which are themselves comprised of multi-disciplinary teams (hereafter "specialties" such as critical care, pathology, and surgery). These teams and specialties collectively aim to provide integrated, family-centered care with the goal of improving both disease and quality-of-life outcomes [17–19].

Ethical Considerations

The organizational psychology literature suggests that team-based models present challenges in collaboration, role-boundary recognition, and delineation of responsibilities among team members [20]. These organizational challenges are compounded with the addition of multiple specialty services. Parents may get "different messages" because professionals within and across specialty teams disagree about prognostic or diagnostic information, or there may be differences in communication styles between healthcare professionals. Through internal focus group and family interviews, we have found that patients and families feel lost and overwhelmed when engaging and negotiating acute and chronic complex health needs with multiple providers. Healthcare professionals also find the team-based/multispecialty model challenging. Specifically, healthcare professionals report feeling moral distress as a result of intra- and inter-team discordance regarding goals and treatment methods. The issue of moral distress will be elaborated in the following section.

In one study exploring factors that complicate communication with patient/families, intensivists and critical care nurses reported engaging in a "pas-de-deux" (a term from ballet referring to a dance involving two people) to manage discordance between team members about patients' plans of care [21]. This pas-de-deux involved an intricate maneuvering where healthcare professionals tried to reconcile disparate prognostic information and divergent plans of care among team members. As healthcare professionals work to reconcile divergent clinical perspectives, clinicians maintain superficial conversations with families so that no one healthcare professional could object to the content of the conversation. The alternative approach healthcare professionals reported using with families while there is disparate opinions or plans of care between providers was to have substantive goals-of-care conversations with patients or families, but using conditional phrasing to account for disparate clinical views, like "but other physicians may disagree," or "we're still not sure. Let's wait and see."

Naturally, the pas-de-deux maneuver can be detected by families, and they likely wonder why healthcare providers seem to be lacking transparency in their communications or why there appears to be discordance in their perspective on diagnostic or prognostic information. Similarly, conditional phrasing invites patients and families to discount the professional judgment of the clinician disclosing information. Both communication approaches inevitably entail compromises in clinicians' professional integrity or morality. Furthermore, both communication approaches lead to very mixed messages, which can create further conflict.

Strategies for Conflict Resolution

The first step to effectively resolve conflicts is to determine the source of the conflict with the patient and/or his or her family. To do this, healthcare professionals (or mediators or ethicists) should ask open-ended elucidation questions of the parties involved to learn more about their perspectives, like "It would be helpful for us to learn more about your perspectives, your values, and your beliefs. Can you tell me more about what you've learned about your child's health from the different practitioners?" or "what is making it difficult for you to make decisions about your child's care?" The utility of these questions should not be underestimated. Answers to these questions can reveal whether and how there might be mixed messages, intra-team discordance, feelings of mistrust, or general apprehension about losing a child.

Once the source of conflict is identified, healthcare professionals should explore what might be a helpful solution to resolving the source of conflict by asking, for instance, "My sense, then, is that a major challenge for you is that you no longer trust the healthcare professionals involved in your child's care. Is that accurate? What do you think we could do to help rebuild that trust?" [22]. Allowing parents to have some input on where and how to resolve the disagreement goes a long way in terms of building rapport and achieving buy-in from all the morally relevant stakeholders involved in a conflict.

An underlying principle across recommendations for resolving conflict between patients/families and professionals regarding requests for potentially non-beneficial therapies is the requirement that professionals, before embarking on negotiations with patients/families, must first define for themselves the medical facts of the case, the territory over which they have the right and responsibility to exercise decisional authority, and the evidence upon which these options and decisions are based (e.g., reasonable treatment options). They must also clarify for themselves what, in the context of the patient's circumstances, decisions the patient/family have the authority to make (e.g., choice between two reasonable options) [23–25]. As mentioned above, in circumstances where multiple treatment options can safely be provided, parents should have maximum decisional authority. In cases where parents do not agree with the only medically reasonable option available, physicians should still engage, teach, and persuade parents to agree with the treatment plan, but they are not ethically obligated to change the plan based on the parents' preferences. An example is the use of antibiotics to treat an uncomplicated viral upper respiratory infection where antibiotics could only cause harm with no potential for benefit.

It can be argued that such a directive approach to communication, where a clinician offers no latitude for shared decision making and retains exclusive decision-making authority, undermines parental authority and gives clinicians' ethical controlling authority. Limiting parental authority and using a directive approach could create dissension among parents who may wish to exercise more parental control. However, we contend that a directive approach is ethically warranted in very limited circumstances in which there is only one medically viable treatment option because to do otherwise produces greater ethical harms by (1) providing

false commitments to parents, (2) undermining transparency, (3) potentially violating professional integrity by "requiring" clinicians to render treatments that cannot reasonably and safely be provided, and (4) undermining patients' beneficence-based interests by jeopardizing their safety. Furthermore, practically speaking, directive communication can mitigate confusion and miscommunication by clearly and explicitly assigning authority for decision making. Many parents willingly relinquish decision-making authority and the burden of decision-making responsibilities in limited cases where there are no alternatives and no decisions for them to make.

In some cases, there really aren't different treatments that can be ethically supported. It would violate professional integrity by providing a particular treatment which would only create harm and produce no benefit. However, practitioners should be careful in how to present what is, in reality, a limitation of parental decision making. It is reasonable to assume that parents have only good intentions when requesting interventions; therefore focusing on how this situation is different than previous situations, rather than on the practitioners' ethics, is important. "Typically, we have discussed treatment options and possible outcomes so that you can decide what option you feel is best for your child. But, in some cases, there really aren't different treatments that we can offer for this problem. We understand it is difficult when options are limited and that it is important for you as a parent to seek all possible options for your child. However, in this situation we can't offer something that will not make the current problem better and will only create harm by adding additional symptoms or complications. Thus, we cannot offer you Treatment X, as the only reasonable treatment option in this case is Treatment Y."

Another helpful conflict resolution strategy is for healthcare professionals to transparently discuss their own struggles and feelings in managing a case because doing so provides clarity in their perspectives. Thus, we would encourage healthcare professionals to explicitly describe how or why the case or conflict is challenging for them, such as "I am struggling here, as well. My job as a doctor is to do everything I can for my patients – to protect them and their well-being so they can live a healthy life. I also understand that as a parent, your role is to protect and advocate for your child so they can get better and live a healthy life. However, what you are asking me to do, if I understand your perspective clearly, is to provide a treatment to your child that would only cause more complications and suffering. I think we can both agree that it is best that we avoid harmful interventions and focus on care that is helpful at this time." Transparency creates a sense of humanity and relationship among the parties involved in a conflict, which in turn can serve as the basis to deescalate the conflict.

A final helpful conflict resolution strategy is to define those areas in which the different parties agree, creating a sense of unity and cohesion among the participants involved in a disagreement. We encourage healthcare providers and families to write out areas where they agree and singularly define those areas where they disagree. By creating a visual aid, the parties can stay on task by focusing exclusively on those areas where they disagree. We encourage doing this activity at the beginning of a discussion with the family and then once again toward the end of the discussion – to determine whether those areas have been resolved through the discussion and to pinpoint what needs to be discussed in future meetings.

Conflict Within Teams and Between Specialties

As mentioned in the introductory paragraphs, the goal of coordinated multidisciplinary, multi-specialty care necessitates a highly complicated organizational arrangement with a variety of features commonly associated with an increased likelihood of conflict – situations where multiple interdependent agents are strongly committed to important goals involving high risk, technical complexity, and strong negative emotions. It is noteworthy that, for the majority of cases, little disagreement exists between disciplines and specialties regarding plans and coordination of care. Yet a small subset of cases generate significant conflict. This section will describe three principal sources of conflict within teams and between specialties. The first two sources relate to divergence of opinions over goals of care and treatment options. The third source involves the interpersonal, group, and inter-group factors that can negatively impact the quality of decisions regarding treatment aims and options as well as the coordination of care and communication within teams, between specialties, and between providers and the patient/family. While it can be tempting to label one party (individual or group) to a conflict as lacking relevant competency or having negative personality traits, we argue that most conflicts in pediatric hematology/oncology clinical work occur between well-intentioned, capable individuals or groups who believe that they are acting with professional integrity in the patient's best interests.

Source of Conflict #1: Goals of Care

Separating goals of care from treatment choices is difficult as goals generally drive the range of choices available or offered. Goals of care can be multiple and overlapping and include cure, prolongation of life, minimization of suffering or side effects, or a peaceful death [26]. While every provider and patient/family may prioritize cure as the initial goal, what is the clinical likelihood of cure given the current circumstances? For lower-risk acute lymphoblastic leukemia (ALL) with a greater than 95% cure rate with chemotherapy, cure is an appropriate goal. For multiply relapsed, refractory malignancies where no standard curative therapies exist, cure may not be an attainable goal. Likewise, in cases of diffusely infiltrative pontine glioma (DIPG), cure is exceedingly unlikely and thus may not be a reasonable goal. Yet, the goal of reducing the symptoms caused by the disease or of prolonging life is achievable with radiation therapy. When no curative therapy exists, the goal of minimizing suffering at the end of life with palliative and hospice care becomes the priority.

There can be significant disagreement about goals of care between providers and disciplines within the hematology/oncology team as well as between specialties based upon diverging opinions regarding prognosis, what constitutes a "reasonable" intervention, or implications for assessed quality of life and suffering. An example

may be a critically ill patient with multiply relapsed disease requiring significant critical care management over a prolonged course. Hematologists/oncologists may still hope for remission or cure with different or experimental treatments and therefore want to attempt further chemotherapy, whereas the intensive care team may believe that survival is unlikely and are therefore being asked to "do things *to* patients and not *for* them." Hematologists/oncologists may be accused of lacking objectivity or having unrealistic goals while intensivists may be accused of dashing a family's hopes, of being overly pessimistic, or of lacking a personal connection to the patient or family.

Ethical Considerations

Each provider is exercising his/her own professional judgment and values when supporting a particular goal. Yet as the estimations of benefits, harms, and suffering vary between disciplines and specialties, providers may be asked to participate in care that runs counter to their own estimations. Is the oncologist "giving up" when transitioning from a goal of cure to comfort care? Is the intensive care team "torturing" the patient with continued procedures near the end of life? Moral distress refers to negative feelings or anguish that arise when a person believes one course of action is morally superior to another, yet cannot follow that preferred course due to external constraints (such as professional, social, or organizational policies) [27].

Requiring any provider to participate in treatments with which they do not agree adds a layer of moral distress to the underlying conflict regarding aims. In the above example, some members of the hematology/oncology team and/or the intensive care team may believe that survival is not possible and that ongoing chemotherapy is creating unnecessary suffering for the patient. Some providers within the hematology/oncology team and across specialties may therefore wish to promote a goal of a peaceful death, with limited invasive procedures. Being asked to continue to provide aggressive treatment to the patient with cure as the goal might make some providers across teams feel complicit in causing harm without an expected proportionate benefit (i.e., survival). Goals of care should be mutually agreed upon by the provider teams after discussions with families and patients. One provider or one team unilaterally changing the goals of care without deliberation with the other provider or teams, even when concerned about increased patient suffering, risks violating professional and ethical standards.

Goals of care can range from curative intent to prolonging life, improving quality of life, or providing adequate palliation of symptoms without cure. These and other goals may coexist. However, conflict may arise when disciplines or teams have goals that appear to be mutually exclusive. As in the example above, one team may be offering treatment with curative intent where the other team seeks palliation at the end of life when cure is doubtful. Each team is exercising their own professional autonomy and moral agency in pursuing what they each believe to be appropriate goals. The hematology/oncology team may be focused on potential benefits, whereas the intensive care team is focused upon avoiding interventions

that may lead to more suffering, pain, or other harms (balancing beneficence and non-maleficence).

Furthermore, intensivists are stewards of a scarce resource (ICU beds), adding utilitarian concerns to estimates of benefit and cost, and an appeal to the principle of justice. Inappropriate treatments at the end of life are a major source of moral distress, moral residue, and burnout within ICUs [28]. Early efforts to address this have led several professional groups to develop and publish a position paper on limiting inappropriate treatment at the end of life [25]. Discussions of goals should include each of the involved disciplines and specialties and should be continually reviewed and adjusted based upon changing clinical circumstances.

Sources of Conflict #2: Disagreement Over Treatment Options/ Interventions

Example disagreements include:

- Surgery vs. chemotherapy vs. radiation
- Chemotherapy vs. transplant
- Relapse therapy vs. early phase clinical trials vs. palliative care

Although this source of conflict may be more visible between specialties, each discipline and specialty brings skills and experience to bear on each case, along with their understandable biases. Typically, the oncologist, with consultation from surgeons and radiation oncologists, develops a treatment plan. In pediatric oncology, that plan is often the adherence to a clinical trial or other protocols considered the standard of care. Sometimes within a protocol the need for a certain modality of treatment is based upon the results of other modalities. For example, a successful surgery may reduce the need for radiation therapy. So how aggressive should the surgeon be? Should the oncologist push for a complete resection instead of a biopsy, knowing less chemotherapy or radiation therapy would be needed? At what cost to normal anatomic structures around the tumor or to the patient from a potentially higher-risk surgery? In idiopathic aplastic anemia, should the hematologist/oncologist proceed with immune suppression therapy, which many consider the standard of care, or should the transplant team push for bone marrow transplant as definitive treatment due to improving outcomes? In a patient with relapsed cancer for which no standard treatment exists, should the patient receive treatment with agents whose efficacy, however limited, is known or enroll on a phase I trial? Providers involved in drug development may prefer enrollment in early phase trials while clinical oncologists may prefer individualized treatment regimens. In each of these cases, a specialty has certain skills and treatments to offer. Each specialty may also over- or underestimate the benefits offered by each specialty, including their own.

Published clinical data may be lacking or not applicable to a case to guide decision making or estimate and compare relative benefits. Uncertainty over which

choice is most likely to meet the goals of treatment, or an unfounded certainty without supporting data over the best choice, can lead to conflict between teams advocating for different treatments. Such conflicts can impair future communication between teams and risk harm to patients and families by increasing anxiety and distrust.

Ethical Considerations

Clinical uncertainty should be shared with the patient and family, including uncertainty regarding the potential benefits and risks of each potential treatment option. For example, the risks of an attempt to completely resect a tumor, the increased morbidity and mortality from that approach, and the benefit of less chemotherapy/radiation therapy later versus the risks from additional chemotherapy/radiation therapy if only a biopsy is performed should be presented to the patient and family. This reflects the virtue of truth-telling which stems from the principle of respect of autonomy. If one treatment option is clearly superior, it should be chosen based upon the principles of beneficence and non-maleficence in the application of the best interest standard. When no option is clearly superior based upon existing data, a stance of clinical equipoise is called for. The ethical principal of equipoise acknowledges that when neither treatment is known to be superior, either treatment is ethically permissible [29]. This has been often used as the ethical rationale for randomized controlled trials in which neither arm of a study is clearly known to offer a greater benefit, making placement of patients on different arms of a study ethically defensible. In clinical circumstances where clinical equipoise is appropriate, treatments recommended by one specialty may not be clearly superior to the treatments recommended by another specialty. In these cases, either choice becomes ethically permissible, and greater deference to patient or surrogate decision-maker opinion is given [23].

Source of Conflict #3: Clarification and Coordination of Roles

The pediatric hematology/oncology team generally includes some combination of physicians, nurses, social workers, chaplains, psychologists, and child life specialists. Varied levels of training and experience as well as discipline-specific knowledge, skill, responsibilities, and scope of practice combine to define a professional role on the team [19, 30]. *Multi-disciplinary* care includes disciplines working independently on a care-related problem from a specific discipline perspective, while *inter-disciplinary* care involves multiple professional disciplines working together on a common care issue. The ideal, *trans-disciplinary* care, is an integrated approach aimed at recognizing and utilizing overlapping roles and functions of team members to synthesize information regarding patient care issues to address complex needs

and care management tasks [31]. While the goals of trans-disciplinary care are laudable, real-time execution faces numerous challenges.

Within teams, the physician's ultimate responsibility and authority for treatment decision making creates a true hierarchy. This hierarchy, combined with other factors, can generate additional power dynamics where other disciplines on the team feel inhibited or are actively discouraged from expressing justified but divergent opinions [32]. These power dynamics can expand a professional difference of opinion regarding treatment goals or options into something more political within the team – a competition for influence or dominance that suppresses collaborative thinking rather than facilitate the rigorous consideration and integration of information from multiple sources sought after in the ideal of trans-disciplinary care. Examples of other generic factors that can impair optional functional relations between professionals include differences in gender, seniority, or rank and differences in the type of relationships established between different providers and the patient/family (e.g., primary or continuity provider vs. current inpatient team member). These dynamics can impact the overall quality of decision making as well as morale of team members. Communication and coordination within the team, with other specialties, and with the patient/family can also be negatively affected.

Clarification and coordination of roles between specialties can, in a way, be seen as aspiring to the same optimal interactions as trans-disciplinary care where the expertise of multiple specialties is effectively combined for the best interests of patients/families. Where many of the issues described in the preceding paragraph can be viewed as instances of "vertical" conflict between levels of a true hierarchy within a team, the problems in relations between specialties are examples of "horizontal" conflict where roles that hold equivalent hierarchical authority have differentiated expertise and often a different type of relationship with the patient/family (e.g., long-term/continuity vs. acute care focused) [33–35].

Ethical Considerations

When multiple specialties are caring for a patient, who should have decisional authority for any given intervention? Common practice and professional societies (e.g., American College of Physicians [36]) dictate that the primary team, who ideally understands the patient's overall health, disease burden, and preferences/goals best, makes the ultimate decision while consultants offer recommendations or provide necessary technical services. Each service, however, acts as their own moral agent with a fiduciary duty to the patient. As a result, each service may present their assessment and treatment preferences that differ from the primary service's assessment and treatment preferences. While it may be their professional obligation to provide such recommendations, to what degree are those recommendations dispositive? What if those recommendations are made to the family before they are discussed with the primary team? The consultants may have fulfilled their professional duty in offering the recommendations, but without context, a patient

or family could become confused by differing opinions and suffer from lack of trust, and relationships between and among the specialties and the family could erode.

Each provider has an overarching ethical obligation to provide skilled, high-quality patient care through deployment of their skills [37]. The American Academy of Pediatrics (AAP) Report on Professionalism in Pediatrics also describes the importance of cooperation and effective communication as components of ideal standards of professional practice [38]. This report highlights the need for self-awareness of one's own limits of knowledge and the need to request assistance from others. While the presumption may be that a patient's primary team makes decisions based upon the advice of consultants, there may be times where deference to consulting specialists is appropriate. It is imperative that all involved providers maintain excellent communication with each other and with the patient and/or family. The focus must always remain on the best interests of the patient and not the interests of providers or teams.

The antecedents to and experiences of team conflict discussed above have several ethical and moral implications. All healthcare providers are guided by their particular professional code of ethics, which generally addresses core principles such as respect for patient autonomy, beneficence, and non-maleficence [31, 39]. As such, each member of the team views potential patient care dilemmas from their particular professional vantage point, which is influenced by the training and professional culture of the given discipline. Professional autonomy is challenged when healthcare providers are required to adhere to their discipline-specific standards and perform within their role and patient care tasks, while being obliged to participate as a collaborative team member in circumstances where decisions of the larger team may be in opposition to the individual's assessment of the clinical situation [31, 39, 40]. The situation is exacerbated if there are hierarchical structures that deter open communication and reflection on all team members' concerns [41, 42]. Team members may experience feelings of powerlessness in interactions with patients/families, uncertainty with regard to who has a voice in medical decision making, and difficulty actualizing the quality of care they believe is their responsibility to the family [43].

Ethical dilemmas also arise when individuals on a team disagree about the right thing to do for a patient [42, 44]. The suffering and potential death of a child creates a tension between the professional teams' ethical imperative to preserve life (beneficence) while doing no harm (non-maleficence). Carnavale terms this tension "the tragic dilemma" in which healthcare providers and parents are in a situation where all available care options lead to an undesirable outcome (disability or death) and thus are unable to emerge from the situation without "dirty hands" [44]. Conflict may emerge when complex clinical situations, such as progressive disease, substantial pain or symptom burden, perceived suffering, and end-of-life issues, are interpreted by each professional based on their caregiving role in addressing patient harms, their access to accurate prognostic information and appropriate care, as well as their implicit/explicit moral framework [19].

Strategies for Conflict Resolution

> When faced with conflict, physicians should display the "virtues of patience, humility, and tolerance" to ameliorate disagreements.
>
> Beauchamp and Childress, *Principles of Biomedical Ethics*, 5th ed. pp 36–39 [45]

Studies of conflict within multi-disciplinary teams suggest that, in certain circumstances, conflict can be constructive, promoting an open discussion and debate among team members, leading to effective problem solving [46, 47]. However, there also is evidence that conflict within teams can result in negative consequences for individual team members, the team as a whole, and the organization [31, 37]. Conflict in the workplace can lead to numerous undesirable outcomes for team members including absenteeism, anxiety, emotional distress, job termination or resignation, low morale, posttraumatic stress disorder, and illness [48]. Similarly, patient safety, quality care, and outcomes all suffer when there is unresolved conflict within teams [35]. It seems reasonable to conclude that these same benefits and risks apply to conflict between specialties.

All health professionals share a commitment to work together to serve the patient's interests. The best patient care is often a team effort, and mutual respect, cooperation, and communication should govern this effort. Each member of the patient care team has equal moral status. When a health professional has important ethical objections to an attending physician's order, both should discuss the matter openly and thoroughly. Mechanisms should be available in hospitals and outpatient settings to resolve differences of opinion among members of the patient care team. Ethics committees or ethics consultants may also be appropriate resources [36].

Reduction of within-team conflict requires addressing the factors discussed earlier that promote conflicts among team members. Developing an inter-professional atmosphere where members of the care team know and respect each other's training and expertise will reduce power differentials and improve trust among team members [30]. Enhancing supportive peer relationships within the team has been shown to decrease negative effects of workplace conflicts and improve job satisfaction [49]. Education and professional development opportunities focusing on conflict resolution training, communication skills around difficult conversations, and reflection can help increase team member empowerment and professional confidence [30, 35, 37, 50].

Johnson and colleagues have described a theory and related strategies for conflict resolution termed "constructive controversy" that has been fruitfully applied across a variety of organizational context [1]. Constructive controversy methods are differentiated from debate in that the aim is fostering curiosity and possible integration of information rather than a necessary rejection of particular points of view. Johnson and colleagues offer guidance on the methods and skills required for effective interventions as well as empirical evidence demonstrating the effectiveness of the methods on measures such as perspective taking, creativity, and self-esteem [51, 52]. This approach seems to fit well with the facilitative approach to ethics consultation where the aim is to articulate the reasoning, including both evidence and values,

underpinning various options and discussing the relative advantages and disadvantages attached to each option.

When conflicts between specialties arise, inter-disciplinary/inter-specialty meetings (i.e., care conferences) are one forum to discuss therapeutic options. Hellsten and colleagues have been piloting care planning conferences that employ constructive controversy principles where there is risk of or ongoing conflict between specialty teams [53]. In this method, professionals from involved specialty teams are required to clearly state their recommended treatment plans and explicate their reasoning, including the evidence base for treatment alternatives and perceived patient/family preferences, in a way that allows open and respectful examination of the facts of the circumstance, a systematic review of ethical principles that may apply and reasoning through the factors in an effort to promote mutual understanding and arrive at a shared decision for a coordinated care plan. While case reports may be a valid and valuable source of information, one should be skeptical of anecdotes for or against any given treatment as they may not be generalizable or relevant to the patient in question and may reflect cognitive bias. Each party should describe their values and acknowledge their potential biases in defending the rationale for their recommendation to further inform the discussion. Uncertainty where it exists should be openly acknowledged. Second opinions from other consultants can be sought. Third parties, such as ethics consultants, can be employed as mediators, particularly if the conflict becomes more confrontational or emotional.

Fasser and colleagues described the "ethics work-up" as a methodical way of considering examining the ethical issues at hand in complex cases and coming to a judgment concerning ethically justified courses of action [13]. Loftis and colleagues developed a standardized procedure for ethics seminars in pediatric critical care that integrates the ethics work-up and found it a useful way for colleagues within a specialty to develop a plan of action based on a disciplined ethical analysis [54]. It is our opinion that implementation of such methods should not only support the best interests of patients and support family participation in decision making but should also reduce the significant personal (e.g., moral distress) and interpersonal (e.g., intra- and inter-team conflict) strains on professionals that can arise in caring for complex patients, promoting enhanced collaboration and career satisfaction.

Conclusion

The preceding sections have illustrated the myriad factors that can predictably generate conflict among the many stakeholders involved in caring for children with life-threatening hematological and oncological diseases. There appear to be common elements in the sources of conflict and in the strategies for conflict resolution. One factor is the strong emotions that are naturally evoked in both the family and providers when the life of a patient is at stake and the impact of these emotions on negotiations for plans of care. For providers, their own emotions are the foundations of an empathic connection to the patient and family that is required

for truly compassionate care. Strong emotions can inform but also confound the judgment of all parties. Strong emotions can also impact relations among professionals. Other factors at play include the complexity of information, uncertainty, and the number and variety of people and perspectives involved. Patients and families depend on medical professionals to guide them through times of extraordinary threat, complexity, and tragedy in a way that acknowledges and incorporates their wishes, fears, and preferences into decision making, but patients/families also depend on professionals to guide them in ways that maintain the highest standards of care (professional integrity) in pursuit of the best interests of patients.

The recommendations for conflict resolution all hinge on establishing transparent, explicit, and reliable practices of negotiation among parties grounded in principles of inclusiveness and mutual respect but also grounded in principles of disciplined, rational deliberation of facts and ethical analysis. The establishment of systematic methods that include empathic inquiry, negotiation of goals, and conflict resolution can provide frameworks for such fraught discussions that help productively contain and manage strong emotions that might otherwise impair the reasoning and decision making of all parties.

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Chapter 5
Unique Considerations for Adolescents and Young Adults

Deena Levine and Liza-Marie Johnson

Adolescence Is a Unique Developmental Period

Adolescent and young adult (AYA) oncology patients are commonly defined by the National Cancer Institute as individuals aged 13–39 years [1, 2]. For the purpose of this chapter, we will focus on the subset of early AYA age 13–21 years (AeYA) as this younger age group is more representative of the ages of AYA most commonly treated in pediatric hematology-oncology centers. Adolescence is a unique developmental period characterized by biological, psychological, and social tasks which vary as an individual passes from early adolescence through mid-adolescence and onward to late adolescence [3]. AeYA represents a unique patient population, positioned between childhood and burgeoning adulthood. This developmental stage is marked by rapid brain maturation and neurocognitive advances; one such example of psychological development is the shift from concrete thinking patterns to more complex abstract thought patterns [3–5]. Socially, the period of adolescence is typically marked by the emotional separation from parents, stronger identification with peers, and greater social autonomy as the AeYA moves toward independence [3–6].

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Informed Consent and Decision-Making in Young Adult and Pediatric Populations

Current Western medical practice seeks to honor individual autonomy by allowing the patient to make his or her own healthcare decision without coercion, provided that the patient has the appropriate decisional capacity and legal empowerment to do so [7, 8]. Healthcare providers should (1) disclose the risks and benefits of recommended and alternative treatments through explanations that are understandable to the patient and specific to the nature of the ailment or condition and (2) check for understanding of the information that has been provided [9, 10]. Decisional capacity, or the ability to understand the choice at hand, is assumed to be present; nonetheless, providers should reflect on the patient and assess that capacity to make the medical decision is present [11, 12]. Decisional capacity is task-specific, for example, to an individual medical decision at hand, and can be assessed by an individual provider. Some individuals may have capacity to make simple decisions but be unable to understand and appreciate the nuances, and risks and benefits, of a more complex medical decision. Competency, on the other hand, is a more global inability to make decisions and is determined by the court [13]. The solicitation of informed consent is limited to personal decision-making in individuals with legal standing (state dependent, most commonly occurs at age 18). In circumstances where the medical decision is made by parents or a surrogate decision-maker (patients lacking decisional capacity), the individual is providing informed *permission* for a medical intervention [9].

In pediatrics, medical decision-making commonly involves a triad of decision-makers: the clinician, the child, and the child's legal guardian (usually a parent). In many cases, this decision-making triad is still applicable with young adult patients (i.e., 18–21) who remain somewhat dependent on their parent(s) for emotional and financial support, especially when ill, even though they have the legal authority to make independent medical decisions [14]. The American Academy of Pediatrics (AAP) encourages clinicians to collaborate with parents and patients when making medical decisions and encourages providers to involve children, "commensurate with their development," and obtain "assent to care whenever reasonable" [9].

There are different methods for assessing the appropriateness of involving a child in medical decision-making; one common method uses age as a threshold. The "rule of sevens," which originated under Edward the Third (1327–1377), if not earlier, assumes that children under the age of seven lack decisional capacity to make their own decisions, select children age 7–14 may have some capacity for decision-making, and children over 14 have capacity to make decisions unless circumstances prove otherwise [15–17]. Although the age threshold may be a reasonable starting point, children should be assessed individually. For example, a 12-year old child with recurrent cancer may already have significant experiences with oncology-based care and be better positioned to understand and appreciate medical choices than a previously healthy 17-year-old child with newly diagnosed cancer. Without legal standing to consent, children *assent* to a medical intervention. Children may also refuse to provide assent, and this refusal is known as *dissent* [9, 18].

In clinical research, particularly in early phase research where the therapy is unproven and the prospect of direct benefit is low, this dissent may be binding (see Chap. 7 by Dr. Bryan Sisk for full discussion of early phase research ethics). When a child refuses to assent to a medical intervention, open discussions should seek to clarify the reasons underlying the child's refusal. To the extent that the intervention being declined is not essential to the child's immediate welfare or well-being, providers should respect the refusal while trying to calm fears and assuage any misconceptions held by the child. In circumstances where the child has demonstrated sufficient knowledge and understanding of the intervention they are refusing and can verbalize the implications of their decision, this dissent should be taken seriously. To honor assent is to respect an intelligent dissent. In circumstances where a child truly has no choice to decline an intervention, the child should not be presented with a false choice. To ask a minor to make a decision and then override his or her decision may be perceived as disrespectful, lead to mistrust, and risk violating the ethical principle of fidelity.

Negotiating the Parent: Patient-Provider Triad

It has been demonstrated that parents of children with cancer prefer a shared-decision-making model in which many defer to the expertise of the provider and/or choose a collaborative medical decision-making process. [19] Adolescents with cancer have been found to desire involvement in the decision-making process as well [20]. For many AYA patients, involvement is characterized by receiving information, voicing preferences, and choosing how treatments are administered [20]. Some AYA patients, especially those on the older end of the spectrum, may desire ultimate decision-making control [21]. Failing to involve AYA oncology patients in medical decision-making can lead to frustration and noncompliance which can have a detrimental effect on their care.

In negotiating the decision-making triad, the first step is building a therapeutic relationship with a foundation of open communication. Suggestions for framing the discussion with AYA and their caregivers are outlined in Fig. 5.1 [22]. AYA oncology patients should be fully informed, as appropriate developmentally, of their disease severity and therapeutic options [23]. There are great potential benefits to disclosure and involvement in AYA patients, including creating a partnership in which the patients feel included and respected and in turn are maximally invested [14]. Procedures should be fully explained to AYA patients, at a developmentally appropriate level, and an attempt should be made to assure the patient's awareness, understanding, and assent [23].

While the goal of shared decision-making is to arrive at a mutually agreeable plan upon which all members of the triad agree, there will inevitably be instances of conflict. In the majority of cases, the parent will ultimately have decision-making authority; however, there are times when can be appropriate for another to assume decision-making priority [24]. When there is only one path toward a reasonable chance of cure and the parents or patient is not aligned with the clinician, the deci-

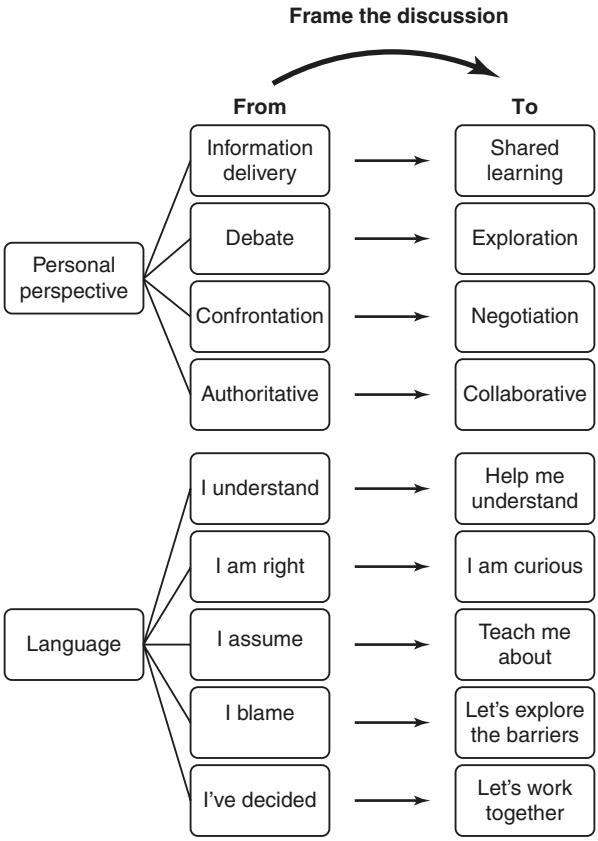

Fig. 5.1 Language matters in pediatric oncology AYA decision-making. Reframing conflict to collaboration through shifting dialogue. (Adapted from: Fedutner [22])

sional priority lies with the medical team, and a court may enforce mandated treatment in cases where refusal of treatment may lead to serious risk of harm [25]. Alternatively, when an AYA patient has progressive or incurable cancer, the patient may be best suited to have decisional priority as he/she is likely to be the best judge of the benefits and burdens in light of their individual suffering, as well as their personal goals and values [24]. Figure 5.2 outlines steps to ensure optimal communication with AYA patients, their caregivers, and the medical team.

Special Circumstances: Emancipated and Mature Minors

Emancipated minors are children under the age of majority in their state of residence who have successfully petitioned the court for the legal authority to make decisions, including decisions about their health, independent of a parent or guardian. Although the emancipated minor laws vary by state, common criteria for

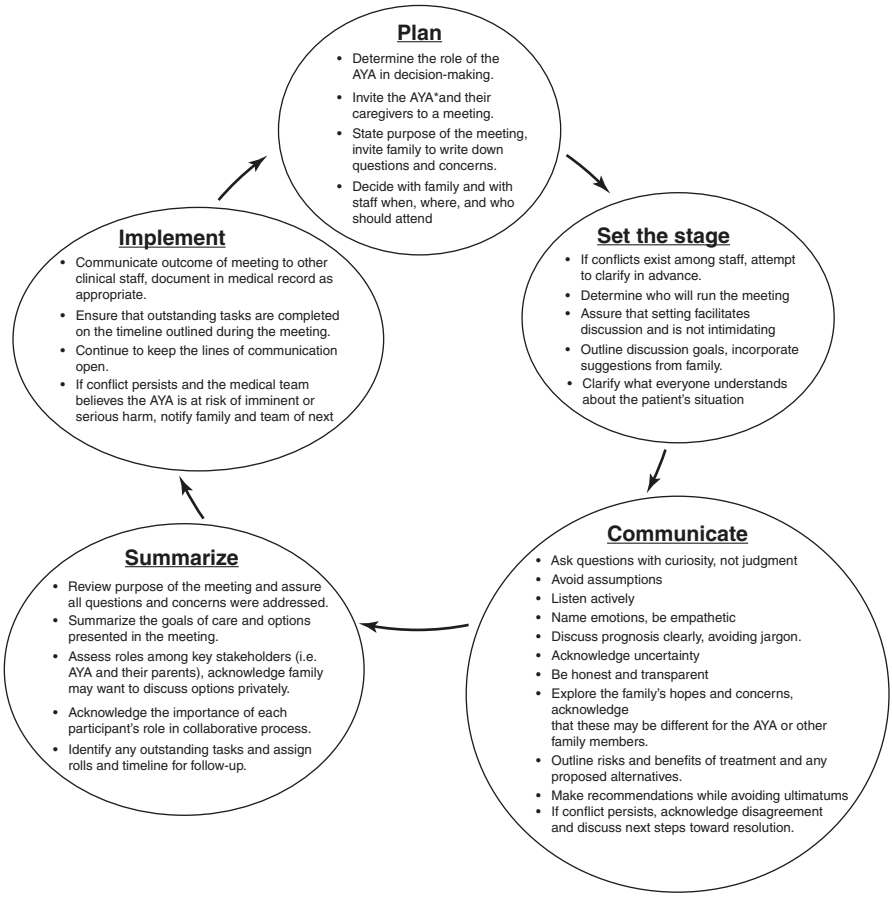

Fig. 5.2 How to optimize shared medical decision-making for AYA patients and their caregivers. Planning the family meeting. ∗When appropriate. Some AYA may defer to their caregiver or be physically/cognitively unable to participate

emancipation include: economically independent and living outside the parental home, married, a parent, or active military service [26–28]. Mature minors are those children under the age of majority who are able to understand a health condition and appreciate the risks and benefits of proposed treatment options to sufficiently consent for treatment independent of their parents [26–28]. Mature minor laws vary by state of residence, but usually require the minor to be older than 14 years of age and be able to demonstrate adult-like decision-making for the choice at hand. Mature minor exceptions commonly apply to conditions in which a minor might be hesitant to seek treatment if parental consent were required, for example, treatment for sexually transmitted infections, contraception, pregnancy, and drug or alcohol abuse.

Case-Based Learning: Potential Conflicts in AYA Care

Case 1: Parents and adolescent Jehovah's Witnesses refusing recommended therapy as it will lead to life-threating pancytopenia needing transfusions of blood products Diamond is a 15-year-old female with standard risk medulloblastoma who underwent a gross total resection at diagnosis and who recently completed radiation therapy. She has no evidence of disease following a recently scheduled disease evaluation and is now refusing chemotherapy because it is likely to result in a need for blood and/or platelet transfusions. Diamond and her parents are devout Jehovah's Witnesses. Diamond clearly articulates the rationale for her refusal and her parents are in full support of her decision. The primary oncologist estimates her chance of cure with recommended chemotherapy to be 85% and 50–60% without additional therapy.

Case 2: Adolescent with metastatic osteosarcoma has significant pain; family refuses regular use of opioid analgesia Jack is a 13-year-old male with widely metastatic osteosarcoma and significant bone pain. Upon admission for routine chemotherapy, Jack reports his pain score as an 8–9 out of 10 and appears very uncomfortable. Jack's father tells him to "be a man" and the child quietly declines the opioid brought in by the nurse. Later, while his parents are at the cafeteria, he begs his nurse to give him medication for pain before they return.

Case 3: A 17-year-old with relapsed refractory AML with marked leukocytosis, disseminated fungal infection, and worsening organ function is demanding, along with his parents, that medical team escalate care to include intubation, mechanical ventilation, and cardiopulmonary resuscitation if necessary Justin is a 17-year-old male transferred to the pediatric intensive care unit 2 days ago for respiratory distress. He is on high settings of noninvasive positive-pressure ventilation, however remains dyspneic and mildly hypoxic. He has a malignant pleural effusion and evidence of diastolic cardiac dysfunction. There are no cure-directed therapies available, and his leukemia has continued to worsen despite the use of palliative chemotherapy agents. His oncologist, the intensive care staff, and the palliative care team are in agreement he is imminently dying from complications of refractory leukemia, yet he and his parents continue to demand escalations of medical support. The medical team all agrees that the use of invasive mechanical ventilation and other cardio-respiratory support will be non-beneficial and potentially harmful.

Case 4: A 16-year-old with Hodgkin's lymphoma refuses to continue recommended chemotherapy because of associated side effects including nausea and vomiting Sarah is a 16-year-old female with Hodgkin's Lymphoma. She received two rounds of chemotherapy which were complicated by side effects of nausea and vomiting. Though her chance of cure exceeds 90% if she completes her planned treatment, Sarah refuses any further chemotherapy. The medical team explains to

Sarah that she could be cured with continued therapy, but Sarah believes that the chemotherapy is making her sick and that she will survive better without further therapy. Sarah's mother respects her daughter's wishes and believes that prayer will ensure her cure, while her father agrees with the medical team who wishes to proceed with chemotherapy despite the refusal.

Factors to Consider

In such cases of complex adolescent and young adult patient, family, and medical team misalignment, there are common key factors for consideration. The maturity of the individual patient is of prime importance as is the capacity of the parents as medical decision-makers. It is critical to assess patient and parent understanding of the medical information and try to identify potential barriers to comprehension and/or compliance. The child or young adult's age is only one factor in evaluating their decision-making capacity. Younger patients with significant illness experience may be more equipped to engage in medical decision-making than an older teen who was just diagnosed with cancer and has no reference for coping with a serious illness. The patient's prognosis, including the chance for treatment to be successful as well as the degree of uncertainty, has important implications in the analysis of such complex cases. It is important to elicit and consider the beliefs, values, motivations, and influences of the patient and parent as these features can be extremely influential in the context of a family's decision-making. For example, in case 2, what if the father had lost a sibling to an opioid abuse or was himself in recovery? Past personal experiences can impact how families view a medical decision. The optimal approach to cases of misalignment involving an AYA patient, parent, and/or medical team is to attempt to arrive at a mutually agreed upon plan through discussion, education, and negotiation. This is best accomplished when built on a foundation of validation and mutual respect. In many cases, it is possible to make provisions for patient or parent preferences, working within their belief system, and still achieve appropriate medical management with all parties in agreement. In some cases, however, it can be difficult to align the AYA, parent, and medical team, and clinical ethics consultation, in addition to legal intervention, may be warranted.

In evaluating case 1, for example, the patient's prognosis with and without chemotherapy are extremely relevant. It would be imperative to determine the patient's understanding of the options and the resulting implications and further explore both the patient's and parent's religious beliefs. The decision-making authority of the parents could be limited if they are exposing the child to serious increased risk of harm through their refusal of recommended therapy with much higher curative potential. The medical team would work with the family to understand that they would attempt to minimize blood transfusions for the patient using any means possible. A court order could be sought to proceed with chemotherapy or to give blood transfusions if indicated without parental consent, which may actually be acceptable or even preferable to the family. Because laws vary by state, consultation with

institutional counsel for state-specific legal precedent is recommended prior to proceeding with request for a court order. An additional consideration would be the anticipated number of transfusions the AYA would need during the proposed therapy. While it might be practicable to override an AYA patient for 1–2 transfusions, this could be logistically challenging if large numbers of transfusions are anticipated (i.e., allogeneic transplant with standard conditioning) or if the adolescent refuses to physically consent to transfusion (i.e., resists and requires restraints). If the AYA is to be enrolled on a research protocol, it may be helpful to review how many previous patients have needed transfusions while on therapy. If there is a high likelihood of transfusion, it may be helpful to consider if there is an alternative therapy. For example, is there an alternative treatment that, while perhaps less efficacious, is still potentially beneficial (i.e., curative) and less likely to result in life-threatening cytopenia requiring transfusion? In our experience, families appreciate when the medical team outlines a willingness to be adaptive to family concerns. In this example, it would be important to discuss the increased risk of relapse or treatment failure if a less myelosuppressive regimen is pursued.

Case 2 is an example of AYA-parental misalignment in which the patient has uncontrolled pain due to parental refusal of medication on his behalf. The patient in this scenario has requested that the medical team override the parent's refusal for the analgesic medication and administer without their knowledge. Despite the fact that the medical team is aligned with the AYA patient in the matter, the team may not behave in direct opposition to the parents' expressed directives. The medical team does however have an obligation to the patient to relieve his suffering. In this instance, a discussion should be had in which the medical team educates the parents regarding the treatment, dispels any possible misconceptions or erroneous notions, and encourages the parents to partner with the medical team to relieve their child's pain and symptoms. The medical team should also ensure that the parents understand that even if their opposition persists, the team has a moral duty to the patient and cannot allow him to suffer as a result of the parents' refusal of appropriate therapy and can attempt to obtain permission to administer treatment through legal means.

Case 3 is an example of family request for potentially inappropriate medical care at the end of life. In this circumstance, the medical team would need to determine the prognosis of the patient from his underlying disease with and without artificial life-sustaining technology and resuscitative efforts. If indeed the interventions would not accomplish their goals for the patient and could be considered medically futile, then these interventions may be non-beneficial and perhaps harmful to the patient. Explaining this to the AYA patient and his parents may increase understanding of the reality and lead to acceptance and eventual alignment with the medical team. There is no obligation to provide non-beneficial medical therapies, and, when inappropriate, interventions should not be offered. When alignment with the family cannot be reached, the medical team may be justified in not performing the potentially inappropriate interventions by way of a do not resuscitate order enacted by the medical team. In these rare circumstances, it is important to consult with the ethics, and possibly legal teams, and to review institutional policy [29]. As always, assess-

ment of the AYA patient's maturity level; understanding of the options, risks, and benefits; and involvement of the patient in the discussions and decisions is an essential part of this process and may aid in aligning the parents as well.

In evaluating case 4, the medical team would need to establish Sarah's level of understanding and maturity. It would likely be helpful for the medical team to fully investigate her perceived symptom-related suffering and propose a plan for improved management in the future. Validating her mother's desire to respect her daughter's wishes, the team can also help empower Sarah's mother in her care and allow for control over acceptable choices. Sarah's father does appear to be aligned with the medical team and could potentially be influential to Sarah or her mother in finding a way to partner for her best interest. Because Sarah's chance of cure with chemotherapy is high and she is very unlikely to survive if she were to discontinue treatment, a court order likely could be obtained to continue chemotherapy against her will if attempts at alignment were unsuccessful.

Conclusion

As evidenced by the four case examples, there are numerous ethical issues that can arise in clinical pediatric hematology-oncology practice. Ethical issues are more commonly rooted in breakdowns in communication, rather than a true conflict of ethical principles (autonomy, beneficence, justice, non-maleficence). The cornerstone of resolving many conflicts is quality, collaborative communication with families and colleagues. It is important to exhibit mutual respect for the involved parties and to seek to understand the differing perspectives of the various stakeholders. Because primary medical caregivers for a patient can sometimes find it difficult to maintain objectivity, assistance from a bioethicist not involved with the patient can be beneficial. Communication should be clear and accurate. For complex patients with many clinical caregivers, it may be helpful to designate 1 or 2 clinicians to share important information with the AYA and their decision-makers. This strategy may reduce the potential delivery of confusing or conflicting information about prognosis or the treatment plan.

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Part III
Ethical Issues Surrounding Children in Research

Chapter 6
Ethics in Genetic and Genomic Research

Amy L. McGuire, Stacey Pereira, Amanda M. Gutierrez, and Mary A. Majumder

The introduction of next-generation sequencing, including genome and exome sequencing (GS/ES), has moved us closer to the practice of precision medicine in oncology. It is estimated that by 2025 oncology will dominate the global next-generation sequencing market, with nearly US$13.6 billion spent on companion diagnostics [100]. These advances in clinical oncology, however, must be built on a solid foundation of research to better understand the molecular profile of different cancers and how they respond to available therapeutics. Several large-scale genomic research studies are ongoing in pediatric oncology. These studies not only generate new insights to improve patient care but they also raise ethical considerations that must be studied and responsibly managed. In this chapter, we will highlight some of the large-scale genomic research studies in pediatric oncology and discuss several ethical issues that they raise: informed consent, return of results, data sharing, privacy and genetic discrimination.

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Pediatric Oncology Genomic Studies

More than 90% of all children with cancer are treated at the nearly 250 institutional affiliates of the Children's Oncology Group (COG), a clinical trials group supported by the National Cancer Institute's (NCI) National Clinical Trials Network. The COG attributes the high pediatric cancer five-year survival rate of 80% to the widespread enrollment of children into clinical-translational trials [21]. Compared to only 2% of adults, more than 70% of children with cancer are enrolled in at least one clinical trial [11, 97]. The COG has a long-standing case–control study that runs across their vast national network and includes clinically validated outcomes data and biological specimens from childhood cancer survivors. The COG also coordinates early-phase clinical trials for children and adolescents with cancer across the 21 member institutions in their Phase 1 and Pilot Consortium. Their Project:EveryChild includes a vast registry of infants, children, adolescents, and young adults with cancer that enables re-contacting for future cancer studies and is linked to a well-annotated childhood cancer biobank that includes tumor, host, and parental germline DNA alongside clinical information.

Two partnership initiatives between the NCI and the COG are the NCI–COG Pediatric Molecular Analysis for Therapy Choice (MATCH) trial and the Gabriella Miller Kids First Pediatric Research Program [32]. The MATCH trial focuses on molecularly targeted therapies for children or adolescents with recurrent or treatment-resistant solid tumors and thus involves a vulnerable demographic with few treatment options. Since it is an offshoot of the previously established adult MATCH trial, the project hopes to better understand the translation of therapies across age demographics. Kids First provides genomic and transcriptomic sequencing and analyses for selected cohorts and aims to build a larger data resource for researchers and clinicians.

Another large longitudinal study of pediatric cancer was launched in 1994. The NCI-funded Childhood Cancer Survivor Study (CCSS) is composed of roughly 36,000 individuals who have survived 5 years past their cancer diagnosis, as well as a sibling cohort. Beyond basic cancer genetics, this study seeks to better understand the long-term effects of treatment and early-life cancer diagnosis. A fraction of the participants in this study are also part of the St. Jude Lifetime Cohort (SJLIFE), which includes a collection of germline samples alongside comprehensive clinical data. In 2010, the St. Jude–Washington University Pediatric Cancer Genome Project was launched to better understand the genetic factors behind childhood leukemias, brain tumors, and sarcomas through comparing tumor and germline genomes. And in 2015, the first study using GS to study the genetic factors of lifetime cancer risk in survivors was funded by NCI and American Lebanese Syrian Associated Charities and included over 3000 members of the CCSS cohort [94].

Several large national genomic research consortia also incorporate projects with a focus on pediatric oncology. For example, in 2010, the National Human Genome Research Institute (NHGRI) [77] and NCI [75] jointly funded the Clinical Sequencing Exploratory Research (CSER) Consortium. This national multi-site research program was established with the mission of investigating the clinical utility of genome and exome sequencing [41]. This multidisciplinary consortium, whose membership includes clinicians, genomic researchers, social scientists, and bioethicists, examines clinical sequencing pipelines and the associated issues surrounding informed consent, return of results, and incidental findings. Although the consortium was not disease specific, it included three projects studying pediatric cancers: BASIC3, MI-ONCOSEQ, and NCGENES. Their achievements include the first study on combined genome sequencing approaches in children with relapsed cancers, which reported 46% of children and young adults having actionable findings that affected the course of their cancer management [72]. In addition, BASIC3 showed nearly 40% of pediatric solid tumor trial participants had potentially actionable mutations when combining results of tumor and germline exome sequencing [86]. In 2017, NHGRI and NCI invested another US$18.9 million in the Clinical Sequencing Evidence-Generating Research (CSER2) Consortium, including support for BASIC3 investigators to expand their work in pediatric cancer genomics through the Texas KidsCanSeq study [83].

The NCI's Office of Cancer Genomics' Therapeutically Applicable Research to Generate Effective Treatments (TARGET) and CGCI (Cancer Genome Characterization Initiative) projects encompass pediatric cancers as well. CGCI focuses on the molecular markers that characterize cancers such as Burkitt lymphoma and medulloblastoma. Beyond investigating the genetic markers that define each phenotype, TARGET focuses on the potential therapeutic implications of each marker for cancers, including acute lymphoblastic and myeloid leukemia, neuroblastoma, osteosarcoma, and forms of kidney tumors. As part of the National Institutes of Health (NIH)'s goal to increase data accessibility and interoperability, the recently launched Genomic Data Commons (GDC) provides a central access portal for these numerous NCI datasets in hopes of further increasing the utility of these datasets and research efforts.

Going forward, Vice President Biden's 2016 announcement of the Beau Biden Cancer Moonshot reinforced these numerous preexisting efforts. The twenty-first Century Cures Act authorized US$1.8 billion over 7 years for this ambitious effort. The report released by its Blue Ribbon Panel Pediatric Working Group recommended focusing on fusion oncoproteins, immunotherapy, and tumor drug resistance [12]. There is strong federal support across departments as NIH's budget allocates significant funds to cancer research, the Department of Health and Human Services (HHS) recently allocated mandatory cancer-related funds, and the U.S. Food and Drug Administration (FDA) is currently developing a virtual Oncology Center of Excellence. These nation-wide trends show the expansion of pediatric cancer research efforts.

Ethical Issues in Pediatric Oncology Genomic Research

Many ethical issues related to genomic research in oncology stem from concerns about germline findings, rather than tumor-only, or somatic, findings. Germline mutations, also called hereditary mutations, are gene changes present at conception that are incorporated into the DNA of all the cells of the body and can be passed on from parent to child. Most of a tumor's DNA sequence is identical to the patient's germline DNA sequence. As such, though some oncology research may target the tumor genome specifically, analysis of tumor DNA may lead to the indirect detection of germline mutations [13]. Further, recent recommendations stress the importance of comparing tumor DNA to germline DNA for more accurate variant targeting and interpretation [54]. Accordingly, genomic research in oncology raises some of the same ethical issues as genomic research in other areas, including issues of informed consent, return of results, data sharing, privacy, and genetic determinism (see Table 6.1 for examples of guidelines and position statements from U.S. professional organizations regarding ethical issues in pediatric genomic research).

Table 6.1 Examples of U.S. guidelines and position statements relevant to pediatric genomic research

Topic	Examples of U.S. guidelines
Genetic testing of minors	American Medical Association, 1995[1] American Society of Human Genetics & American College of Medical Genetics and Genomics, 1995[2] American Academy of Pediatrics & American College of Medical Genetics and Genomics, 2013[3] American Society of Human Genetics, 2015[4]
Genetic testing of minors for adult-onset conditions	American Medical Association, 1995[1] American Academy of Pediatrics & American College of Medical Genetics and Genomics, 2013[3] National Society of Genetic Counselors, 2017[5]
Pediatric assent for research	American Academy of Pediatrics, 2016[6]
Return of genomic research results	National Heart, Lung, and Blood Institute, 2010[7] American College of Medical Genetics and Genomics, 2013[8] American Society of Human Genetics, 2015[4] National Academies of Sciences, Engineering, and Medicine, 2018[9]

[1]AMA [4]
[2]ASHG and ACMG [5]
[3]AAPCBCG and ACMGGSELIC [3]
[4]Botkin et al. [14]
[5]NSGC [81]
[6]Katz et al. [55]
[7]Fabsitz et al. [29]
[8]Green et al. [39]
[9]Botkin et al. [74]

Informed Consent in Pediatric Genetic and Genomic Research

As is true for all research subject to federal research regulations involving children, pediatric assent (where appropriate, as described below) and parental permission are required for participation in genomic studies (45 CFR §46.408; 21 CFR §50.55). Most parents of pediatric cancer patients are willing to enroll their children into genomic research because they hope that it will benefit their child or at least help future cancer patients. For example, in the BASIC3 study, which evaluated the incorporation of genomic sequencing into the care of newly diagnosed pediatric cancer patients, 83% of eligible families who were approached for study participation enrolled into the study, with no significant enrollment differences based on race or ethnicity [91]. Of the families who declined participation in the study, most cited being overwhelmed with their child's recent cancer diagnosis as the reason for decline, with concerns about genetic privacy being the second-most cited reason [91].

Assent refers to a child's affirmative agreement to participate in the research. When obtaining assent it is important to determine each child's level of understanding and to match the presentation of information to the child's capabilities [34, 101, 103], rather than assume a lack of decisional capacity [90]. Typically, Institutional Review Boards (IRBs) determine when assent is required, taking into consideration the age, maturity, and psychological state of the pediatric participant population. Many institutions set an age cutoff when assent is required; however, there is great variability in what the minimum age is, with one study finding that it ranged from 7 to 15 among different institutions [58].

In a qualitative study of parents' and children's perspectives on the child's role in assenting to genetic research [34], Geller et al. found that most children want to make the final decision about research participation, but also want parental input. Meanwhile, most parents preferr to make the initial decision about feasibility of enrolling their child in the research, though they would not force their child to participate in nontherapeutic genetic research if the child did not want to. Yet, at least one study found that 38% of children who were interviewed did not feel that they had the freedom to decline research participation [101]. This undermines the assent requirement and suggests that alternative processes are necessary to ensure that pediatric patients have the chance to refuse research participation without any interference or undue influence from their parent(s), physicians, and/or study personnel.

In the Geller et al. study [34], the child's desire for autonomy was higher if the child was older/more mature and the research was less risky and invasive. Parents and children agreed that the greater the risk associated with the study, the more authority the parent should be given in making decisions [34]. This suggests that both parents and children need to be given ample time to ask questions about the research during the informed consent process. However, there is much room for improvement when it comes to obtaining both parental permission and pediatric assent for research participation. Often, neither adult participants in clinical tri-

als nor pediatric participants understand basic information necessary to make an informed decision about research participation. For example, Joffe et al. found that although 90% of the 207 adult patient-participants they studied who were enrolled into cancer clinical trials were satisfied with the informed consent process and considered themselves to be well-informed, 74% did not understand that they may receive nonstandard treatment, 63% did not understand the potential for incremental risk from participation in a clinical trial, and 70% did not understand the unproven nature of the treatment [52]. Similarly, in interviews with parents of children enrolled in clinical trials, Chappuy et al. found that while 81% of parents felt that they understood the information they received at the time of consent, 19% of parents did not understand that their child was enrolled in research, and half of the parents could not describe the goals of the clinical trials [19]. The authors found that understanding differed by the type of information: most parents understood the potential benefits that the research offered their children but fewer parents understood the basic research protocol elements. Fifty-one percent of children 7–18 years old who were enrolled in pediatric oncology research also did not know that the treatment they received was research, and 49% did not remember enrolling in the research [101]. Unfortunately, efforts to improve the informed consent (and pediatric assent) process generally have had only limited success, with the most effective intervention being one-on-one education [31, 96].

When participants conflate the goals of research with the goals of clinical care, it can result in a therapeutic misconception. This has ethical implications, as it may result in a misunderstanding or "misestimation" of the risk/benefit ratio of the research [7, 48, 52]. Typically, research is justified when there is clinical equipoise, meaning that there is not enough evidence to know whether the intervention will be more or less beneficial than the standard of care. Participants and parents of pediatric participants are expected to assume a similar equipoise when deciding whether to participate in the research. However, a 2011 study by de Vries et al. found that in pediatric oncology research, equipoise is almost never achieved as research and treatment goals are intertwined. The authors argue that since parents are occupied almost completely with the well-being of their child, their judgment and understanding of the risks of research and experimental therapies are impaired. Parents are also confronted with the possible guilt of not giving the child the best possible treatment options by not enrolling them in research. As a result, the authors go as far as to argue that parents do not actually have freedom to reject participation [25], which is supported by findings from Chappuy et al. where parents stated that they felt they did not have a choice about research participation, as consenting to research participation was the best available option for their child [19]. Even when the research involves genomic testing, with little to no prospect of direct benefit for the child, interviews conducted for the BASIC3 study found that parents feel that it is their parental responsibility to consent to participation [65].

Re-consent of Patient-Participants at Age of Majority

Genomic research often involves the ongoing use of biospecimens, health data, and genomic information, beyond the time of direct involvement from the participant, thereby complicating the model of one-time, static pediatric assent and parental permission in pediatric research. It is therefore important to consider which materials may be stored for future use and to plan for and communicate during the initial consenting process any procedures for re-consenting participants once they reach the age of majority, as well as any plans for continuing to use materials via a waiver of consent, where applicable (45 CFR §46.116).

Ideally, informed consent should be solicited from pediatric participants when they reach the age of majority for their continued research participation [1, 16]. Re-consenting participants when they reach adulthood is particularly important for research that is greater than minimal risk and for research that requires ongoing contact. If re-consent cannot be obtained for interventional research activities, the activities should cease until consent from the participant can be obtained [16]. Re-consent should also be sought for the continued use of identifiable biospecimens, health data, and genomic information, especially if results are going to be returned [16]. Allowing participants to review consent documents and, when applicable, results disclosure information with a genetic counselor respects their autonomy and enables them to decide as adults if they would like to continue in research activities [1].

It is possible, however, to obtain a waiver of consent to continue using participants' previously collected data and biospecimens if re-consent is not practicable or if all identifiers are removed from the materials (45 CFR §46.116). Re-consent may be impracticable if participants cannot be reached with reasonable effort. In that situation, at least one study found it to be generally acceptable to continue the research with a waiver of consent [37]. More controversial is whether the research can continue if re-consent is deemed too burdensome, expensive to accomplish, or disruptive. The burden and expense of re-consent can best be dealt with by developing a plan and building it into the funding proposal at the outset [104]. In terms of the ethics of re-contact, qualitative interviews with patients who were re-consented at the age of majority for the BASIC3 study suggest that re-consenting and continuing such research once the patient-participant has reached adulthood is not ethically disruptive. Of the 12 participants who have been re-consented, none have declined, and none have expressed any major concerns (unpublished data).

Return of Results

A number of controversies also surround return of results generated in the context of pediatric genomic research. Some of the ethical issues are common to all genomic research, while others are specific to pediatrics. One general question is whether

investigators have an ethical duty to return individual genomic results to participants in the research setting. In addressing this question, commentators have drawn on ethical principles including respect for autonomy, beneficence, and nonmaleficence. They have also highlighted considerations such as the different goals and procedures in research versus clinical settings, limited research budgets, and the financial and other burdens associated with returning genomic results in a responsible manner.

Members of several CSER Consortium committees, in collaboration with the electronic MEdical Records and GEnomics (eMERGE) Network, a multisite network that combines DNA biorepositories and electronic health record systems in an effort to develop tools for implementing genomic medicine, have published a set of guiding principles for return of genomic results. One of the principles recognizes an investigator's duty to share results with participants in some circumstances. Specifically, the guidance states that "[a]nalytically and clinically valid information that is of an important and actionable medical nature and that is identified as part of the research process should be offered to a research participant" [51]. Researchers do not, however, have a duty to look for actionable genomic findings that would not otherwise be found during the research process. Further, "[p]articipants should have the right to refuse any results that are offered," although where return of results is integral to the study, refusal will be equivalent to declining participation in or withdrawal from the study. A position statement of the American Society of Human Genetics (ASHG) focused on genetic testing in children and adolescents reaches a similar conclusion, stating that those engaged in genomic sequencing research are not ethically required to search for and return findings that would be considered secondary or incidental, although it may be ethically acceptable for them to do so with informed consent [12]. These recommendations are consistent with recommendations from U.S. National Commissions on Bioethics and other expert groups [56].

Recognizing that the return of individual research results is ethically justified in many circumstances and becoming more commonplace, a committee of the National Academies of Science, Engineering, and Medicine (NASEM) recommends that investigators develop a plan that addresses return of results, submit this plan for approval by an IRB, and discuss return of results with participants as part of the informed consent process [74].[1] It also recommendeds that investigators address how results will be communicated and that results only be returned if they are confirmed in a clinical laboratory accredited under the Clinical Laboratory Improvement Amendments (CLIA), generated in a research laboratory with an established quality management system, or with IRB approval [68, 74, 92].

Whether pursuant to a plan or not, investigators may find themselves in receipt of genomic findings that have important health implications for a pediatric research participant. The CSER Consortium/eMERGE Network guidance document states

[1] Note that under the revised Common Rule, secondary research with a study plan that includes return of individual research results to participants is excluded from an exemption for secondary research using identifiable information or biospecimens, even if the research falls within the scope of a broad consent to future research use and satisfies other criteria [22].

that parental discretion to refuse the return of genomic results, including secondary or incidental findings, may be limited where those results or findings "hold high and actionable health significance for the minor during childhood" [51]. The 2015 ASHG position statement distinguishes the research from the clinical setting. When genomic testing is conducted for clinical purposes and there is "strong evidence" that a finding has "urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat," ASHG recommends that the clinician communicate those findings regardless of the general preferences stated by the parents. However, when testing is conducted in a research setting, the ASHG guidance document references ongoing debate and states that IRBs are in the best position to determine whether and how to disclose findings [14]. A group of bioethicists and researchers affiliated with the Network of Applied Genetic Medicine of Quebec has adopted a more definitive position, stating that individual results including any incidental findings concerning a child *must* be returned if a set of criteria is satisfied (e.g., clinical validity, significant implications for the child's health, effective treatment that should be implemented before adulthood, review board approval) [92].

Assuming investigators have adopted a plan that involves return of at least some individual genomic results, a general ethical issue they face is how to handle variants of uncertain clinical significance, often referred to as VUS or VOUS. As the term suggests, these are variants for which insufficient evidence exists for either assignment as either pathogenic or benign. Variant interpretation can be challenging, especially for findings that are not associated with the individual's clinical symptoms.

The potential benefits of receiving VUS include providing families with information that may later be revealed as significant, empowering them to seek reassessment.[2] The potential harms include creation of needless anxiety [73]. Sorting out consequences is difficult given studies suggesting that there is no single standard response to uncertain information [57, 102]. In the clinical context, this means that the level of certainty required for reporting will typically be higher for findings that do not have established associations with the patient's particular symptoms or diagnosis. Commentators have argued that the same considerations that limit reporting in the clinical context create a "strong presumption" in the research context in favor of limiting results (especially incidental findings) returned to those judged highly likely to be pathogenic [46]. Researchers who have studied responses to disclosure of uncertain information recommend incorporating information on VUS and uncertainty as an aspect of genomic testing into the pretest counseling process [9, 57, 95].

[2] Whether healthcare providers have a duty to recontact patients in the event a VUS is reclassified is unclear in the clinical context [18]. Some have argued that caution should be exercised about imposing expansive legal duties to return results or follow up on findings in the research setting [19], and that any ethical duties in the research setting should terminate with study completion [86], although this has been identified as an area of continuing debate [54].

A final controversy specific to the pediatric context is whether to return genomic results related to adult-onset conditions that are not actionable before the age of 18. A range of ethical considerations enter into this debate. Some commentators give significant weight to preserving the child's future autonomy to decide for or against testing. This is supported by the argument that children have a "right to an open future" that limits parental discretion to take steps precluding the child from developing and pursuing an independent life plan. Others counter this argument by pointing to the discretion generally accorded to parents to make decisions based on their own assessment of child well-being, including decisions that may constrain the child's future options. Parental discretion typically extends to taking into account the interests of the family as a whole so long as some threshold of harm to the child is not exceeded or a case can be made that disclosure is consistent with best interests broadly considered [44, 53].

Consequences are also featured prominently. As part of the case against disclosure of results for adult-onset conditions, some point to potential psychosocial harms. These include direct psychological harm to the child (e.g., changed self-image, increased anxiety, regret) and indirect harms due to the changes triggered in family relationships (e.g., distortion of parental perception of the child, alteration of dynamic due to feelings of guilt) [56, 59]. The evidence from studies that disclose results for adult-onset conditions is limited, but the available empirical data does not substantiate concerns about significant psychosocial harms to children [1, 14, 56]. Other commentators highlight potential psychosocial benefits from disclosing, especially if the child and/or family are already experiencing distress due to uncertainty about whether the child is affected by a condition that runs in the family [56, 106].

Other kinds of potential harm from disclosure include discrimination in the event of a positive result. Other potential benefits include identifying disease-causing variants that may also be found in adult family members for whom this information is actionable. Health benefits to family members also presumably benefit the child. These considerations prompted the ACMG to recommend disclosure of a set of actionable, pathogenic variants in all patients undergoing exome or genome sequencing in the clinical setting, regardless of patient age and age of onset for the condition [39].

Debate about testing children for adult-onset conditions began in relation to testing for Huntington Disease, and that origin has shaped, and perhaps distorted, the discussion [6]. Some commentators caution that there may be ethically relevant differences across conditions generally grouped together in the "adult-onset" category [18]. The ASHG concludes that the case for deferring testing until the child can make an autonomous choice about testing is strongest where there is evidence that many or most potentially affected adults decline testing, as is true with Huntington Disease [14]. Divisions of opinion about the best course of action with respect to testing children for adult-onset conditions extend beyond the bioethics community to pediatric professionals, members of the general public, and parents undergoing BRCA testing [9, 15, 93].

The current general recommendation from the ASHG is that, absent an appropriate clinical intervention in childhood, "parents should be encouraged to

defer predictive or pre-dispositional testing for adult-onset conditions until adulthood or at least until the child is an older adolescent who can participate in decision making in a relatively mature manner" [14]. Although testing may be reasonable in some cases, thorough discussion of the relevant considerations is always an important first step. The European Society of Human Genetics has continued to adhere to a more conservative approach, finding testing for adult-onset conditions acceptable only if preventive interventions can be initiated in childhood [28].

There may also be ethically relevant differences between a decision to test a child for an adult-onset condition and a decision to disclose information about an adult-onset condition discovered during the course of research. Addressing the research setting specifically, the CSER/eMERGE guidance document states that "[i]nvestigators may reasonably offer the parents of minors participating in pediatric research the option of accepting or refusing results for adult-onset conditions along with counseling on the implications for the child's best interests and the parents' health status" [51]. The guidance from other groups is generally consistent with this approach, although more emphasis is placed on the exceptional nature of offering results related to adult-onset conditions and the stringent requirements that apply [60, 92].

Suggested best practices where a plan has been adopted that encompasses offering disclosure of results for adult-onset conditions include special attention to this choice in the informed consent process and, if the results include a pathogenic or likely pathogenic variant, a mechanism to contact the child at age of majority, and/or development of a plan for disclosure to the child and other potentially affected family members [1, 53]. In addition, ideally, a genetic counselor will be involved in both the informed consent and results disclosure processes.

Genomic Data Sharing, Privacy and Discrimination

Since the beginning of the Human Genome Project (HGP), a central tenet of genomic research has been open, public data release. In February 1996, representatives from the major DNA sequencing centers in five nations came together and agreed that in order for laboratories involved in the HGP to work together to create a reference human genome they must each commit to the core tenets of open science. The resulting Bermuda principles called for the rapid public release of all generated sequence data [99]. This commitment to open science has been foundational to other large-scale sequencing projects aimed at creating a community resource, such as the HapMap Project [79] and the 1000 Genomes Project [49].

As the cost of sequencing precipitously declined and it became possible to analyze an individual's entire genome sequence [62, 105], some began to worry that policies that called for the public release of DNA data did not sufficiently protect the privacy of individuals from whom the data were generated [61, 64, 66]. In 2004, Lin

et al. demonstrated that individuals could be uniquely identified based solely on their DNA [63], and in 2008, Homer and colleagues showed that it was even possible to identify individuals by matching their DNA to aggregated datasets [47]. Both of these studies required access to a reference sample from the individual in order to match his/her DNA to publicly available genomic data. In 2013, however, Melissa Gymrek and colleagues were able to uniquely identify 50 families from the publicly available 1000 Genomes Project database simply by linking their information to other publicly available information, including information from genetic ancestry sites [42]. Legally, HHS and the Office of Human Research Protections (OHRP) have maintained the position that, despite these findings, genomic information is not "readily" identifiable and so research using de-identified or coded biological specimens or DNA data does not automatically constitute research involving human subjects [30, 45]. Thus, there are currently no regulatory restrictions on the public release of de-identified DNA data. From a policy perspective, however, concerns about the privacy of individuals whose genomic information is being shared has led to the creation of controlled access databases, such as NIH's database of Genotypes and Phenotypes (dbGaP), and a requirement that informed consent be obtained for genomic data sharing [82].

As genomic research advances, the vision of precision medicine where treatments are tailored to the individual patient based on her genetic makeup, unique environmental factors, and specific biochemistry is beginning to come more into focus. In order to fully achieve this vision, however, we will need access to millions of individuals' genomic and health data. Ideally, these data will be shared broadly in a medical information commons (MIC). In 2011, a committee of the National Academy of Sciences described an MIC as "a data repository that links layers of molecular data, medical histories, including information on social and physical environments, and health outcomes to individual patients… [with data] continuously [being] contributed by the research community from the medical records of participating patients" [80]. Over the past 7 years, many initiatives have taken strides to build and contribute to such an MIC (e.g., The Precision Medicine Initiative [or All of Us Research Consortium [2]], the Million Veteran's Project [71], the NCI's Genomic Data Commons, and the NIH Data Commons [24]). The Global Alliance for Genomics and Health was founded in 2013 as an international collaboration to facilitate data sharing [36]. In addition to catalyzing collaborative projects aimed at sharing data, the Global Alliance developed an application programming interface (API) to allow for the interoperable exchange of data [98] and published a Framework for Data Sharing that provides principles for the responsible sharing of genomic and health data [88]. This Framework calls for, among other things, transparency, participant engagement, and appropriate protection of individual privacy.

These efforts reflect a renewed commitment to the tenets of open science that were reflected in the Bermuda Principles over 20 years ago, with increased attention to the rights and interests of individuals from whom DNA data are generated. Yet, despite all of the enthusiasm for sharing data, it continues to be viewed as one of the most intractable policy challenges for genomic medicine [38, 69, 70]. We have proposed that there are at least five reasons why sharing data today is even more com-

plicated and difficult to achieve than it was in 1996: (1) genomic initiatives are cropping up all over the globe, making it necessary to create a global infrastructure, standards, and norms of practice; (2) concerns about privacy and identifiability of genomic data have created the need for more protective measures to be adopted; (3) genomic data today are not just generated and used for scientific purposes, they are increasingly being generated in a clinical context and used for medical decision making; (4) commercial laboratories are highly diverse and many have a profit motive to hoard data; and (5) genomic data is most useful when it is linked to other health-related information about the individual; thus sharing de-identified raw sequence data is no longer sufficient [23].

Despite these challenges, studies suggest a general willingness among patients, research participants, and members of the public to share their genomic data [33]. In a randomized study of consent for data sharing, we found that when given a choice, 53% of research participants ultimately chose to share their genomic information in an open-access database. Thirty-three percent agreed to share their data but only in controlled-access databases, and 14% opted out of all data sharing [67]. Parents of pediatric patients were generally more restrictive in their data-sharing decisions for their children because of concerns about future risks to their child, but the majority (73.5%) still agreed to share their child's data to advance research [17]. We observed a similar response from participants who shared biological specimens with a cancer research biobank. While controlled-access data sharing was a condition of participation in the biobank, participants were given the option of also allowing their genomic data to be shared via open-access mechanisms. Of the 194 participants who were given this option, 122 (63%) agreed to open-access sharing [87]. Some studies suggest that even groups that have reasons for distrusting researchers may be willing to share their data. For example, focus groups with African Americans found that the vast majority (80%) would hypothetically participate in genomic research if their data were going into a restricted access database, and half (50%) would participate even if their data were going to be shared in an open-access database [43]. However, another study of ours involving focus groups with underserved HIV+ individuals suggests that having a stigmatized condition (like HIV) might be a mitigating factor in one's willingness to share data, as 63% of the HIV+ participants reported that protecting their privacy is more important to them than advancing research by sharing data [89].

Fear of genetic discrimination is a major motivating factor for those who choose not to share their genomic information [50, 84]. The Genetic Information Non-Discrimination Act (GINA) [78], which became federal law in the United States in 2008, prevents health insurance providers (Title I) and employers with 15 or more employees (Title II) from requesting, requiring, purchasing, or using an individual's genetic information to make decisions about their job or insurance coverage [35]. While GINA is a progressive step in protecting individuals from genetic discrimination, it has many limitations. Title I of GINA only prevents discrimination by health insurance providers and does not include life, disability, and long-term care insurance providers. GINA is also not retroactive, it does not require insurance companies to pay for genetic testing or treatment, and it allows insurance companies to ask for

a minimum amount of genetic information in order to make decisions on medical tests and treatments. GINA also does not apply to military members or federal government employees with TRICARE or Veterans Health Administration (VHA) health insurance, though these groups have similar policies to protect against genetic discrimination [8, 35]. In addition to GINA, individuals in the United States are currently also protected under the Patient Protection and Affordable Care Act (ACA), also known as Obamacare, which prohibits private individual and group health insurers from denying coverage and charging higher premiums to individuals based on their genetic information [76].

It is not clear whether GINA or the ACA have done much to alleviate the fear of genetic discrimination. Several surveys suggest that only about 20% of the adult population is even aware of GINA [40, 85]. Of those who are aware of GINA, many do not fully understand what it does and does not protect against [27, 40], and when respondents are informed about the protections provided under GINA, about one-third of them feel less concerned about potential discrimination but one-third report feeling more concerned [40].

Conclusion

Genomic research has the potential to dramatically change the field of pediatric oncology. Understanding variations in tumor cells as well as inherited cancer syndromes is critical for the clinical care of patients and their families. As an increasing number of children participate in genomic research, it will be important to develop clear policies for obtaining pediatric assent, re-consenting children at the age of majority, returning genomic findings to minors and/or their parents, and sharing data in a responsible way.

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Chapter 7
When Cure Is Not the Goal: Ethical Issues Surrounding Early-Phase Research

Bryan Sisk and Eric Kodish

Introduction

Pediatric cancer was once a uniformly fatal disease. Sidney Farber, a pioneer of pediatric chemotherapy, was initially criticized for tormenting children by administering experimental chemotherapy when it would have been kinder and gentler to "let them die in peace." [1] Now, almost 70 years later, the 5-year survival rates in pediatric leukemia are greater than 80% [2]. Clinical studies have served as the engine for these successes. Today, approximately 80% of children with cancer are enrolled in clinical trials. However, the benefits of these studies to society must be balanced against the risks to individual participants, and research subjects must be protected from coercion, exploitation, and any undue harm.

Ethical concerns in clinical research have garnered attention ever since the atrocities of Nazi doctors were revealed after the conclusion of World War II. These doctors conducted unethical, inhumane experiments on human subjects without their consent, many of them children. After the conclusion of the Nuremberg Trials, the Nuremberg Code was developed as a basic framework for the protection of human subjects participating in clinical research. This code stated affirmatively that "the voluntary consent of the human subject is absolutely essential." [3] Societal concerns regarding unethical research practices were exacerbated by several subsequent

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scandals, reinforcing society's call for protections [4]. What began with the Nuremberg Code was followed by the Helsinki Code, Belmont report, the founding of the Bioethics movement, increased legal protections of research subjects, and development of Institutional Review Boards.

Because of children's vulnerable status, additional protections have been developed for pediatric research. The ethical foundations of pediatric research were discussed in detail previously. In this chapter, we will focus on the unique ethical issues related to early-phase research in children, using Phase I trials as the model to explore these issues. To frame our discussion of these ethical issues, we will first provide an overview of clinical trial design and implementation in pediatric cancer. We will then review the ethical issues related to informed consent in Phase I trials, followed by a discussion of the prospect of benefit, as well as the ethics of trial design and accrual models. We will conclude by discussing whether the development of novel therapeutic approaches to pediatric cancer in the future may require a reappraisal of the current ethical considerations related to pediatric Phase I oncology trials.

Overview of Clinical Trial Design in Pediatric Oncology

Clinical trials in drug development are separated primarily into three different phases. The goal of Phase I oncology trials is to determine the maximally tolerated dose (MTD) and to investigate the pharmacokinetics of an experimental agent [5]. The dose of the agent utilized in Phase II and III trials, therefore, is determined by Phase I trials. In adult Phase I oncology trials, a novel agent is tested for the first time in humans. Generally, Phase I participants are cancer patients with advanced disease for whom frontline therapies have failed. Pediatric Phase I oncology trials, however, typically occur subsequently to adult Phase I (and often Phase II) trials [5]. Therefore, investigators typically have more pharmacokinetic knowledge about the experimental agent before it is used in children.

The goal of a Phase II study is to describe the response rate and adverse events of a novel agent used against a particular type of cancer. For molecularly targeted therapies, these studies often assess biologic correlates of response in addition to toxicity of the tested agent [2]. If a phase II trial does not demonstrate a robust enough response rate, or if the toxicities are too great, then the experimental agent will not proceed to a phase III trial [5].

Phase III studies are the last step before a treatment is generally accepted as effective and integrated into the standard of care. These costly trials are generally large, randomized, and spread across multiple institutions. Classically, Phase III trials test the addition of a single agent to the standard treatment regimen in order to determine if the new agent improves outcomes and/or increases toxicity in the context of combination chemotherapy. The new agent examined by these studies is initially evaluated in Phase I and II studies to determine pharmacokinetic characteristics, effective

dosage, toxicities, and side effect profiles. While Phase II studies are primarily designed to evaluate efficacy, the focus in Phase I is on safety.

Given that Phase I studies are not primarily aimed toward improving outcomes for participants, these studies raise several unique ethical concerns which will be discussed for the remainder of this chapter. These ethical issues generally fall into two categories: (1) concerns related to informed consent and (2) concerns related to the structure, implementation, and expected outcomes of pediatric Phase I oncology trials. We will first address the paradigm of consent, assent, and permission.

Consent, Assent, and Permission

Informed consent (IC) is a person's ability to choose autonomously for oneself [6], and it entails two main components: (1) informing the research subject about the risks, benefits, and likely outcomes and (2) acquiring consent, which includes assimilation of the information [7]. For consent to be truly informed, there are multiple elements that must be present during the IC process, as listed in Table 7.1. IC rests on the ethical principle of respect for persons, which includes respecting the patient's basic right to exercise autonomy or self-determination [8]. This principle is rooted historically in the decision of *Schloendorff v Society of New York Hospital* in 1914: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages." [9] Years later in response to the heinous experiments of the Nazi's, the Declaration of Helsinki stated that "the voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent." [10] This ethical basis was further solidified by the Belmont Report, which established three pillars that govern ethically sound research involving human subjects: (1) respect for persons, (2) beneficence, and (3) justice [11].

Since the advent of modern bioethics, adults have generally been presumed competent unless proven otherwise. However in pediatrics, children and adolescents are largely presumed incompetent, with exceptions of legally emancipated minors [13, 14]. Given the presumed incompetence of children, parents historically provided proxy consent for their children. However, this approach was challenged in the late 1970s and 1980s, with growing favor for a model of child assent and

Table 7.1 Elements of informed consent [12]

Competence
Disclosure of information
Understanding of material information
Voluntariness
Consent and authorization of a plan

Table 7.2 American academy of pediatrics' elements of assent [16]

Helping the patient achieve a developmentally appropriate awareness of the nature of his or her condition
Telling the patient what he or she can expect with tests and treatment(s)
Making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy)
Soliciting an expression of the patient's willingness to accept the proposed care. Regarding this final point, [the committee members] note that no one should solicit a patient's views without intending to weigh them seriously. In situations in which the patient will have to receive medical care despite his or her objection, the patient should be told that fact and should not be deceived

parental permission [7, 8, 15, 16]. Assent can loosely be defined as a child's agreement with an intended treatment plan (Table 7.2). The concept of assent was initially introduced in the 1977 report by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [11, 17]. The Commission recommended that assent be solicited from all potential research subjects aged 7 years and older [11]. Subsequent federal regulations have not maintained an age limit, but defer these decisions to individual Institutional Review Boards [18–20]. Soon after in the 1980s, several physicians and ethicists began to strongly advocate for the child's voice in decision-making, further promoting the concept of assent in both research and clinical decision-making [8, 15, 16].

Despite this decades-long support for pediatric assent, there is still no firmly established definition. In general, "Child Assent refers to affirmative agreement of a minor who is to take part in the informed consent procedure in a way adapted to his or her capabilities, while their legal representative has the formal role of consenting." [21] As such, assent has served as a counterbalance against the social forces that have historically concentrated authority largely in the hands of physicians and parents [22]. This move toward a process of pediatric assent and parental permission has further engaged children in the decision-making process and supported the ethical justification of pediatric research. Given that participants of phase I trials are less likely to receive direct benefit and more likely to experience toxicities (discussed later), the concepts of consent, assent, and permission become even more central to the ethical discussion.

Are Parents and Patients Informed?

The validity of the consent and assent processes relies on the child's and parents' decision being informed, voluntary, reasonable and rational, and importantly that the child has capacity to understand the information [11]. General principles of consent, assent, and capacity were discussed in a previous chapter. We will focus on unique aspects of the consent process related to early-phase research.

In a pediatric Phase I oncology trial, children and parents consent to enrollment in the setting of relapse, progression of disease, and/or failure to respond to previously studied treatment regimens. When engaging in this IC process, families are faced with the choice of supportive care alone, "off-label" treatment (treatments with medications that had not been previously studied or proven to have benefit for the particular cancer) or enrollment in a Phase I trial. Given the high emotional burden of these decisions and the potential for misinformation, the IC process has several potential ethical pitfalls.

The most egregious ethical violations of the IC process would entail physicians intentionally misrepresenting the prospects of a trial or outright lying to patients. However, such blatant violations are exceedingly rare. In fact, a large majority of physicians reported describing Phase I studies without any attempt to influence parents' decisions [23]. Similarly, another study of pediatric Phase I oncology IC conversations found that risks and benefits were discussed during 95% and 88% of conversations, respectively [24]. Rather than egregious violations or intentional mistruths, the most pertinent ethical concerns in the IC process for early-phase research are related to communication.

The quality of communication during the IC process is crucial to ensure that patients and parents are sufficiently informed to make a rational and reasonable decision. One part of this communication is facilitated by IC documents, forms that summarize the risks, benefits, alternatives, and purpose of the trial. Numerous studies in adult and pediatric settings have reviewed IC documents to assess their readability. Uniformly, these studies have shown that IC documents are routinely written at a high level that ranges from 11th to 17th grade level, significantly higher than the education level of most patients and families undergoing the IC process [25–29]. This means that many IC documents do not fulfill the purpose of informing families. When written documents are unintelligible to parents or patients, these families are likely to rely more greatly on verbal information from the physician during IC conversations [30]. IC conversations, however, have also been shown to have much room for improvement.

One group of researchers audiorecorded IC conversations at six institutions and subsequently assessed the reading level of language used, as well as whether critical consent elements were discussed. They then compared these findings to IC documents from the same trials. They found that IC conversations contained fewer words and had a lower reading level when compared to IC documents. However, these conversations were also more likely to omit critical consent elements, such as voluntariness and dose-limiting toxicities. While parents and children were likely more able to understand the verbal communication, they were not presented all critical information that could inform their ultimate decision [31].

These challenges in IC communication can lead to significant misunderstanding. In one study of adults, 93% of subjects stated that they understood all the information presented to them, yet only 33% were able to state the purpose of the study [32]. Similarly, another study of adults found that 90% of subjects were satisfied with the IC process, but a large majority of subjects did not have a meaningful understanding of key characteristics of the trials. Perhaps even more concerning,

only 46% of healthcare providers in this study recognized that the main purpose of clinical trials is to benefit future patients, rather than the enrolled subject [33]. In a study of the pediatric IC process, only 32% of parents demonstrated a substantial understanding of the scientific purpose of a Phase I oncology trial. In fact, 35% of parents demonstrated little or no understanding, with lower levels of understanding in minorities and parents of lower socioeconomic status [34].

Given these apparent shortcomings, several investigators have asked parents, children, and physicians for recommendations on how to improve the pediatric Phase I IC process. Researchers and pediatricians have recommended providing a Phase I fact sheet to families, addressing key themes repeatedly over time, simplifying the language, length, and content of the IC process, providing more dedicated training for physicians involved in the IC process, and staging the IC process [23, 24, 35]. Parents and children have recommended that physicians provide more information, improve the structure of the IC process, and incorporate specific behaviors, such as providing information in a straightforward and honest manner, and providing information that is tailored to the specific needs of each individual family [34]. Enacting some of these recommendations could lead to an improvement in the IC communication process.

Motivations and Voluntariness of Decision

Families can have many different motives for enrollment in pediatric Phase I trials. The most apparent motivation is hope for a medical benefit or cure [36–38]. In the adult literature, numerous studies have shown this hope to be a stronger driver for enrollment than either altruism or trust in the physician [32, 36, 39–41]. In one study, "more than 90% of patients said they would still participate in the study even if the experimental drug had severe adverse effects, including a 10% chance of dying." [42] Similarly in pediatric studies, hope for a cure and prolonging the child's life were the main reasons for enrolling in pediatric Phase I oncology trials [43].

Given this powerful drive to "try everything" in the face of terminal illness, questions of voluntariness arise when considering enrollment in Phase I trials. A voluntary action is one that occurs without "being under the controlling influence of another person or condition." [12] Voluntariness can be inhibited by direct coercion from a physician or family member; however, this seems to rarely be the case. As one group pointed out, "there is no coercion if an alleged agent of coercion has no intention to coerce." [12] In other words, coercion must be intentional, and many pressures may affect decision-making without being coercive per se.

Rather than coercion, patients or parents may feel pressured by the circumstances of their child's illness. For example, the burden of a life-limiting illness itself can pressure families to make certain decisions, as can the recommendations of family, friends, and physicians. Several adult studies have shown that patients with terminal cancer continue to hold out hope for a cure and often desire to "try everything" in hopes of a miracle cure, or at least some medical benefit [39]. In fact, in both adult

and pediatric studies, the feeling of having "no choice" but to join a trial is commonly expressed [44–46].

Voluntariness can also be inhibited when other options are not discussed with a patient or when prognosis and likely outcomes are not fully disclosed. As Mack and Joffe noted, physicians at times avoid difficult prognostic discussions by "discussing prognosis in vague or overly optimistic terms, waiting for patients to ask for prognostic information, avoiding discussions of prognosis unless the patient is insistent, and focusing conversation on treatment rather than on outcomes." [47] Such reluctance to engage fully in difficult discussions may deter physicians from discussing other options, such as hospice or palliative care. Some physicians have worried about the negative connotation of discussing palliative or hospice care with patients, fearful of sending the signal of "giving up." [48] This is particularly worrisome because Phase I trials and palliative care can be mutually beneficial, rather than mutually exclusive.

The poor prognosis of children who are eligible for such studies can pressure many parents to "try everything." They often describe the worry of "giving up" on their child if they do not seek further treatments, and they perceive Phase I trials as treatment. Additionally, they may feel pressured by family or physicians to opt for enrollment. In order for a decision to be truly voluntary, it must be made without being under the controlling influence of another person or condition. Given the emotional burden of decisions regarding enrollment in Phase I trials, it is an oversimplification to say that consent is purely voluntary.

Therapeutic Misperceptions

Another ethical challenge in Phase I oncology research is that parents and children often misperceive the goals and likely outcomes of trials. Such misunderstanding can take many forms (Table 7.3). The most commonly discussed form is *therapeutic misconception*, first coined by Appelbaum and colleagues in 1987 [49]. In therapeutic misconception, the children or parents conflate entry into a research trial with clinical care. Therefore, they may assume that the experimental agents are intended to benefit their child. Such a misunderstanding is ethically challenging: If parents enroll their child on a Phase I oncology trial with the understanding that their child

Table 7.3 Therapeutic misperceptions in clinical research

Therapeutic misconception	Conflate participation in a Phase I oncology trial with receiving treatment
Therapeutic misestimation	Understand distinction between research and treatment, but overestimate likelihood of benefit
Therapeutic optimism	Understand low likelihood of benefit, but hope they will be in the minority of participants who benefit from enrollment
Unrealistic optimism	Understand low likelihood of benefit, but have unrealistic certainty that they will benefit from enrollment

will be receiving routine oncology care rather than an experimental agent, then they are not truly informed in their decision. They may be accepting risks without fully understanding the goals and likely outcomes of the trial.

There are many components of the Phase I context and enrollment process that can exacerbate this therapeutic misconception. When enrolling in a Phase I trial, parents often bring their child back to the same hospital where they have been receiving standard care, sit in the same hospital room, see the same doctors, and engage in an IC process that is similar to when their child was first diagnosed. When combining these confusing aspects of the IC process with the parents' natural drive to protect their child and hope for a cure, it is easy to see how therapeutic misconception can develop and persist. Physicians may also maintain some level of therapeutic misconception when enrolling research subjects. For example, one study showed that 59% of pediatricians believed that children would receive benefit from enrollment in Phase I oncology trials, despite objective data in the literature showing that only 5–10% of children generally have objective responses in such trials [50].

The concept of therapeutic misconception has become a "catch-all" term over the years, leading one group to state that "therapeutic misconception has been used loosely to refer to any number of misunderstandings that subjects may have in the research context." [51] As a result, several authors have proposed additional, more precise terms. The first such term is *therapeutic misestimation*. Parents with therapeutic misestimation do not conflate research with clinical care as in therapeutic misconception. Rather, these parents understand the purpose of the trial, but they either underestimate the risk or overestimate the statistical chance of benefit from study enrollment. For example, a parent may assume that enrollment in a Phase I trial has a 40% chance of benefitting their child, rather than the 5–10% objective response rate that is expected.

Further along this spectrum lies *therapeutic optimism*, in which the parents hope for the best possible outcome for their child. A parent may understand that only 5% of subjects are expected to benefit from participation in a trial, but they still hope their child will be in that 5%. A pediatric study highlighted such therapeutic optimism, showing that parents expected their child to benefit from participation in the trial despite understanding that the odds were poor. The main benefits they hoped for included prolonged life or "buying time" until another therapy became available [44]. Such optimism is a natural part of being a parent and is a natural part of the human-coping process. Many parents maintain hope of a cure for their child's incurable cancer, even though they understand their child will die [52].

However, optimism can also become ethically problematic when it becomes unrealistic. Parents with *unrealistic optimism* understand all the information presented to them, but they believe their child has a better chance of benefit than other children in a similar situation. Parents in this situation may "know" that their child will be one of the 5% who benefit from the trial [53]. Such unrealistic optimism can potentially impede the parents' or child's ability to become fully informed because they are not able to accept the information presented to them. Similarly, unrealistic

optimism could impede voluntariness of a decision because parents are unable to fully process the risks and benefits of trial participation.

If physicians believe that a family is enrolling a child in a Phase I oncology trial in the setting of therapeutic misperceptions, they should work to dispel the misperception. If a parent or child misunderstands the purposes of a trial, information can be portrayed in a more suitable manner, or perhaps in a staged process. However, parental understanding is not the same as parental acceptance of the information. When unrealistic optimism is revealed, the consenting physician is placed in a more difficult position.

Kodish has previously proposed that such unrealistic beliefs "may – as a matter of ethical integrity – have to prohibit study enrollment," with the goal of maintaining respect for persons throughout the consenting process [53]. However, there are also risks in refusing trial entry for terminally ill children. Such refusal runs the risk of diminishing hope, which may be crucial to the parents' or child's coping. Additionally, such refusal could represent paternalism on the part of the physician and a subversion of the parents' or child's wishes. Beyond these ethical concerns, such a decision is likely to have a negative impact on the physician–parent–patient relationship. As a child nears the end of life, a strong relationship with caregivers is essential to foster trust and a sense of support for the entire family. If this relationship is diminished because of trial refusal, these families may be susceptible to impactful psychosocial harms. These harms might affect the end of life for the child, as well as bereavement for parents who may feel they were unable to "do everything" to help their child. The ethics of trial enrollment refusal and the downstream effects should be further investigated to support patients, families, and healthcare professionals in this difficult situation.

Federal Policy Related to Early-Phase Research

To contextualize parental hopes, we will next discuss the objective data regarding the potential for benefit in Phase I oncology trials, and we will also review the debate over the concept of "therapeutic research" and the "prospect of direct benefit." To begin this discussion, we must first define benefit. In pediatric trials, an objective response is defined as partial or complete tumor remission. Phase I oncology trials in recent years have shown objective response rates of 5–10% in both pediatrics and adults [54, 55]. When individual cancer types are evaluated, response rates can range from <3% to >17% [56]. However, objective response rate may not be the only meaningful response. For example, stable-disease rate or less-than-partial response could arguably be considered meaningful responses. One review article found that 34.1% of adult patients experienced stable disease or less-than-partial response [54]. Similarly, effect on quality of life and symptom control are other important outcomes that, unfortunately, are rarely recorded in Phase I clinical trials.

Toxicity is equally important as an outcome, especially since Phase I trials are designed to identify toxic dosage levels. Although toxic death rate is fairly low in these trials (less than 1%), dose limiting toxicities can be fairly frequent, ranging from 15% to 25% depending on the trial [54–56]. In fact, the classical design of Phase I trials mandates that a certain proportion of participants will experience toxicity as an endpoint in order to determine the MTD.

Overall, there is a small, but not infinitesimal, likelihood of benefit expected from enrollment in a Phase 1 oncology trial, and there is also a moderate risk of toxicity. These data are the starting point for the debate over whether pediatric Phase 1 oncology trials should be considered "therapeutic research." However, to fully understand the importance of this distinction, we will first review the regulations that govern pediatric research.

In Subpart D of the Code of Federal Regulations (CFR) 45 part 46, pediatric research is categorized based on the risk level and the potential for direct benefit [18] (Table 7.4). Pediatric Phase I oncology trials can be allowable under CFR §46.405 or CFR §46.406, depending on whether the Institutional Review Board (IRB) determines that the research subject is likely to have the prospect of direct

Table 7.4 Code of federal regulations (CFR) subpart D

Code	Requirements
§46.404 – Research not involving greater than minimal risk	Adequate provisions for soliciting assent of children and permission of parents
§46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	Risk justified by anticipated benefits to the subjects Anticipated benefit is at least as favorable as alternative approaches Adequate provisions for soliciting assent of children and permission of parents
§46.406 – Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition	Risk represents minor increase over minimal risk The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical care The intervention or procedure is likely to yield generalizable knowledge about the subject's disease or condition which is of vital importance for the understanding or amelioration of the disorder or condition Adequate provisions for soliciting assent of children and permission of parents
§46.407 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	IRB finds that research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting health or welfare of children Reviewed and approved by Secretary of Health and Human Services, after consultation with a panel of experts in pertinent disciplines

Additional protections for children involved as subjects in research [18]

benefit from involvement in the study. If the study is deemed to offer the prospect of direct benefit, then children can be enrolled in studies with "greater than minimal risk" because the risk is balanced by the potential for benefit under CFR §46.405. For studies with no prospect of direct benefit, however, enrollment of children is acceptable under CFR §46.406 only if the risk of participation represents a minor increase over minimal risk. Given the significant risk of toxicity and the small risk of toxic death in Phase I oncology trials, enrollment is generally considered more than a minor increase over minimal risk, which precludes enrollment under CFR §46.406.

Therefore, the prospect of direct benefit and associated risks of enrollment in pediatric Phase I oncology trials have major implications on whether research is allowable under CFR §46.405. If a trial is not otherwise approvable by any of the previously mentioned regulations, it can only be approved under CFR §46.407, which requires approval by the local IRB in addition to approval by the Secretary of the U.S. Department of Health and Human Services in conjunction with a panel of national experts. This process carries with it extra cost and delay in trial implementation. This policy structure makes it clear that the debate over the prospect of direct benefit has major implications on the permissibility of pediatric Phase I oncology studies in the United States.

The Prospect of Direct Benefit

The Declaration of Helsinki, originally published in 1964, declared that there is a fundamental distinction between "research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific." [10] Since this time, the classification of "therapeutic" versus "non-therapeutic" research has continued to be debated in the literature. Some have argued that the entire concept of "therapeutic research" is flawed, because all research has a scientific aim at its core. "The aim of clinical research is to develop generalizable knowledge by means of scientific investigation involving groups of participants; the aim of medical care is to benefit particular patients." [57] It could be argued that such a distinction of research types further perpetuates therapeutic misperceptions in the eyes of both parents and physicians. For example, the American Society of Clinical Oncology states that "Phase I cancer trials can represent a real therapeutic option for some patients who have failed to respond to other treatments or for whom no other therapies exist," a statement that clearly conflates the concepts of research and clinical care. [58]

If therapeutic research is defined as any study that has the prospect of direct benefit rather than research that is intended to benefit the subject, however, then the argument is altered. Kodish has argued that Phase I oncology trials offer the prospect of benefit if this benefit is considered relative to other options [59]. As empirical studies have shown, 5–10% of subjects are likely to have an objective response to the experimental therapy, and an additional 20–30% may have prolonged disease

stability during the trial. Therefore, such an experimental trial likely offers an equal or greater prospect of direct benefit compared to alternatives, which include palliative care alone or "off-label" chemotherapy.

Other authors have questioned what the appropriate comparator is for a risk/benefit analysis in Phase I oncology trials. One group argues that palliative care alone is not an appropriate comparator, because subjects who opt for enrollment in a clinical trial have already forgone the choice of supportive care alone in preference of "treatment." Furthermore, they argue that FDA approved treatment regimens are not appropriate comparators because subjects enrolling in Phase I trials do not have this option available to them. Rather, they argue, "off-label" treatments are the appropriate comparison, because the potential risks and benefits are similarly unknown [57].

Despite the small chance of benefit for subjects who enroll in Phase I oncology trials, other ethicists have argued against using the terminology "direct benefit." For example, Friedman-Ross argues that using such terminology may promote therapeutic misconception, which can compromise the IC process [5]. Such language could inadvertently lead to a delay in parental acceptance of their child's terminal prognosis, and "make it harder for parents to acknowledge their child's suffering if they decide to pursue cure at all cost." [5] Therefore, Friedman-Ross opposes classifying pediatric Phase I oncology trials as offering the prospect of direct benefit, because "doing so ignores the fact that the researcher's intent is focused on showing safety, not efficacy." [5]

Conversely, another group aimed to distinguish between the concept of "therapeutic" research and the prospect of direct benefit. They maintain that Phase I oncology trials are not "therapeutic" because the intent of the study is scientific rather than therapeutic. Further, they argue that no research should be considered therapeutic, because all research has scientific questions at the core. However, they also state that "Bioethicists who rightly see that Phase I trials are not therapeutic draw the mistaken inference that they offer no prospect of direct benefit." [57] The prospect of benefit, they argue, is determined by the probability of outcomes, not by the intent of the study. In their view, ethicists should focus on the risk-benefit assessment for individual subjects. While this area continues to be debated, we believe there is sufficient evidence to support that pediatric Phase I oncology trials offer the prospect of benefit to participants that is comparable to the available alternatives, even though direct benefit is not the scientific aim of these studies.

Ethics of Phase I Study Design

When considering the risk-benefit ratio in pediatric Phase I oncology studies, one must evaluate the likelihood of benefit and the likelihood of toxicity. Because the optimal dose is (by definition) unknown at the initiation of the study, some children will receive too low of a dose and some will receive too high of a dose. In fact, some argue that the risk of underdosing in Phase I cancer research is more ethically problematic than the risk of toxicity [5]. Nearly all pediatric cancer therapies are first

studied in adults. Therefore, some claim there is a greater chance of response in pediatric trials and a better understanding of potential toxicities [5, 55]. To minimize the number of pediatric subjects required to complete a Phase I oncology study and to increase the chances that children in the study will receive a potentially therapeutic dose, pediatric trials have historically begun at 80% of the maximally tolerated dose (MTD) determined in adult Phase I studies [55]. Starting at such a high dose increases the chances that a child enrolled early will receive a high enough dose to maintain the prospect of benefit.

The other ethical imperative in pediatric Phase I oncology trials is to expedite completion of studies. Phase I trials are the gateway through which all new treatments must pass. If this gateway becomes a bottleneck leading to delays in drug development, children will continue to suffer and die from these diseases. Balancing safety and efficiency is central to the ethics of study design. To fully understand these ethical concerns, we will review the most common study designs in Phase I oncology trials, highlighting how each model attempts to balance efficiency with safety (Table 7.5).

The traditional Phase I trial accrual design was the 3 + 3 dose escalation study, which is a rule-based design. In such a study, a minimum of three participants are enrolled at each dose of the experimental agent. Pre-defined dosage levels for each cohort are established before the trial begins, with the first (lowest) dose in adult studies determined by calculating a percentage of the LD50 (lethal dose for half of a group of test animals) in mice. At any given dosage level, if at least one participant experiences a dose-limiting toxicity (DLT), then another three subjects are enrolled at the same dosage level. If a DLT is found in two participants at a dosage level, then the MTD has been exceeded. Subsequently, three more subjects are enrolled at the next lower dosage level. The MTD is then defined as the dosage level at which none or one out of six participants experience a DLT and two participants experience a DLT at the next highest level. Importantly, accrual to the study is suspended until toxicity data are collected and evaluated in the cohort of three subjects, which can lead to delays in accrual [61].

Table 7.5 Advantages and disadvantages of dose escalation methods

Dose escalation method	Characteristics
3 + 3 design	*Advantages*: Easy to implement; emphasis on safety *Disadvantages*: Relatively slow dose escalation; more subjects exposed to low dose of experimental agent
Rolling six (and other accelerated titration models)	*Advantages*: More rapid dose escalation compared to 3 + 3 design; subjects more likely to receive potentially efficacious dose *Disadvantages*: Greater potential for exposure to toxic dose of experimental agent
Model-based designs	*Advantages:* Most rapid dose escalation designs; decreases amount of time to completion of Phase I studies *Disadvantages*: Requires statistical expertise and specialized infrastructure to implement; minimal data collected for pharmacokinetic characterization of experimental agent

Adapted from Le Tourneau et al. [60]

The 3 + 3 design was initially developed to minimize the number of subjects exposed to toxic or lethal doses of the experimental agent. Inherent to this paradigm is a normative ethical commitment that safety is more important than efficacy. (The *Abigail Alliance v von Eschenbach* case addressed this issue in the judicial system.) This emphasis on safety also led to decreased efficiency and increased number of participants exposed to low doses of the experimental agent. To address this inefficiency, Skolnik et al. proposed a modification of the 3 + 3 design, creating an accelerated titration design which they called the "Rolling Six" design [62]. In the Rolling Six schema, "patients are continually accrued based on the data available at the time of enrollment, allowing up to six patients to be enrolled at a time, increasing the dose level in accordance with patient data at the time of accrual." [61] "Specifically, a fourth subject can be enrolled if at least one of the first three subjects has not been fully followed and no more than one of the previous three subjects has experienced a DLT." [63] Similarly, a fifth subject can be enrolled if the above applies to the previous four subjects, accruing up to six subjects in a dosing cohort. If at any time a dosing cohort of six subjects is followed without developing a DLT, then a new cohort of six subjects will be enrolled at the next highest dosage level. Similarly, if any two subjects develop a DLT at the same dosage level, and the next lowest dosage level was already tested, then this lower dosage is considered the MTD.

To test the safety and efficiency of the Rolling Six design, the authors ran 1000 study simulations using historical pediatric Phase I oncology trial data. These study simulations showed that the Rolling Six design could decrease the estimated time to study completion by an average of 56 days without increasing the number of DLTs [62]. This design has since become the standard for the Children's Oncology Group and is almost exclusively utilized in pediatric Phase I oncology trials [63].

In recent years, there has been increasing emphasis on developing better Phase I accrual designs to further decrease risk of both toxicity and underdosing while also improving efficiency of trial completion. These efforts, largely occurring in adult Phase I oncology trials, have led to the new category of model-based accrual designs. One such design is the Continual Reassessment Method (CRM), which has subsequently been tested with several modifications. In such model-based designs, "all patients are treated at the dose thought to be closest to the MTD, which corresponds to the dose at the target dose-limiting toxicity level." [60] The estimate of MTD is based on Bayesian statistics, and the dosage estimate is updated for each subject who enters the trial. As such, model-based methods utilize all toxicity information that is accrued during a trial. However, these model-based designs require biostatistical expertise and specialized software, as opposed to a rule-based design which is relatively simple to implement. Additionally, model-based designs may expedite identifying the MTD to the extent that it deprives investigators of data needed to fully describe the pharmacokinetics of the experimental agent [60]. Despite the potential benefits of model-based designs, they have not yet been regularly integrated into pediatric oncology.

Novel Phase I trial accrual designs offer more efficient means of enrollment and can lead to quicker completion of Phase I trials [64]. As such, they may help to

maximize the use of resources in pediatric studies, ideally leading to quicker development of novel treatment regimens for children with cancer. Each model also has shortcomings, however. Perhaps the biggest shortcoming of all these accrual designs is their reliance on toxicity as the outcome of interest. As molecularly targeted therapies continue to be developed, toxicity may not be the appropriate outcome for studies. Next, we will discuss how novel therapeutics may impact the ethics of pediatric Phase I oncology trials in the future.

Novel Drugs and Designs: Future Ethical Challenges and Opportunities

Historically in Phase I oncology trials, toxicity of a compound has been tightly linked to its anticancer efficacy. In terms of pharmacologic science, cancer drugs generally have a narrow "therapeutic index." As such, finding the MTD has been essential in order to maximize the chances of improving outcomes for future subjects. On this basis, all previously discussed trial designs were focused on expediting accrual so that new drugs that turn out to be "winners" are brought speedily through the drug development pipeline. New understanding of cancer biology is beginning to challenge this paradigm, however.

As researchers have developed an improved understanding of the molecular mechanisms of cancer development and progression, molecularly targeted therapies and immune-based therapies are beginning to supplement cytotoxic therapies. Chimeric antigen receptor (CAR) T-cell therapy, for example, is currently being studied in some pediatric malignancies. CAR T-cells are patient's T-cells that are harvested and reengineered to express a synthetic receptor that is specific for a tumor antigen. This therapy has shown great promise in leukemia [65]. Immune checkpoint therapy is another immune-based treatment modality that is slowly trickling into pediatric oncology. This therapy targets the components of the immune system that prevent autoimmunity. By inhibiting these immunologic checkpoints, the immune response against cancer is significantly enhanced, which will hopefully lead to increased clearance of cancer [66]. However, tinkering with the immune system in this way can also lead to significant toxicity from autoimmunity [67]. Beyond immunotherapy, a growing list of small molecular inhibitors have shown promise in preclinical studies, with a wide array of targets including tyrosine kinase, serine/threonine kinase, histone deacetylase, proteasome, and DNA topoisomerase, to name a few [68, 69].

Whereas toxicity was the appropriate marker for Phase I oncology trials that focused on cytotoxic therapies, future trials will need to focus further on efficacy against the target tissue. For example, one group of researchers reviewed adult Phase I oncology trials with molecularly targeted agents and found that higher doses did not necessarily lead to better outcomes than lower doses [70]. In fact, it may be possible to utilize dosages of targeted agents that have anticancer activity with minimal side effects or toxicities, thus obviating the need for determining the

MTD. It is likely that in the future, "alternate end points reflecting target modulation and downstream molecular effects [will be] more relevant surrogates of activity than toxicity, and can assist in prioritizing drug candidates for further development." [71]

With these changes in the development and outcomes of Phase I oncology trials, the ethical framework will need to continually be reevaluated. If Phase I trials focus less on toxicity and more on agents targeted against mutations present in a subject's tumor, the risk-benefit calculation is likely to shift. When toxicity is no longer a primary outcome, subjects should theoretically be at a decreased risk of toxic effects. Additionally, targeted therapies should (at least in theory) increase the prospect of direct benefit for subjects who enroll in Phase I trials. However, identifying the appropriate endpoint to show efficacy of the experimental agent is likely to require samples of tumor tissue. This could result in the scientific need for invasive, clinically unnecessary procedures, such as additional bone marrow or tumor biopsies [72]. These procedures carry their own risks and burdens and will need to be incorporated into the ethical discussion of pediatric Phase I oncology trials.

Another ethical challenge confronting the future of precision medicine in pediatric oncology is a lack of appropriate Phase I trials for pediatric subjects. Pediatric cancer is a rare disease, especially when compared to adult cancers. Therefore, any drug developed explicitly for pediatric patients would be unlikely to yield a large profit, making it difficult to recoup investment in the drug development process. As a result of this economic pressure, current pediatric cancer therapies almost exclusively trickle down from adult oncology studies. This is problematic because most pediatric cancers have unique biology which is different from that seen in common adult cancers. Due to the financial disincentive to invest in rare diseases, these cancers may become orphaned diseases in which "hand-me-down" adult drugs are largely ineffective. If investments continue to be made solely in developing drugs targeted toward adult cancers, then pediatric cancer patients may be left behind in this pursuit of precision medicine.

Conclusion

In this chapter, we have reviewed the unique ethical challenges related to pediatric Phase I oncology trials. These ethical challenges relate largely to informed consent or to trial design and implementation, and there are persistent disagreements among ethicists regarding both topics. However, all would agree that Phase I clinical trials play a pivotal role in accelerating or delaying the pipeline for new pediatric cancer treatments. As new treatment modalities are developed and new trial designs are implemented, old ethical challenges will be solved and new ones will develop. The ethics of early-phase research in pediatric cancer is complex and challenging. Continued dialogue between cancer investigators and ethicists will be necessary to promote the proper balance of risk and benefit as scientific progress evolves but commitment to foundational ethical principles endures.

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Part IV
Supportive Care

Chapter 8
Advance Care Planning

Allison Caldwell, Melody J. Cunningham, and Justin N. Baker

Overview of Advance Care Planning

Definition

Advance care planning is the process by which a patient and family, in consultation with healthcare providers, make decisions about current and future health care [2]. It is regarded as the gold standard for all patients facing serious illness, including the pediatric population [5]. While historically advance care planning programs and research efforts centered on adult patients, and a predominantly geriatric population [5], these efforts have expanded to incorporate children and young adults, in concordance with the growth of pediatric palliative care programs [6]. Similarly, the model for advance care planning, which in its conception focused largely on completion of advance directives, now involves discussion of goals of care, patient and family values, systems of belief, and patient prognosis as they inform patient care and medical intervention [7]. The process of advance care planning occurs as an

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ongoing conversation, rather than a discrete or finite decision, and adapts alongside the trajectory of illness, in synchrony with patient and family goals. The American Academy of Pediatrics (AAP) Policy Statement on Pediatric Palliative Care and Hospice Care Commitments, Guidelines, and Recommendations states that the palliative care clinician should "facilitate clear, compassionate, and forthright discussions with patients and families about therapeutic goals and concerns, the benefits and burdens of specific therapies, and the value of advance care planning [8]." The policy statement emphasizes the importance of engaging in advance care planning over time, as an illness and treatment course evolves, and at least annually in the care of a child with a chronic, complex illness [8]. Advance care planning should begin early in the course of illness; should be shared among the patient, family, and healthcare provider; and should occur as a structured process [9, 10].

Ethical Principles Underlying Advance Care Planning

The ethical imperative to provide compassionate patient- and family-centered care in the relief of suffering [11] extends to the care provider's obligation to engage in advance care planning with a child and family facing serious illness. Though the process of advance care planning cannot eliminate all ethical conflict and uncertainty, it seeks to uphold the care provider's responsibility to do good, to avoid causing harm, to respect both parental authority and patient individuality, and to provide care equitably in accordance with patient values and beliefs, regardless of means [10]. This occurs through early, honest discussions with a patient and family, framed in the context of their values and experiences and the medical recommendations of the clinical team, in order to align around the goals of care.

Of particular consequence in the field of pediatric oncology are the concepts of patient autonomy, surrogate decision-making, and the related legal doctrine of informed consent. The contemporary legal notion of patient autonomy took shape in the 1914 case, *Schloendorff v. Society of New York Hospital*, in which Justice Benjamin Cardozo ruled that: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body…This is true except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained [2]." This ruling upholds respect for persons within the medical field, particularly a patient's right to informed decision-making, which is embodied in the process of informed consent for medical intervention. The components of informed consent include: the provision of information, an assessment of the patient's understanding, and the patient's capacity to make the necessary decision in the absence of coercion [12].

Within pediatrics, the application of informed consent is limited, as children are most often considered to lack the capacity to make serious medical decisions [13], with exceptions arising in the care of adolescent and young adult patients. Decision-making typically occurs through a parent or surrogate, on the basis of parental authority. Parental authority, which has in some cases been termed parental auton-

omy, hinges on parental responsibility for raising a child, parental close knowledge and understanding of the child, the responsibility to live with the outcomes of decisions made, and inherent investment in the best interests of the child [13]. However, decisions should be made with the assent of the child whenever possible. The AAP recommends that patients participate in decision-making commensurate with their developmental stage; the patient should provide assent to care when reasonable [12].

Involvement of the pediatric patient in decision-making should be promoted as part of an ethical approach to advance care planning. Such involvement requires that the care provider facilitate developmentally appropriate awareness of the patient's medical condition by discussing what can be expected from upcoming treatments and testing, assessing the patient's understanding of a clinical situation and the factors affecting patient response, and determining the patient's willingness to participate in care [12]. With development, experience, and coaching, the patient's ability to engage in the medical decision-making process as an agent in his or her health care will increase.

Communication in Advance Care Planning

Communication is at the core of successfully implemented family-centered advance care planning. The two exist inextricably. Effective advance care planning mandates and improves the quality of communication [7]; likewise, communication with patients and families depends on the discussion of the goals of care, value systems, and prognosis that structure advance care planning. A patient's values, beliefs, goals of care, and best interests are upheld through facilitating open and ongoing discussions among the patient, family, and medical care provider that are then shared with the patient's medical team and community.

Parents value communication and caring relationships with providers, especially when facing the end of their child's life [14–17]. The individual pediatric patient is intimately a part of a family, community, and social network of support that informs parent–patient decision-making. The communication necessary and inherent in effective advance care planning allows patients and families to communicate their desired care preferences with their entire medical team, and with their greater community, reducing confusion and reiteration of often difficult conversations [6]. The process of advance care planning supports end-of-life decision-making by bolstering parents' emotional supports, the quality of information provided, and medical understanding, and by enhancing the communication skills of medical providers [14].

Pediatric cancer care is based on truthful, sensitive, empathic communication with the patient, in a family-centered and child-focused approach [18]. This occurs by establishing a trusting, long-standing relationship between care provider, patient, and family and consistently employing clear, honest, and effective communication [19]. Communication may be viewed as a tool in the implementation of advance care planning and may prove a therapeutic intervention in itself. Development of the communication skills of the medical care provider has been shown to improve family outcome and experience [20].

The AAP recognizes three core elements of physician–parent–child communication. These tenets establish the groundwork for an approach to conversations in pediatric advance care planning: (1) informativeness or the quantity and quality of health information provided by the physician; (2) interpersonal sensitivity or affective behaviors that reflect the healthcare provider's attention to, and interest in, the parents' and child's feelings and concerns; and (3) partnership building, or the extent to which the healthcare provider invites parents and child to express concerns, perspectives, and thoughts collaboratively [21].

Discussions focused on advance care planning are centered on patient and family goals of care, as informed by the patient's clinical status and prognosis. The conversation takes a team-based approach, with focus on a family's goals and achievable hopes. One such proposed conversational structure involves: (1) reviewing the major challenges confronting the child and family; (2) discussing goals and hopes; (3) discussing alternative care options; (4) examining the risks and benefits of each therapeutic option; (5) exploring tradeoffs; (6) forming a plan; and (7) planning next steps and follow-up [1]. Although the discussion might vary in structure and form, at its core it focuses on providing thorough, informative, and relevant medical information, followed by a discussion of goals of care within the context of patient and familial hopes, values, cultural and religious belief systems, and community. The developed plan is documented, and implemented, with the recognition of the ongoing nature of the advance care planning discussion.

Multiple studies have indicated the safety and importance of the inclusion of the pediatric patient in the communication process. Pediatric patients and survivors of pediatric cancers have a recognized capacity to be involved in decisions surrounding treatment and at the end of life [14, 22]. Furthermore, parents of children with cancer recognize the importance of decision-making alongside their child [23]. Children are aware of both their diagnosis and prognosis, without having been informed by an adult, and often understand more than presumed [21]. For the pediatric patient, provision of developmentally appropriate and welcomed information, inclusion in decision-making, and having choices allow an increased sense of control in the face of the chaos and fear of cancer diagnosis, as well as an enhanced sense of trust in the healthcare team [21]. The pediatric patient should not be forced to participate in advance care planning discussions, but he or she may be encouraged and supported in this endeavor through coaching and the use of developmentally appropriate language and decision-making tools [21, 24].

Timeline for Advance Care Planning

The advance care planning discussion is not discrete; it occurs in an ongoing fashion in accordance with the trajectory of illness and the evolution of a patient's and family's goals of care. The trajectory of pediatric illness, and that of cancer specifically, may not prove predictable; therefore, advance care planning becomes all the more important as it seeks to anticipate and prepare for both acute illness and a gradual worsening in health status. Pediatric cancer that is life-threatening may be

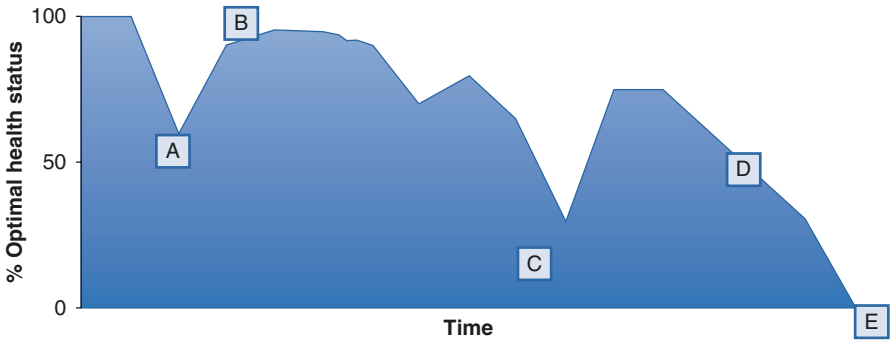


Fig. 8.1 Health status of a child with serious illness over time [1]
A. Acute decompensation and hearing bad news
B. Recovery and accommodating to a new life
C. Acute decompensations and unexpected recoveries
D. Slow decline preceding death

viewed graphically as a gradual worsening of health status from baseline marked by periods of acute illness (e.g., sepsis, significant disease progression), and subsequent improvement to a new baseline of health (Fig. 8.1). Periods of change, and of worsening health within a child's life, are associated with a higher risk of suffering [1]. As such, addressing goals of care both early in the course of illness, and again as the child faces each new challenge, continually aligns the patient, family, and healthcare team in working toward a common goal, which may evolve over time [3].

Planning for the end of life is imperative in caring for children with life-threatening cancer and their families and is the responsibility of the healthcare provider in shaping the advance care planning dialogue over time. However, given the challenges presented by prognostication and the barriers to advance planning, this discussion may occur late in the course of illness and out of immediate necessity. By contrast, when physicians and parents share the recognition that there is no longer a realistic chance for cure, earlier discussion of hospice, improved quality of care delivered by a home care team, earlier documentation of resuscitation status, and reduced cancer-directed treatment in the last month of life occur [14]. Time-appropriate prognostic communication that is family-centered and accessible to the patient allows parents to make the best possible decisions for their child and focus on quality of life, with reduction in the distress associated with uncertainty. This allows time and space for a child and parents to reframe goals and create hopes anew [25].

Barriers to Advance Care Planning

Despite recommendations to incorporate advance care planning early and often into the care of pediatric oncology patients with serious and life-threatening illness, these conversations are often documented late in illness, with resuscitation status

not documented until near the time of death [26, 27]. Inconsistent communication in advance care planning risks parental confusion, distress, and incomplete transfer of important information [26]. Historically, healthcare providers have identified unrealistic clinical expectations by parents, differences between physicians', patients', and parents' understanding of prognosis, and parental unreadiness to engage in advance care planning discussions as barriers to advance care planning. In addition, physician concern about taking away hope, physician uncertainty about prognosis, and self-doubt regarding the ability to skillfully engage in advance care planning discussions have been cited as hindrances in allowing broad-reaching advance care planning [5]. Notably, overcoming these impediments to advance care planning hinges on improved provider communication skills and education.

Parents of children with cancer remain hopeful, despite simultaneously holding expectations of poor prognosis [28]. It is within this seeming contradiction that care providers might hastily identify parental expectations as unrealistic. Yet, the exploration of the depth and breadth of parental and patient hopefulness might facilitate and support it, identifying hopes that *are* possible, and that coexist with the gravity of the prognosis [28].

Similarly, effective communication might be used to transfer information regarding prognosis from clinician to parent and patient. This can be achieved by creating an open environment for questions and assessing parents' and patients' understanding throughout the conversation. While offering specific prognostic timelines is challenging and often proves inaccurate, general timeframe estimates (i.e., days to weeks, weeks to months, months to years) might be implemented in order to convey tangible information and thus allow informed planning and decision-making [29].

Parental and patient unreadiness to participate in advance care planning has been attributed to anxiety, fear of death, fear of losing hope, lack of insight, and denial of disease severity; however, lack of readiness to engage in advance care planning should not be presumed, despite the significant emotional distress caused by pediatric cancer and illness. Patients and parents may not realize that advance care planning discussions should take place with their clinician or may not take the lead in initiating these conversations [26]. Furthermore, increased disclosure of information, particularly prognostic information, allows preservation and even enhancement of parental and patient hopes, rather than engendering false hopes and mistrust and furthering fear [28]. The honest disclosure of information in a supportive environment strengthens the trusting relationship of the patient, parent, and physician, allowing space for emotional expression, support, and thus, the preservation of hope.

Discussing poor prognosis and illness progression might take an emotional toll on the healthcare provider, posing a potential barrier to advance care planning discussions. Providers may find it helpful to consider that honest disclosure and engagement in advance care planning reduce hospitalizations, as well as deaths in the intensive care unit, and allow space for parent and family reflection and time shared meaningfully [29, 30]. Emphasis, therefore, must also be placed on fostering the education, communication skills, and resiliency of healthcare providers who have the responsibility of advance care planning.

Shared Medical Decision-Making and Advance Care Planning

Approaches to Discussing Goals of Care

Integral to the process of advance care planning is the discussion of goals of care. A goal in this context is defined as a hope for the future health and well-being of the child or young person. Dedication to significant and meaningful personal goals affords a sense of well-being and purpose [3]. Patients' and parents' goals of care will likely evolve over time [17] and may represent both short- and long-term plans for the future. In eliciting these goals through discussion, particular strategies might be implemented in order to best structure these conversations so that the care provider might listen to, support, and align with patient and family.

One such proposed method is described by the mnemonic, PERSON [4]: *perception* of current health status, *exploration* of the patient's life prior to illness, *relating* the patient's story to their present illness and important medical information, investigating *sources* of worry and fear while sharing the hopes and concerns of the medical team, *outlining* the plan moving forward, and *notifying* others, including the interdisciplinary medical team and other family members [4]. This model emphasizes the intimate nature of the conversation as a reflection of the life and legacy of the individual patient. It does not allow the discussion to be reduced to its singular components, whether resuscitation status or treatment goals. Importantly, the goals-of-care discussion considers the patient–parent–clinician triad a team and opens a space for honesty and shared hopes and worries.

Regoaling is defined as parental disengagement with initial goals and reengagement with new goals [3]. This process typically occurs sequentially over time and may involve incremental or stepwise movement toward the new set of goals (Fig. 8.2). Regoaling may occur as a child's illness worsens; however, a parent faced with the serious illness of their child may also persist—and need to persist—in the pursuit of their original goals for cure, no matter that those goals have become unattainable [3, 31]. When possible, the medical care provider can facilitate the process of regoaling, in alignment with illness trajectory, through a purposeful approach to discussing and re-discussing the goals of care. Parents expressing a mixture of positive and negative emotions surrounding their present experience may indicate a readiness to reconceive of goals of care. Exploring parental hopes, and providing suggestions for what might be possible (e.g., care at home), can support goal identification. Providing clear, direct medical information in a setting that allows time for parental acceptance, emotional expression and support, and provider assessment of parental understanding will facilitate this process, allowing for a positive experience within the discussion itself, despite saddening contexts. The relationship, honesty, safety, and emotional and social supports provided are constructive as parents face difficult transitions and decisions [3].

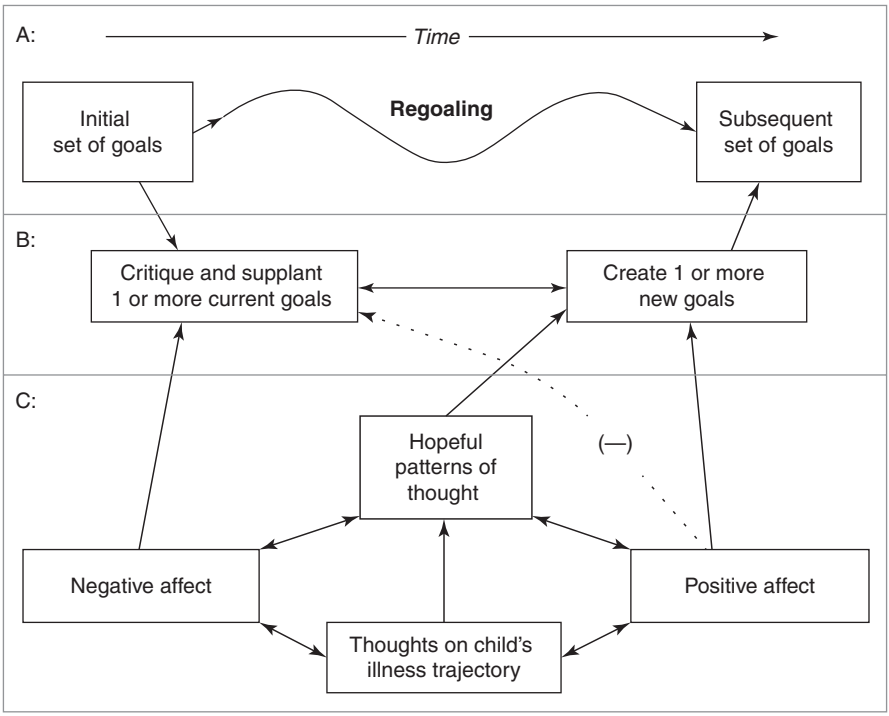


Fig. 8.2 Regoaling [3]

Factors that Influence Patient and Family Decision-Making

Children and young adults with cancer, their parents, and other family members are faced with many healthcare decisions as they endure a journey marked by both physical and emotional challenges. This process occurs under the guidance of a trusted healthcare team, and as such, an understanding of patient and parental decision-making gives the clinician the tools necessary to offer this vital support.

Parents of patients with pediatric cancer have identified the decisions to forgo further disease-directed therapy, begin phase 1 therapy, maintain or forgo mechanical support, and forgo resuscitation as the most common difficult decisions faced [14, 32]. Despite the variable nature of the particular decision at hand, multiple factors have been identified as contributing to the parental and patient decision-making process. Parents have identified information about their child's health and disease status, explained by a physician team member, as crucial. Trust in the healthcare team and support provided by the team are highly influential [23]. These findings have been mirrored in studies focused on adolescent patients, in which the medical information provided to the adolescent and the recommendations of healthcare providers and parents were given significant weight in the decision-making process [23].

Decision-making, specifically at the end of life, is affected by the flow of information, disclosure of prognosis, development of physician–patient and physician–parent relationships, patient and family preferences and goals of care, and availability of treatment alternatives. Again, paramount in this context is parental and patient trust in the clinician, identified as the most important factor in the parental decision-making process at end of life. This is more particularly described as a relationship established with a clinician who is willing to engage in end-of-life discussions framed by the background, characteristics, and experiences of the unique child and family [33].

Multiple themes have emerged within the body of literature examining the decision-making process of the pediatric cancer parent, including communication, prolongation of life, and prognostic understanding [16]. Direct, honest, accurate, and consistent information delivered in a compassionate, reassuring, and individualized manner affects parental decisions constructively. Individualized, family-centered care encompasses an understanding of patient and family values, beliefs, religion, socioeconomic circumstances, and consideration for quality of life.

Parents' decisions are further framed by the hope for more time with their child, or prolongation of life, highlighting the significance of concurrent provision of palliative and cancer-directed therapy within pediatric oncology. Communication and time function indivisibly with understanding of prognosis as decision-making factors. Communication is key in the transfer of prognostic information from clinician to parents, and well-communicated prognosis is crucial in decisions based on the hope for life prolongation [16].

Parental decision-making in the setting of incurable and progressive pediatric cancer might best be encapsulated in the conception of the "good parent" or the self-perceived role of the parent. This role has been defined by parents of children with cancer as making informed, unselfish decisions in the child's best interests, remaining by the child's side throughout illness, ensuring that the child feels cherished, teaching the child to make good decisions, serving as the child's advocate, and promoting the child's health [34]. The healthcare provider can thus seek to support parents and family members by better understanding a parent's hopes, self-identified role, and the values guiding decision-making.

The Role of the Healthcare Provider in Decision-Making and Clinician Bias

The healthcare provider enters into a partnership with a patient and family, taking up a responsibility for fostering family-centered care and shared decision-making. The care provider becomes a conduit for the transfer of prognostic information and for the discussion of potential avenues of care moving forward. The general model of shared decision-making proposes that clinician, patient, and family discuss illness trajectory and the options for treatment, including risks and benefits, with a goal of arriving together at a shared and well-understood plan [35]. Within the

framework of shared decision-making, the care provider is attuned to the individual needs of the patient and family, extending beyond medical information. A conversation occurs within the context of patient and familial hopes, goals of care, sense of meaning and spirituality, and social circumstances. The child's quality of life and depth of suffering and the parents' emotions and sense of responsibility should be attended to by the care provider engaged in discussions about serious illness [36].

The provider, therefore, works to establish a trusting and long-term relationship with the patient and family in order to provide holistic and compassionate care. Effective communication through clear, concise, and direct language in discussion of prognosis and therapeutic options aids understanding, which can be ensured through open dialogue that invites and encourages parental engagement. The clinician takes on the role of active listener [37] and collaborative communicator [38]. The concept of collaborative communication hinges on five core tasks: the establishment of a common goal or set of goals toward which collaborative effort is directed; expression of mutual respect and compassion; the development of a complete understanding of differing perspectives within the discussion; ensuring clarity and correctness of the communicated information; and the management of intra- and interpersonal processes affecting communication, reception, and understanding of information shared [38] (Fig. 8.3).

As a partner within a collaborative and reciprocal model of shared decision-making, the medical care provider strives for a sense of introspective awareness. Personal emotion and values, concern for future regret, and a sense of doubt in recommendations made can deeply affect the tenor of the discussion, alter the presentation of information, and steer the outcome away from the patient's values and goals [35]. It is important to remain mindful that acceptable patient and familial outcomes may differ from the acceptable outcomes the clinician imagines for herself or her loved ones [35, 39]. Furthermore, the clinician must be cognizant of response to patient and familial emotional expression to avoid withholding or tailoring information in a way that might prove misleading. Rather, prognostic disclosure can occur with sensitivity and preserved accuracy, in accordance with the patient's and parents' social and emotional state, in order to serve as a supportive intervention [40].

1.	Establish a common goal, or set of goals that guide a collaborative effort.
2.	Exhibit a mutual respect and compassion.
3.	Develop a sufficiently complete understanding of differing perspectives.
4.	Assure maximum clarity and correctness of what is communicated.
5.	Manage intrapersonal and interpersonal processes that effect how information is sent, received, and processed.

Fig. 8.3 Five core tasks in collaborative communication [38]

Role of Prognostic Uncertainty and Illness Trajectory in Decision-Making

Prognostic disclosure in pediatrics and pediatric oncology has evolved over the course of decades, from a predominant focus on protecting patients and families from painful information, to a growing contemporary acceptance of open communication and the concept of hope as *supported* by prognostic information [41]. Though prognostic disclosure is often an emotion-laden experience, parents of cancer patients want to be informed in order to support ongoing decision-making and to maintain hope [40, 42]. Despite growing dedication to the sensitive and compassionate discussion of prognosis, a high level of prognostic uncertainty still impedes clinician ability to accurately estimate life expectancy [43]. Furthermore, physician inaccuracy in prognostication is typically optimistic, and increasingly so as the duration of the patient–physician relationship lengthens [43]. The uncertainty of prognosis should be discussed with care and honesty in order to best support patient and familial values and overarching goals of care. One such model for discussion of prognostic uncertainty proposes first normalizing future uncertainty as a fixed concept in the human condition, then attending to patients' and parents' emotional responses to uncertainty, and finally helping patients and families manage the effect of uncertainty on preserving quality of life and the ability to make decisions based on the information presently known and the goals of care [44]. Refocusing on the present and preserving hope help to ensure that a patient's goals, sense of meaning, and quality of life remain at the center of daily care.

Advance Care Planning and the Adolescent Patient

Adolescent and young adult patients diagnosed with progressive or terminal cancer require distinct consideration, as they grapple with deep physical, psychological, and emotional challenges presented both by cancer and by coming of age and agency. Adolescents with advanced cancer can participate in complex decision-making processes, including decisions surrounding the end of life, and can understand the consequences of their decisions [45]. Exclusion from desired participation in important discussions risks feelings of isolation, anxiety, and uncertainty in the adolescent patient [46].

Adolescent and young adult decisions are often relationship-based and directed by concern for others [45]. Teens value medical decision-making that is shared with parents and healthcare providers [22, 45, 47]. Adolescents with cancer report that involvement in advance care planning is helpful in reducing distress about future uncertainty and establishing realistic goals for care and quality of life [24, 48]. Adolescent and young adult involvement can also be supportive for parents and surrogate decision-makers, opening a direct dialogue on the goals of the adolescent and allowing family members to form a commitment to honor these goals [24]. At the

same time, the degree of desired involvement of the patient varies on an individual basis [22] and requires careful balancing of principles of truth-telling, nonmaleficence, parental authority, and patient need within the context of an adolescent's world and interpersonal relationships [48].

The clinician navigates a relationship between parents and the adolescent patient, seeking to provide individualized care that operates within the framework of familial dynamics, values, beliefs, and cultural practices, while keeping open channels of communication and support between patient and parents, clinician and patient, and clinician and family. Allowing parents to define their role and their conception of the "good parent" early in the clinician–parent relationship allows sensitivity to family structure and practices. Discussing a patient's worries and fears with parents while relaying that direct discussion with the patient regarding illness may reduce parental and patient suffering and distress and allows parents informed agency. Patients should direct the extent of their involvement in information disclosure, advance care planning, and decision-making. Attention should be paid to establishing a systematic approach to conversations with adolescents early in care. The use of developmentally appropriate, nonjudgmental, compassionate, and concise language, as well as the involvement of a teen's social supports, is a highly important strategy in achieving success during difficult conversations with adolescents [48].

Clinicians should consider establishing a policy of honesty and openness with families early in the care relationship, setting the expectation that this approach will continue even if the nature of discussions shifts with progression of disease and reassessment of goals of care. Although truth telling benefits most adolescents and their families, discussing the patient's and parents' hopes, worries and goals of care may identify those for whom it is not beneficial [48]. Ideally, with time, relationship-building, compassion, and sensitivity to the patient's and family's beliefs and values, a structured path for difficult conversations will be forged.

The Pediatric Patient, Decision-Making, and the Concept of Capacity

Children and young adults are recognized to have moral standing and the right to self-determination, and therefore have the right to take an active role in their own medical care [21]. In upholding this ethical standard, clinicians are compelled to engage young patients in care. Pediatric patients should be involved in health-related decision-making, in accordance with their development, using a patient- and family-centered approach [12]. This involvement becomes particularly important when the decisions to be made have no one "right" answer and depend greatly upon the patient's goals and concept of quality of life [49]. Involving children and young adults in the decision-making process seeks to uphold patient autonomy, facilitate open and honest communication, and improve the patient's understanding of care and participation in goal setting. It also serves to enhance a sense of agency or control over the perceived chaos of the experience of serious illness and respects the

capability of the pediatric patient, allowing for the development of more complex decision-making skills over time [49].

Decisional capacity can be defined as a patient's ability to make informed decisions and requires four key elements: (1) understanding, (2) appreciation of the consequences and significance of the decision, (3) reasoning or weighing the risks and benefits of various options, and (4) choice or the ability to express a value-based decision once made. Decisional capacity depends on the specific decision at hand, and therefore may shift relative to the complexity of the necessary choice [50]. Although, in most cases, pediatric patients are not deemed to have capacity for serious medical decisions, rendering parents the primary decision-makers, this concept is not absolute [13] and depends on the individual patient, the decision at hand, and (in the United States) variable state laws regarding minors' ability to consent for specific medical care or interventions [12].

Children and young adults benefit from involvement in serious conversations and medical decision-making as they, too, seek to create realistic goals for themselves and make sense of the uncertainty inherent in advanced pediatric cancer. Both clinicians and parents are responsible for creating opportunities for conversation with the young patient, seeking patient assent for medical decisions when possible and appropriate. In support of this effort, the clinician might focus on creating an open, supportive space for young patients to express themselves in a medical world often filled predominantly with unfamiliar adults. Allowing young people to approach and process conversations on their own schedule will prove beneficial, as will sensitivity to the questions, worries, and emotions of the patient. Clinicians and parents, as active listeners, can support children and young adults as they navigate illness, their sense of self, a range of emotions, and their interpersonal relationships, and establish their own framework for involvement in medical care and decisions [25].

Divergence in Goals-of-Care and Decision-Making

The experience of coping with advanced cancer brings with it a wide range of complex emotions and thoughts and a contemplation of personal values and goals that affect healthcare decisions, interpersonal relationships, and interactions. Within this, conflict or disagreement can arise surrounding medical decision-making and planning for the future. Though a divergence in views can occur between other members of the medical team, at present, focus will be placed on the clinician–patient–parent dynamic.

A diagnosis of terminal cancer and the imminent and tragic loss of the life of one's child often causes a parent to hope for a cure, despite prognosis. This hope might pervade parental decision-making, in contrast to a clinician's hope to shift toward a goal of comfort. Conversely, a clinician might propose additional cancer-directed therapy that does not coincide with parents' or patient's goals of care. The young adult patient, in particular, might express goals that differ from both parent

and clinician. Differences in opinions and beliefs, or instances of miscommunication, occur commonly within medicine and require a purposeful approach to mediation.

One such approach emphasizes addressing conflict directly, shifting focus toward the perspective of the patient and family, allowing for productive, rather than destructive, communication [51]. This approach entails the following: (1) recognizing that there is disagreement; (2) identifying a nonjudgmental starting point for discussion; (3) listening to and acknowledging the other person's viewpoint; (4) identifying the reason for conflict, and reframing it as a shared interest; (5) brainstorming options that address a shared concern; and (6) identifying options that incorporate the needs of all those involved [51]. Rather than seeking to convince a family, the clinician might focus on listening in order to understand their differing perspective and thus, work toward improved communication with the patient and family [52]. Conflict will likely not be resolved following a single conversation; however, each conversation presents the opportunity to move constructively toward resolution and toward strengthening the clinician–patient–parent relationship. When conflict resolution does not appear possible, assistance may be sought in external resources, including ethics consultation, risk management, and the involvement of another trusted healthcare provider [52].

Advance Care Planning for the End of Life

Legacy

Legacy-making is defined as a creation or performance that is remembered and that can occur either intentionally or serendipitously. Children with advanced cancer or another serious illness perceive illness and know when they are dying [53]. Similar to adults, children may attempt to put their affairs in order, may worry about and try to protect their loved ones, and will hope to be remembered [54]. The meaning, memory-making, and spirituality inherent in the ritual of the legacy project allow children and young adults to assuage these worries [55]. The act of legacy-making has been associated with an increased sense of dignity, purpose, meaning, and will to live and an improvement in suffering and depression [55]. Children and young adults find legacy work to be an outlet for self-expression and for communication about life and death. This type of project has been associated with distraction from pain and negative thoughts and reduction in caregiver stress. Legacy creation allows children with serious illness to affect the lives of others, prepare for death, and provide comfort and inspiration to loved ones [53]. Loved ones will have a tangible symbolic object, a conduit for open communication, and a means for coping with both childhood illness and death [53].

Projects may take any shape, including the creation of artwork, poetry, stories, songs, memory books, hand and foot molds, photographs, and videography.

Activities can include making a life review, taking a meaningful trip, writing letters, delegating belongings to loved ones, or meeting or talking with an important person. Patients and their families may view participation in research both in life and after death as a part of the child's legacy [56]. Although legacy work often occurs as a child nears the end of life, these projects can have greater impact when initiated early in serious illness and should be considered following diagnosis [53]. The medical care provider is in a unique position to consciously recommend and engage in legacy work with patients and can consider this very important work a part of the advance care planning effort and a means to involve the child and young adult in developmentally appropriate reflection. Involvement of child life experts, social workers, psychologists, and other team members who have a special bond with the patient will further enrich legacy work [55].

As in all work in advance care planning and with children with advanced cancer, openness and sensitivity to patients' and families' beliefs and values guide a clinician's approach to legacy-making. For some family members, legacy projects raise painful emotions. In some cases, parents interpret legacy-making as an indication that the end of life is near and, therefore, choose not to participate or feel reluctant to have their child participate [53]. Pediatric patients themselves may feel hesitant or may not want to participate in legacy-making. In such a situation, reframing to focus on the patient's life review and on serendipitous legacies already created may open the door to both intentional legacy work [55] and to meaningful reflection that positively benefits both children and their families.

Location of Care at the End of Life

Planning for the end of life and preparing for death allow families the chance to focus on meaningful time together and minimize intrusive medical interventions in sacred moments [10]. The process of advance care planning encompasses planning for the location of care at the end of life and at death, allowing both the young patient and parents to make an informed decision based on their wishes, beliefs, and customs. Although most children in the United States who die from cancer die in the hospital, the opportunity to plan the location of death may actually be more significant for a patient and family than the actual place of death [57]. Parental preparedness is cited as a significant factor in high-quality end-of-life care, and those parents presented with the chance to plan express less decisional regret surrounding place of death, regardless of the chosen location [57]. Therefore, planning for location of the end of life may reduce the risk of complicated grief. Families given the option most often choose home as the child's place of death, followed by the hospital where they received care; freestanding pediatric hospices are chosen the least often [58].

In deciding the location of death, patients and families often consider where they want to spend their precious remaining time together in the most meaningful way. The wishes of the child and young adult are strong determinants of the planned

location, as are hopes for safety and security, the support of trusted healthcare providers, the availability of specialty care, and understanding of the prognosis [59]. As such, the healthcare provider has the responsibility *not only* to engage in a timely discussion on prognosis and desired location of death but also to thoroughly explore resources available to facilitate patient and family goals for end-of-life care [60]. This might mean working closely with a home care or home hospice agency to provide comprehensive, holistic pediatric community-based palliative and hospice care [61], or providing easily accessible and consistent pediatric palliative care services. It may also entail creating an appropriate environment within the walls of a busy hospital [57, 59, 62]. Instances will arise in which the preferred location for end-of-life care and death become challenging, requiring a reevaluation and potential shift in plan; yet, maintaining open and honest communication throughout this process will allow continued focus on patient and family values and patient comfort.

Resuscitation

The implementation of formal orders to forgo cardiopulmonary resuscitation (CPR) first occurred in the 1970s in the wake of newly established resuscitation methods and reports in medical literature describing increased suffering and prolongation of death in situations in which CPR had been deemed unlikely to be beneficial [63]. In 1994, the American Academy of Pediatrics published guidelines on forgoing life-sustaining medical treatment, including CPR and "all interventions that may prolong the life of patients," particularly when goals of care are focused on comfort [64]. CPR refers to the administration of chest compressions, vasoactive medications, and defibrillation, in conjunction with the initiation of mechanical ventilation. Orders to limit these interventions are termed Do-Not-Resuscitate (DNR) orders, or, in an effort to highlight the limited efficacy of resuscitative efforts, Do-Not-Attempt-Resuscitation (DNAR) orders [63].

Advance care planning, as a whole, describes an ongoing process of decision-making couched in the goals of care of the patient and parents, rather than the singular completion of a document detailing resuscitative planning or the instatement of a DNR order. A parent's understanding that a child no longer has a realistic chance for cure is often delayed when compared to that of the child's primary oncologist [65], and discussions about death with the patient and family often do not occur until the last month of life [66]. Further, initial discussions on resuscitation goals often take place during acute illness or when death has become imminent [67], limiting the patient's ability to participate [68]. In contrast, timely discussion of resuscitation during a period of medical stability, and pre-emptive contemplation of goals should a patient's condition worsen or improve, seeks to prevent suffering at the end of life and prolongation of the dying process when no further curative interventions remain. Early discussions may not result in a formative decision, and decisions made may shift over time in accordance with the patient's clinical condition [69]. However, early discussion allows families the time to prepare for the

worst while continuing to hope for the best. Discussion of resuscitation requires the simultaneous and ongoing discussion of patient prognosis and familial goals of care. Parent, patient, and clinician decisions surrounding implementation of a limitation of resuscitation are guided by the hope to improve quality of life and quality of death [33].

The implementation of a DNR order or a limitation in resuscitation is relevant only in therapeutic decisions made during cardiopulmonary arrest and does not address goals of care beyond this very specific setting. Thus, resuscitation decisions make up only a single component of a greater advance care planning discussion and of a patient's and family's goals for care. Decisions to limit resuscitation in the future should not limit concurrent efforts to actively ease suffering or to initiate or continue interventions that seek to uphold goals of care in the prearrest and present state [67].

Use of Artificial Nutrition and Hydration, Blood Products, and Antibiotics at the End of Life

In addition to resuscitation, other interventions, including the use of artificial nutrition and hydration, blood products, and antibiotics, should be discussed as a part of the advance care planning process. Though these interventions are frequently instrumental in achieving the goals of cure or life prolongation, they may not align with goals of care at the end of life and, in certain situations, may pose greater risk than benefit. The AAP supports withholding and withdrawing medical interventions when expected burdens of the intervention outweigh potential benefits, in conjunction with parental decisions made in consultation with the medical team [70].

Artificial nutrition and hydration in the end stages of cancer may no longer provide comfort and can prolong the dying process. Medically administering fluids at the end of life can result in dyspnea, edema, skin breakdown, increased infection risk, electrolyte disturbance, thrombosis, and pain [70]. Discontinuing these interventions may improve comfort by decreasing respiratory secretions, cough, edema, nausea, vomiting, urinary output, and metabolic rate [70]. Furthermore, fasting has been associated with an analgesic effect produced via release of endorphins and resulting in feelings of well-being [71], as well as ketone production, resulting in hunger reduction and improved clarity of thought [72]. Dry mouth is the most common symptom associated with the suspension of artificial hydration and may be relieved by sips of fluids, artificial saliva, lip balm, and ice chips, among other methods [73]. The transition from conceptualizing nutrition and hydration as life-sustaining, to viewing it as a potential source of discomfort is challenging, particularly given the frequent emotional, cultural, and traditional practices associated with feeding a loved one. In caring for a family whose child is at the end of life and no longer receiving nutrition and hydration, a clinician might work to ease this distress through clarity of information, emotional support, and prompt attention to signs of the child's discomfort [74].

The palliative use of transfusion in young patients with advanced cancer benefits those experiencing dyspnea, weakness, fatigue, headache, or bleeding [75, 76] in the setting of anemia or thrombocytopenia. Fatigue, in particular, has been described as a source of high levels of distress in children with advanced cancer [77]. The decision to proceed with or to forgo transfusion of blood products is dependent on the individual goals of the patient and family and the balance of expected risks and benefits of the transfusion. A pediatric patient with advanced disease who is seeking quality time with loved ones and time to complete legacy projects may benefit from symptom management through transfusion, particularly if transfusion is accessible and does not require prolonged hospitalization. However, as the end of life nears, transfusion may represent a greater burden than benefit, contributing to fluid overload [78], and may be deemed invasive, and therefore inconsistent with goals of comfort.

Pediatric patients with advanced cancer are at high risk of infection because of suppressed immune function. Antibiotic use at the end of life must be considered in the context of the individual patient, familial goals of care, and the potential risks and benefits of proposed therapy [79]. Although antibiotic initiation may prolong life by resolving infection and may decrease the discomfort associated with infection-related symptoms [80], it also poses potential burdens of medication-related side effects, the need for invasive lines for administration and laboratory tests, such as blood cultures [81], and prolongation of the dying process [82].

Cumulatively, treatment decisions on implementing artificial nutrition and hydration, blood transfusion, and antimicrobial use in a young patient at the end of life are made on an individual, goal-derived basis. They are analogous to one another in the need to weigh burden with benefit within the context of patient and family goals, under the guidance of medical expertise. These decisions require the support of the medical team around the family, beginning in the contemplative stages of advanced care planning, and extending through a patient's final days.

Cancer-Directed Therapy

Parents of children with advanced cancer often hold dual goals of care in synchrony—lessening suffering and extending life [14, 65]. Although cancer-directed therapy had not historically been considered to be a part of intensive palliation and symptom management for advanced disease [83], that view has now expanded to encompass cancer control and meet nuanced patient care goals. When goals of care are no longer curative, patients and families might consider enrollment in a phase 1 or 2 clinical trial [84] or initiation of a second-line or alternate chemotherapy agent, in addition to focus on symptom-directed care. Frequently, seeking cancer- *and* symptom-directed therapies and supportive measures becomes integral to the

self-designated parental role, cementing the importance of the concurrent provision of cancer care [31]. Significantly, in the final 3 months of life, mild cancer-directed therapy (oral, outpatient, or minor procedure) can be associated with improved psychological well-being in children [77], hence potentially contributing to improved quality of life.

Although cancer-directed therapy may have a role in supporting a patient's quality of life, extending life, and supporting parental responsibility, such benefits occur in a setting in which continued pursuit of therapy corresponds with the patient's and family's hopes and goals, with medical recommendations. Healthcare providers are obligated to provide prognostic information to the best of their ability and to allow patients and families to make an informed decision surrounding care at the end of life. Often, when a clinician and parent recognize together that no further curative options remain, care becomes increasingly tailored to lessening suffering, and the young patient is less likely to receive cancer-directed therapy in the last month of life [65].

Autopsy and Organ Donation

Young patients with cancer and their families may consider both autopsy and organ donation as a part of a legacy [46]—a form of altruism that might allow other children and families to avoid similar suffering and loss or convey a sense of unity with families facing the same illness [85]. Through autopsy, bereaved parents might receive additional information about the patient's illness and cause of death. In some cases, information gained through autopsy offers solace in grief and a sense of meaning [85, 86]. Similarly, though cancer is often a contraindication to organ donation, the donation of corneal tissue and heart valves is commonly possible and may be perceived in a positive light by patients and families as part of an altruistic legacy [22, 87].

The discussion of both autopsy and organ donation is difficult and may be deferred as clinicians seek to reduce distress in patients and families [88]. Bereaved parents have indicated a preference for discussion of autopsy only after it has become clear that cure is no longer possible. Conversation on autopsy should be approached sensitively, bearing in mind the pain of anticipated loss. Such discussion should be undertaken by a clinician with whom the family shares a relationship, when possible, and should be informational, indicating the details of the procedure, whether autopsy would help other children in the future, whether it would help the medical team in learning about a child's cancer, and when and how parents might receive results [85, 88]. Most importantly, approach to discussing autopsy and organ donation with patients and families occurs on an *individualized* basis, with utmost sensitivity to religious beliefs, cultural practices, familial traditions, and patient and family hopes and readiness.

Practical Tools in Advance Care Planning

Pediatric Advance Care Planning Documents

This chapter champions involvement of the pediatric patient in the process of advance care planning while reinforcing the importance of clinicians' recognition of a patient's developmental stage, readiness to participate in advance care planning discussions, and familial beliefs and values. The advance directive document is a tool that can be used to facilitate a pediatric-specific approach to identifying a patient's goals of care, healthcare decisions, and conception of end of life.

The Patient Self-determination Act of 1991 mandates that all adult patients who are hospitalized or receiving long-term care receive information on advance directives and that their preferences be documented during hospitalization or long-term care admission [89]. Legally, these requirements do not pertain to most pediatric cancer patients; however, they emphasize the importance of structured, normalized advance directive use in lending voice to the preferences of the individual in anticipation of a time in which he or she is no longer able to participate actively in decision-making [90]. Adolescents have been granted legal rights in certain U.S. states to make medical decisions pertaining to routine medical care, pregnancy, substance abuse, sexually transmitted infections, parenthood, mental healthcare, marriage, homelessness, and other issues. End-of-life care has not been addressed through policy, and legal decisions have been made on a case-by-case basis, with focus placed on the best interests of the adolescent and the adolescent's capability to decide to forgo medical interventions at the end of life [91]. Given that children as young as 3 years may be aware of their prognosis, those as young as 10 years may be able to participate in discussion and decisions surrounding end-of-life care, and those as young as 14 years may have an adult-level understanding of diagnosis [22, 92], it becomes the responsibility of the medical care team to provide the pediatric patient early opportunity to document advance care plans.

Advance directives can be divided into two categories based on legal status: statutory directives, which include a living will or durable power of attorney, and non-statutory advance directives, which identify healthcare preferences or healthcare proxy in written or oral form [93]. A written or orally documented advance directive might identify a proxy, or surrogate, to make decisions based on the patient's preferences and best interests and might also delineate a patient's healthcare preferences in specific medical situations.

To proactively approach the pediatric advance directive, multiple pediatric-specific tools have been created. These include "Voicing My CHOiCES™," "My Wishes," and "The Advance Care Planning Readiness Assessment" (Fig. 8.4). The adult advance care planning document, "Five Wishes," is also useful with adolescents and young adults [94]. The readiness assessment poses three questions to gauge a patient's ability and interest in engaging in advance care planning discussions: (1) would talking about what would happen if treatment is no longer effective be helpful?; (2) would talking about medical care plans in advance be upsetting?; and (3) would you feel comfortable talking or writing about what would happen if treatments are no

longer effective? [95]. "Voicing My CHOiCES™," particularly, was designed through feedback provided by adolescents and young adults about their preferred method and format for documenting expression of wishes for treatment, care, support, and how they hope to be remembered after death [46]. It depicts how the patient would like to be supported, comforted, and identify surrogates. It details life-support preferences, the patient's spiritual wishes, addresses how the patient would like to be remembered by family and friends, and includes notes to loved ones [95].

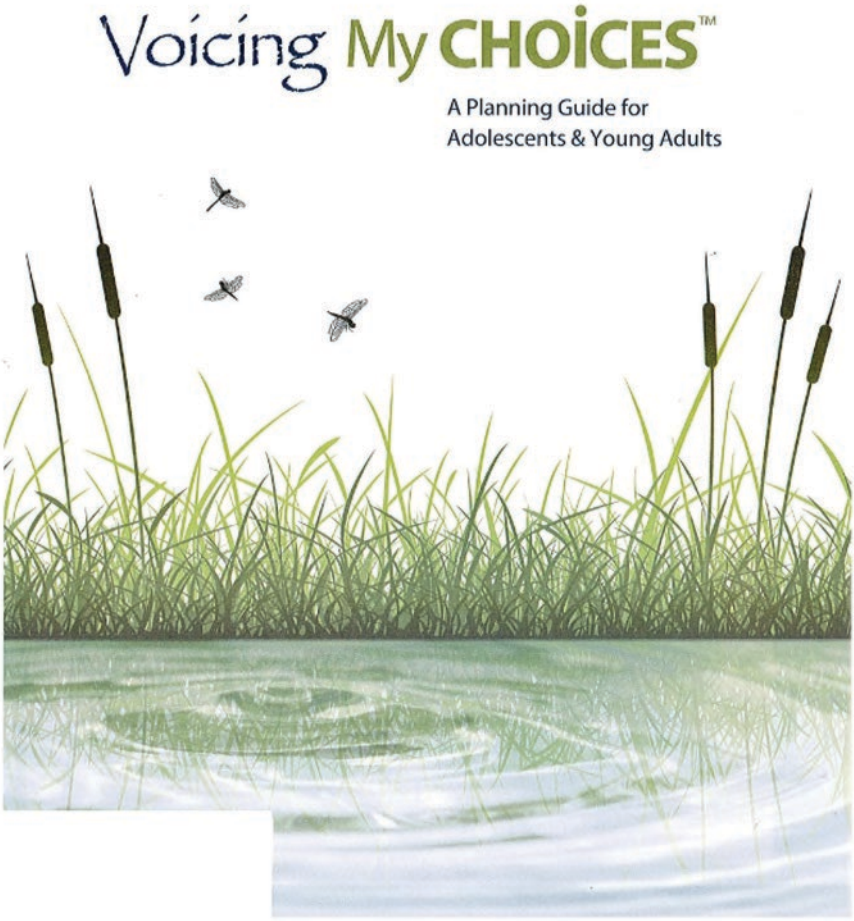


Fig. 8.4 Pediatric advance care planning sample tools. Copyright Aging with Dignity. All rights reserved

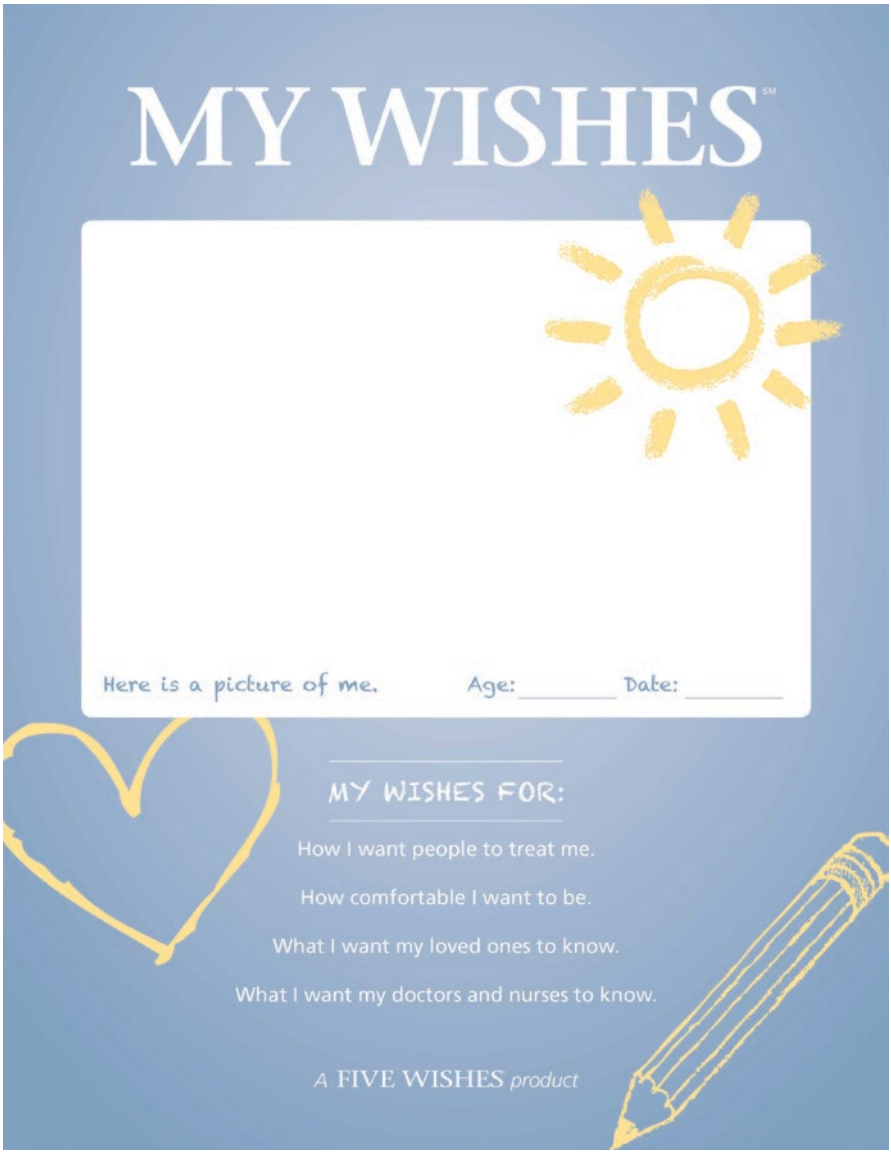


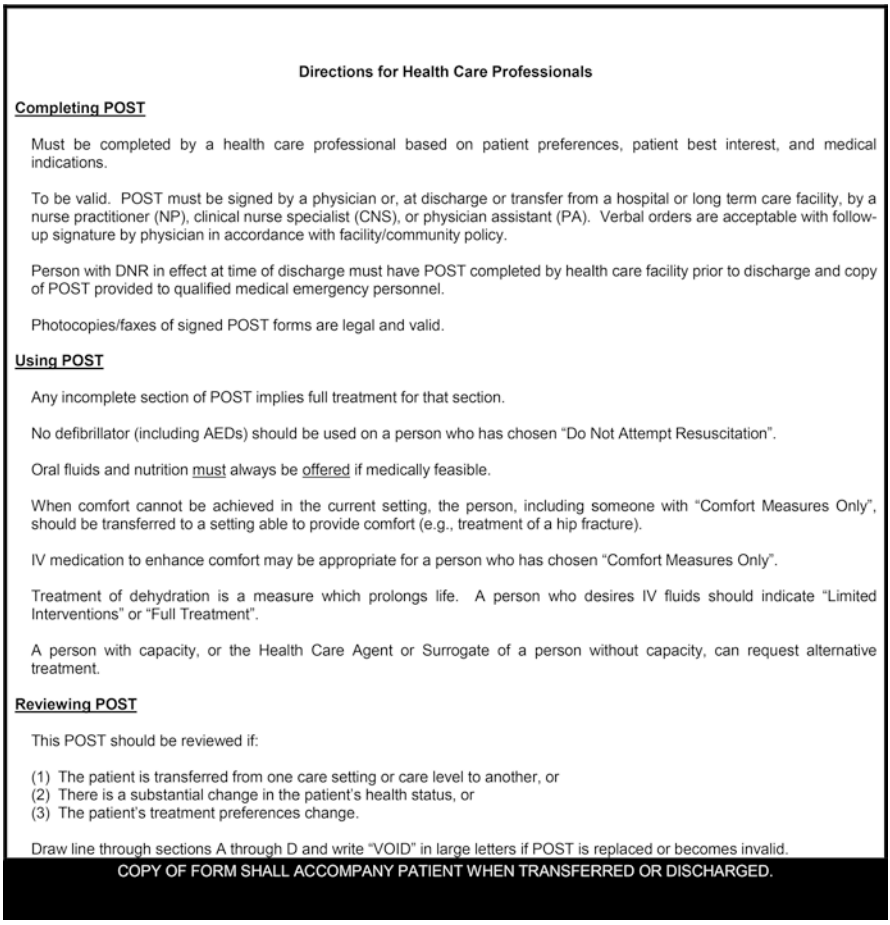
Fig. 8.4 (continued)

Involvement of the patient in advance care planning strengthens the patient's trust in family and in the healthcare team and restores the patient's voice, sense of self, and independence [46]. Working through an advance care document with a trusted health-care provider allows engagement in discussion, clarification of the document, and support through emotionally challenging sections of the document [95]. Furthermore, when a family-centered approach to the advance directive is

implemented, the active involvement of both pediatric patient and parent, or surrogate decision-maker, improves openness of communication within a family, increases congruence in patient and parent goals of care, reduces the burden of surrogate decision-making, and enables patient empowerment and preparation [24].

Orders for Life-Sustaining Treatment

Medical or physician orders for life-sustaining treatment (MOLST or POLST) are standardized, transferrable forms delineating a patient's treatment preferences in several common life-threatening circumstances. An example of such a form can be found in Fig. 8.5. As medical orders, the MOLST or POLST form serves a separate



Directions for Health Care Professionals

Completing POST

Must be completed by a health care professional based on patient preferences, patient best interest, and medical indications.

To be valid. POST must be signed by a physician or, at discharge or transfer from a hospital or long term care facility, by a nurse practitioner (NP), clinical nurse specialist (CNS), or physician assistant (PA). Verbal orders are acceptable with follow-up signature by physician in accordance with facility/community policy.

Person with DNR in effect at time of discharge must have POST completed by health care facility prior to discharge and copy of POST provided to qualified medical emergency personnel.

Photocopies/faxes of signed POST forms are legal and valid.

Using POST

Any incomplete section of POST implies full treatment for that section.

No defibrillator (including AEDs) should be used on a person who has chosen "Do Not Attempt Resuscitation".

Oral fluids and nutrition must always be offered if medically feasible.

When comfort cannot be achieved in the current setting, the person, including someone with "Comfort Measures Only", should be transferred to a setting able to provide comfort (e.g., treatment of a hip fracture).

IV medication to enhance comfort may be appropriate for a person who has chosen "Comfort Measures Only".

Treatment of dehydration is a measure which prolongs life. A person who desires IV fluids should indicate "Limited Interventions" or "Full Treatment".

A person with capacity, or the Health Care Agent or Surrogate of a person without capacity, can request alternative treatment.

Reviewing POST

This POST should be reviewed if:

(1) The patient is transferred from one care setting or care level to another, or
(2) There is a substantial change in the patient's health status, or
(3) The patient's treatment preferences change.

Draw line through sections A through D and write "VOID" in large letters if POST is replaced or becomes invalid.

COPY OF FORM SHALL ACCOMPANY PATIENT WHEN TRANSFERRED OR DISCHARGED.

Fig. 8.5 State of Tennessee physician order for scope of treatment [104]

A COPY OF THIS FORM SHALL ACCOMPANY PATIENT WHEN TRANSFERRED OR DISCHARGED

Tennessee Physician Orders for Scope of Treatment (POST, sometime called "POLST")

This is a Physician Order Sheet based on the medical conditions and wishes of the person identified at right ("patient"). Any section not completed indicates full treatment for that section. When need occurs, first follow these orders, then contact physician.

Patient's Last Name

First Name/Middle Initial

Date of Birth

Section A *Check One Box Only*

CARDIOPULMONARY RESUSCITATION (CPR): Patient has no pulse and is not breathing.

☐ **Resuscitate (CPR)** ☐ **Do Not Attempt Resuscitation (DNR / no CPR) (Allow Natural Death)**

When not in cardiopulmonary arrest, follow orders in **B, C,** and **D.**

Section B *Check One Box Only*

MEDICAL INTERVENTIONS. Patient has pulse and/or is breathing.

☐ **Comfort Measures Only.** Relieve pain and suffering through the use of any medication by any route, positioning, wound care and other measures. Use oxygen, suction and manual treatment of airway obstruction as needed for comfort. **Do not transfer to hospital for life-sustaining treatment. Transfer only if comfort needs cannot be met in current location. Treatment Plan: Maximize comfort through symptom management.**

☐ **Limited Additional Interventions.** In addition to care described in Comfort Measures Only above, use medical treatment, antibiotics, IV fluids and cardiac monitoring as indicated. No intubation, advanced airway interventions, or mechanical ventilation. May consider less invasive airway support (e.g. CPAP, BiPAP). **Transfer** to hospital if indicated. Generally avoid the intensive care unit. **Treatment Plan: basic medical treatment.**

☐ **Full Treatment.** In addition to care described in Comfort Measures Only and Limited Additional Interventions above, use intubation, advanced airway interventions, and mechanical ventilation as indicated. **Transfer** to hospital and/or intensive care unit if indicated. **Treatment Plan: Full treatment including in the intensive care unit.**

*Other Instructions:*_____

Section C *Check One*

ARTIFICIALLY ADMINISTERED NUTRITION. Oral fluids & nutrition must be offered if feasible.

☐ No artificial nutrition by tube.
☐ Defined trial period of artificial nutrition by tube.
☐ Long-term artificial nutrition by tube.

*Other Instructions:*_____

Section D *Must be Completed*

Discussed with:
☐ Patient/Resident
☐ Health care agent
☐ Court-appointed guardian
☐ Health care surrogate
☐ Parent of minor
☐ Other: _____(Specify)

The Basis for These Orders Is: (Must be completed)
☐ Patient's preferences
☐ Patient's best interest (patient lacks capacity or preferences unknown)
☐ Medical indications
☐ (Other) _____

Physician/NP/CNS/PA Name (Print)	**Physician/NP/CNS/PA Signature** **Date** NP/CNS/PA (Signature at Discharge)	**MD/NP/CNS/PA Phone Number:** ( )

Signature of Patient, Parent of Minor, or Guardian/Health Care Representative

Preferences have been expressed to a physician and /or health care professional. It can be reviewed and updated at any time if your preferences change. If you are unable to make your own health care decisions, the orders should reflect your preferences as best understood by your agent/surrogate.

Name (Print)	Signature	Relationship (write "self" if patient)	
Agent/Surrogate	Relationship	Phone Number ( )	
Health Care Professional Preparing Form	Preparer Title	Phone Number ( )	Date Prepared

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Fig. 8.5 (continued)

purpose from an advance directive. Life-sustaining medical treatment is defined as any intervention that prolongs the life of the patient and includes therapies such as mechanical ventilation, CPR, dialysis, antibiotics, parenterally or enterally administered fluids or nutrition, and organ transplantation [64]. The MOLST or POLST form is typically divided into four sections: resuscitation status, preferred level of medical interventions (comfort measures, limited additional interventions, or full treatment), antibiotic therapy preferences, and preferences regarding administration of artificial nutrition [96]. The completion of orders for life-sustaining treatment increases conversations about patient goals and treatment preferences and is associated with a decrease in unwanted emergent resuscitations [97]. In the United States in 2016, a total of 47 states had adopted a POLST program, used predominantly in the care of adults [98]. However, orders for life-sustaining treatment are increasingly being implemented in the pediatric setting, in some cases by law, for hospitalized children [97]. The standardized use of forms describing orders for life-sustaining treatment in pediatrics normalizes the process, but requires broader clinician training and implementation of advance care planning discussions.

MOLST or POLST forms are transferrable between healthcare settings, allowing for use in the home by emergency medical services (EMS), in school, and in the emergency room. This allows patients and families the assurance that treatment preferences will be respected regardless of their environment. Use of a MOLST or POLST form is particularly effective when coupled with dissemination of a family's most recent treatment preferences to the healthcare team in a clear and simple manner [38, 99]. Within the school environment, the AAP recommends that both pediatricians and parents meet with school, EMS, and legal counsel to discuss goals of in-school care, with review of goals of care and the child's medical condition at least every 6 months [100]. In implementing a MOLST or POLST form, treatment preferences can be changed at any time based on the decision of a parent or surrogate alongside the patient and in accordance with the trajectory of illness and clinical situation.

Withholding and Withdrawing Medical Interventions

Ethical Approach to Withholding and Withdrawing Medical Interventions

Children and young adults with cancer for whom cure is no longer possible and goals of care have transitioned to comfort may decide, along with parents and the healthcare team, to limit or forgo life-sustaining medical treatment. In the United States, most pediatric deaths in hospitals occur after critical care interventions are forgone [70]. This decision, made in alignment with patient and familial values and medical recommendations, is nonetheless often emotionally, socially, and spiritually challenging for family and medical providers, rendering an

understanding of ethical guidelines, such as the seminal guidelines provided by the AAP for withholding and withdrawing life-sustaining medical treatment, essential for clinicians.

Importantly, there is no ethical or legal difference between discontinuing a medical intervention that has already begun and withholding an intervention not yet started, however, it is important to acknowledge with families that these actions may "feel" very different [64]. The omission of a life-sustaining medical intervention is considered an active decision, equivalent to the decision to discontinue a medical therapy. A medical treatment that is no longer beneficial should be discontinued to prevent associated harm to the patient [64], upholding the ethical tenets of beneficence and nonmaleficence. For a patient with advanced cancer, an intervention might be initiated as a part of a timed trial, for a defined period of time, in order to ascertain potential medical benefit. Clinicians' fears surrounding withdrawal of therapy should neither preclude initiation of a potentially beneficial therapy nor should they prohibit discontinuation once the therapy has become nonbeneficial. The course of treatment throughout illness is determined by the goals of the patient and family, the best interests of the patient, and the potential benefits and burdens of available treatment options [64]. It is the clinician's responsibility to inform the patient and family of potential therapeutic options and to advise families on the recommended choice for the individual child. A clinician who is unable to participate in limiting or withdrawing life-sustaining treatment, despite patient and family goals, is responsible for facilitating transfer of care to a more appropriate provider [64].

Parents provide consent for most medical treatment for children who are not legally considered either emancipated or mature minors, yet the expressed wishes of the child regarding life-sustaining medical treatment are given considerable weight. The child or young adult should be included in goals-of-care discussions pertaining to potential interventions, in accordance with the child's development, capacity, desired level of involvement, and family values. Young adults who have been legally emancipated, or determined to be mature minors, can themselves decide to limit medical interventions [64].

Potentially Inappropriate Medical Interventions and Medical Futility

The definition of medical futility has evolved over decades and is now interpreted narrowly as being a medical intervention that *cannot* accomplish an intended physiologic goal [101]. It is accepted that clinicians should not offer or provide futile medical interventions in the rare circumstance that such an intervention is requested. Conversely, ethical conflict or controversy in critical care and end-of-life situations often centers on the continuation or initiation of a medical intervention considered by the clinician to be nonbeneficial or potentially harmful. In such a situation, the

term "potentially inappropriate" is used to define medical interventions that pose some chance of accomplishing the hoped for physiologic effect, but are not recommended or are refused by the clinician because of underlying ethical concerns. Ethical concerns may include an extremely low likelihood that the intervention will be successful, concern surrounding the likely outcome or intended goal or the high cost of the intervention [101]. Notably, potentially inappropriate medical interventions can be differentiated from those defined as medically futile, in that clinician recommendations depend on value-laden judgments regarding what is considered appropriate treatment in advanced illness [101] and on available prognostic information. Within the pediatric intensive care setting in the United States approximately 6.5% of pediatric patients receive broadly defined potentially inappropriate medical interventions [102]. In the United Kingdom, potentially inappropriate medical treatment occurs in an estimated 13% of pediatric critical care cases [103]. These situations are ethically and emotionally challenging for all involved, requiring a fine balance of patient and surrogate autonomy with a clinician's obligation to uphold a patient's best interest and to prevent harm within potentially time-limited clinical circumstances.

Often, an approach that focuses on collaborative, proactive communication, prognostic honesty, and shared decision-making is best equipped to prevent intractable conflict. The American Thoracic Society Policy on Responding to Requests for Potentially Inappropriate Treatment in Intensive Care Units advocates institutional strategies to improve communication, including end-of-life communication education, conflict-resolution, and emotional support skill-building, as well as the early involvement of expert consultants, namely ethics and palliative care consultation [101]. In the event that formal conflict-resolution measures are required, the recommended institutional approach is as follows: (1) consult mediation experts to continue collaborative communication and negotiation; (2) provide notice of the mediation process to surrogates and family; (3) provide a second medical opinion; (4) Provide a review of the case by an interdisciplinary hospital committee; (5) facilitate an opportunity for transfer to another medical facility, when clinically possible; (6) provide information on pursuing external judicial appeal to surrogates and family members; and (7) implement the resolved clinical decision [101].

Notably, two specific types of requests for treatment fall outside the accepted categorization of either futile or potentially inappropriate medical treatment. These include legally proscribed and legally discretionary treatments, which are interventions that may in fact result in the desired treatment goal, but are specifically prohibited by law, or for which judicial precedent or public policy permits limitation of use [101]. Examples include manipulating the process of organ allocation or administering medication for the purpose of physician-assisted death in a U.S. state in which such action is illegal [101]. Though such requests will occur exceedingly rarely, exploring the patient's or surrogate's hopes and goals in the request, clearly explaining the reason for refusal, exploring alternative options, and providing ongoing social and emotional support will prove beneficial.

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Chapter 9
Symptom Assessment and Management Across the Cancer Trajectory

Melody Brown-Hellsten

I want to go out because I feel ok, but my body isn't ok. I don't quite understand that. It is frustrating and I get mad. I am used to being outside all of the time.

After we get his chemo we don't really go out. We just stay home and make as pleasant a weekend there. The smells of everything bothers him. Even if I were to do the housekeeping I can't use certain things. I just have to wait until he is better. It is just the way it is.

Introduction

Children undergoing cancer treatment experience substantial symptom burden related to the disease, treatment, and alterations in family life [1–4]. Not surprisingly, children receiving cancer-directed therapy as well as survivors of childhood cancers have reported poorer psychological, social, and physical health-related quality of life as compared to siblings, same-age peers, and children with other chronic conditions [2–5]. Too often, symptoms are seen by patients, families, and providers as part of the treatment process leading to a complex interaction of under-reporting of symptoms by children and parents and under-recognition of the extent of symptom burden by providers [6, 7]. The obligation to relieve pain and suffering related to disease is inherent in both medical and nursing codes of ethics related to principles of beneficence, patient autonomy, and veracity [8–11]. It is incumbent on health-care providers to attend to the known symptom burden of children and their family members by engaging in open and honest conversations aimed at establishing the expectation that symptoms will be managed to the best of their ability to maximize quality of life and minimize unnecessary suffering.

Much of the research in symptoms in childhood cancer focuses on multi-item assessment tools that rate individual symptoms experienced [12–15]. However,

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qualitative interviews with children about their symptom experience demonstrate that rather than discrete, quantifiable experiences, children and adolescents experience symptoms as a state of being in the context of multiple, overlapping symptoms [16–18]. Assessing individual symptoms common to particular cancer treatments or diseases limits opportunities for children who are experiencing a global level of discomfort to report more complex symptom experiences [6, 17]. Additionally, the complex nature of cancer and treatment-related symptoms creates challenges in management, risking increased symptom distress and poor quality of life [12, 17].

Childhood cancer providers have a moral and ethical responsibility to act intentionally to mitigate the harms of cancer treatment with the goal of maximizing not only quality of life but also overall treatment outcomes. As such, oncology providers should be familiar with the available evidence regarding the symptom experience of patients and families, genetic and immune-related mediators of cancer-related symptoms, and multimodal approaches to managing symptoms across the cancer trajectory. This chapter will explore current research and practice in symptom assessment and management in childhood cancer. The growing body of evidence provides both challenges and opportunities for researchers and clinicians to advance effective, evidence-based childhood cancer pain and symptom management for all children to achieve our ethical obligations to address suffering in all forms over the course of childhood cancer care.

Symptom Assessment in Childhood Cancer

Symptoms, Symptom Distress, and Symptom Experience

Cancer treatment is inexorably linked to several common symptoms as well as numerous toxicities and treatment complications; however, patient and family suffering as a result of treatment-related symptoms can and should be minimized. A growing body of literature has demonstrated that unpleasant symptoms are an expected and often accepted part of cancer treatment [6, 18]. Children who experience overwhelming symptoms risk delays or alterations in therapy that can compromise treatment outcome [7, 19].

To better discuss current knowledge in symptom assessment and management as it relates to children with cancer, it is important to have a clear understanding of the terms used by cancer symptom researchers and clinical experts. In its most basic and objective definition, a symptom is the presence of a physical or mental feature that indicates disease [20, 21]. Beyond this primarily biomedical definition, symptoms are also subjectively defined as a phenomenon recognized by a person as a change in normal function, sensation, or appearance [22–26]. *Symptom distress* reflects the amount of physical and mental suffering experienced from specific symptoms on the part of the person experiencing the symptom, which results in an overall sense of distress related to a perceived threat of illness [24, 25]. *Amplification*

of symptom distress occurs through the amount of attention given to the symptom as well as the context of the symptom occurrence and coping mechanisms of the person experiencing the symptom [25]. Lastly, an individual's *symptom experience* represents the perception and cognitive/emotional appraisal of the symptoms – to include frequency, intensity, distress, and the associated meaning given to symptoms as they occur and are expressed to a health-care provider [24]. As such, symptoms are a subjective experience that requires both a biologic and meaning-centered approach to adequately address the totality of the patient's discomfort. Patient/caregiver report of the symptom experience is also influenced by cultural, individual, and disease-specific characteristics as well as the consequences of the symptom on functional status, mood, and quality of life. [20, 24]

Multidimensional/Interrelated Symptom Experience

Symptoms experienced as the result of a diagnosis of cancer and accompanying treatment have both multidimensional and interrelated qualities [27, 28] that affect the symptom experience and add challenge and complexity to adequate symptom management. Multidimensional aspects of symptoms include the physical nature of symptom, frequency of symptom occurrence, and the severity and associated level of distress, in addition to the effect of the symptom on the emotional, social, and spiritual well-being of the child (Fig. 9.1). An adolescent with osteosarcoma receiving chemotherapy may experience moderately severe and distressing pain related to tumor size and location, leading to emotions of frustration/anxiety about the pain.

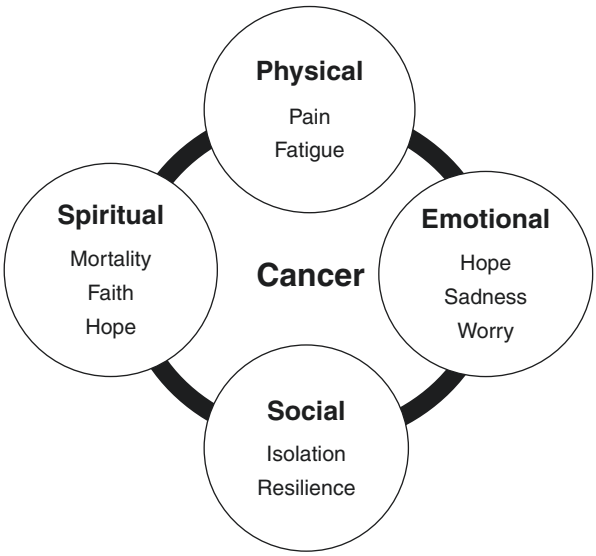

Fig. 9.1 Multidimensional symptom experience

Consequent limitations in their social interactions with friends can lead to irritability, creating tension with parents and siblings. The reality of having cancer may also lead the adolescent to question why they got cancer, engendering feelings of guilt or weakness, perhaps questioning their faith in God or a greater power. Lastly, sadness over the perceived loss of long held plans for their future and fears of their own mortality [7, 29] further add to symptom distress. The interplay of these factors related to the symptom experience can, in turn, amplify the symptom distress experienced by both the child and family as they grapple with the altered family dynamics brought about by the cancer diagnosis.

Another layer of complexity with regard to the symptom experience is the interrelatedness of symptoms with the underlying disease, side effects, comorbidities, and adverse events (Fig. 9.2). A child with leukemia in delayed intensification may experience physical symptoms of fatigue and weight loss from the side effects of persistent or uncontrolled nausea and vomiting in the setting of chemotherapy and underlying comorbid hepatic complications. This scenario may further complicate symptom distress as invasive interventions to address comorbidities are performed and additional medications with additive side effects are prescribed over time possibly increasing symptoms and distress. Studies examining polypharmacy at 42 children's hospitals found that nearly half of all children were exposed to a potentially dangerous drug interaction (PDDI), with the risk of exposure increasing for older children, those with prolonged hospitalization, or those who had complex medical conditions. By far, the greatest risk of PDDI was respiratory depression (20%) [30]. Children in intensive care settings had even greater exposure to PDDI (81%) with the cumulative number of distinct medications increasing from 7 to 45 by PICU day 30 [31].

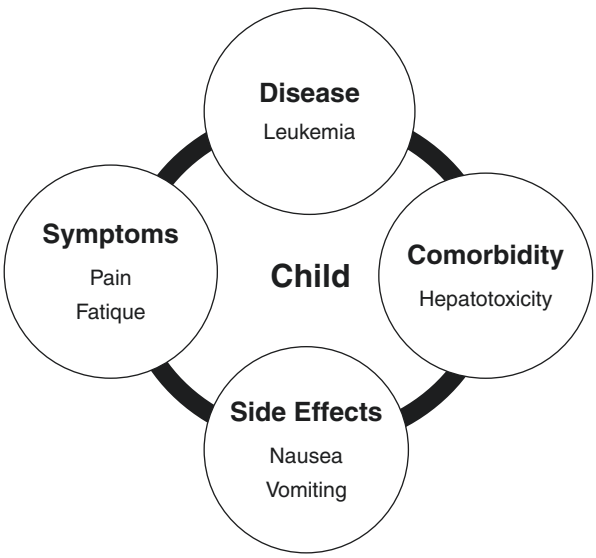

Fig. 9.2 Interrelated symptom experience

Symptoms and Suffering

Suffering is often used by researchers and clinicians to describe the experience of cancer treatment and symptoms in children. Cassell [32] defines suffering as "a state of severe distress associated with events that threaten the intactness of the person." Suffering as it applies to an individual is a phenomenological experience arising from a perception of threat to their personal integrity or limitations to significant aspects of their life [32]. This broad definition encompasses multidimensional sources of suffering that include physical, emotional, spiritual, and existential factors. Suffering is a deeply subjective personal experience and cannot be objectively assessed by an outside observer; therefore much like pain, one must believe the person's experience of suffering is as they describe it [32, 33].

Early symptom research in childhood cancer focused on understanding how children and families experienced the diagnosis of cancer, its treatment, and resulting symptoms. Parents recalling the symptoms experienced by their child in the last week of life were asked to assess the degree of suffering as a result of each individual symptom, with nearly 90% of parents sharing that their child suffered a lot or a great deal from at least one symptom and 50% of children suffered from 3 or more symptoms [34, 35].

Interviews with parents of children with cancer-related pain [18] offered visceral descriptions of seeing their child in pain as "unendurable," and feeling "helpless"; as if "watching your child dangle from a rope off a cliff." Pain was also impactful to the family as a whole, causing disruption in marriage and family life, sleep deprivation, feelings of guilt and failure as a parent, and a constant struggle for normalcy [36].

Interviews of children with cancer, their parents, and siblings have also explored broader symptom experiences and have similarly characterized reported symptom distress as suffering [6, 37]. Woodgate's seminal work on symptom experiences [9], based on 230 longitudinal interviews with 39 children with cancer and their families, provided insights into children, their parents, and sibling's beliefs and expectations about cancer. Findings centered on the family's belief that uncomfortable symptoms were a necessary and expected part of cancer care that were to be endured in order to survive. In fact, if symptoms were minimal or not present, there was concern that the chemotherapy was not working. Families also believed that suffering from symptoms was directly related to treatment not the disease. Similarly, there were no "getting used to" symptoms, as suffering would always be present while the disease was being treated. Children and families found it difficult to distinguish which symptoms were most difficult to bear, as they often could not be separated from one another, but rather existed as a gestalt. Lastly, symptom management was seen as "sort of helpful"; however children and families did not expect symptom relief, which leads to symptoms' being unrelieved, ignored, or uncontrolled [9].

Contemporary exploration of the experiences of children with cancer and their family have reported presence of physical and emotional suffering as a result of: lack of preparation for the complex care needs of their child; the strain of prolonged or repeated hospitalizations; job-related and financial stress; and taking on the role

of parent to a seriously ill child [38]. Lastly, greater symptom burden, severity of the child's condition, and intensity of treatment has been associated with increased parental distress [39–41].

Resilience

Although childhood cancer treatment often leads to periods of disease and symptom-related stress and suffering, most children and their families are able to effectively cope with the demands of cancer treatment and return to reasonable levels of functioning after the diagnosis [40, 42, 43]. Key aspects of family functioning that promote resilience include family cohesion, conflict management, adaptability, communication, family support, spiritual coping, and overall family functioning [43].

The diagnosis of cancer and the illness burden associated with treatment is often seen as a traumatic life event; however studies evaluating post-traumatic stress in children and families suggest that the unique nature of being diagnosed with cancer can facilitate positive coping and growth [40]. Post-traumatic growth theory regards exposure to serious life events as an opportunity for individuals to restructure their assumptions about themselves and the world to make sense of or find meaning in the traumatic experience [40, 44, 45]. Studies on post-traumatic growth suggest that children and families who had had fewer life stressors and were functioning well prior to diagnosis tended to have more post-traumatic growth related to their cancer experience. The stress of the cancer experience was viewed as drawing the family closer to each other, increasing parent/child bonds, and in essence looking for the "silver lining." There remains a small group of families, however, that have more substantial struggles during cancer treatment, particularly families with a younger child with cancer, those in active phase of treatment, and those with higher cumulative life stressors or a less cohesive and supportive family structure [40–42, 46]. This high-risk patient/family group requires further research and clinical attention to better understand factors that affect coping and symptom distress as well as developing management strategies to address coping and symptom distress.

Symptom Assessment in Childhood Cancer

Thorough assessment of symptoms is a necessary precursor to effective symptom management. It is commonly accepted in pain and symptom assessment research and clinical care that the best source of information regarding symptoms is the patient. Unfortunately, most clinical encounters have been shown to consist of providers and parents exchanging the majority of the information regarding the patient, while children and adolescents participate substantially less in the discussion [47–50]. Patient-reported outcome measures of cancer symptoms have been advanced by numerous federal agencies and professional societies as essential in pediatric cancer research and clinical care [51–53] as a means to improve patient outcomes and overall survival [54] as well as reduce costs associated with poorly managed symptoms [55].

While there is increased interest and inherent benefit in clinical implementation of patient-reported symptom screening, there are numerous challenges that need to be overcome [50, 51]. Studies of patient-reported symptom burden that included feedback to providers regarding symptoms that exceed pre-determined levels of severity did not significantly improve symptoms [56, 57]; however patients and parents reported some improvement in emotional health-related quality of life (HRQOL) and improved scores on total sickness measures [52]. Such studies highlight challenges to clinical implementation of standardized symptom assessment tools. Variability and level of distress from symptoms across diseases and patients requires careful consideration of measures to be introduced over the course of care and how to respond to endorsed symptoms and associated frequency, severity, and distress reported. Practical challenges to the use of standardized symptom assessment include providers' lack of familiarity with patient-reported symptom screening tools as well as how to interpret the data in an actionable way in real time that does not impede workflow.

There are a number of valid and reliable pain and symptom assessment scales for children and adolescents with cancer that allow both direct patient and parent proxy report to screen for the occurrence of common cancer treatment symptoms [58]. With or without patient-reported symptom measures, multidimensional assessment of the child's symptom experience should be a discussion between the child and/or parent and the oncology clinician. Open and encouraging exploration by the provider should include not only the presence of symptoms but also a thorough discussion of the perceived severity and distress and the effect of symptoms on the child's function and quality of life, as well as what medications and home management strategies help to alleviate symptoms. Challenges in clinicians consistently eliciting such a thorough exploration of the symptoms include the child's age and ability to recall and describe their symptoms; underreporting due to child and parent expectations and beliefs about symptoms; under-assessment by clinicians, patient, family, and provider communication style; and clinician time constraints [55, 59].

Symptom Burden in Childhood Cancer

The availability of valid and reliable pain and symptom assessment scales has led to an expanding body of literature reporting on the prevalence of symptom burden experienced by children over the course of treatment and into survivorship. The majority of studies using a multi-symptom assessment instrument involve the child or adolescent providing direct report of the symptoms they experience and included multiple oncologic disease groups, across various stages of treatment, in both inpatient and outpatient settings [1, 12, 16, 60]. Child participation and response rates are high across studies, and researchers report that patients as young as 7 years old are able to complete symptom assessment tools, in English or translated versions, although adolescents (≥10 years of age) represent by far the largest group of patients in symptom assessment studies [1, 61–75].

Symptom Prevalence, Severity, and Distress

There are limited studies on the incidence and prevalence of pain in children with cancer, and even fewer exploring the type and characteristics of the cancer pain experience [76–80]. Cancer pain can present as episodic, persistent, or chronic, and some children experience complex cancer pain syndromes requiring multimodal treatment. Across various studies, about 50–60% of children with cancer and their parents report clinically significant pain over the course of treatment [79–82].

Common sources of pain include needle procedures, mucositis, procedural/surgical pain, phantom limb pain, and neuropathic pain from tumor or chemotherapy agents [83, 84]. Pain is often the most commonly reported symptom at diagnosis and, depending on the underlying disease, has been reported as being present from one to three or more months prior to diagnosis [81]. Additionally, pain is problematic for many children throughout treatment, at end of life, and well into survivorship [34, 76, 79, 80, 85–88].

In addition to pain, children with cancer report multiple concurrent symptoms in all diseases and phases of treatment. Across all studies, children and/or their parents report between 3 and 11 concurrent symptoms during active treatment and at end of life (EOL) [14, 34, 64, 65, 71, 72, 76, 85, 86, 89–91]. The most frequently occurring symptoms in both younger children and adolescents across all symptom reports in order of prevalence were lack of energy, pain, lack of appetite, nausea, drowsiness, worry, and sadness. Older children and adolescents undergoing treatment have been shown to experience higher symptom burden than younger children [14, 75, 92, 93]. Similarly, children receiving chemotherapy report higher symptom burden and distress than children not receiving chemotherapy [65, 66, 94, 95]. Both solid and CNS tumors have been associated with higher symptom prevalence and severity than leukemia and lymphoma [65, 76, 96].

Race and gender differences in symptoms were generally not significant across studies; however, in many of the US and European studies, white/caucasion participants constitued the largest groups. Further research is needed in other ethnic populations to better understand possible differences between various populations. In a large multisite randomized controlled trial, female gender was associated with higher symptom burden [76]. Interestingly, across studies, the most frequent or severe symptoms endorsed by both children and parents were often not the most distressing. Less evident symptoms, such as sadness, lack of appetite, and pain when present, were often rated as more severe and distressing [64, 65, 67, 71, 72, 76].

Studies that assessed parent/child concordance found that symptoms reported by children tended to also be the most frequent symptoms reported by parents [61, 64, 65, 97–100]. Baggott [99] noted that parents rarely underestimated their child's symptoms; however parents did overestimate psychological symptoms compared to their child's report. Studies using parent ratings of symptoms by both parents [93, 101] demonstrated concordance between mothers' and fathers' ratings of symptoms; however mother's ratings were more likely to be higher than fathers.

In repeated measured studies, children and adolescents receiving initial treatment experienced a wide range of symptoms that were generally more frequent and distressing in the early stages of treatment and subsequently diminished in frequency and

level of distress over the course of treatment [1, 19, 61, 71, 73, 93, 101]. This pattern was reported in both inpatient and outpatient settings, with hospitalized children reporting greater numbers of symptoms and greater distress than outpatients [15, 64, 65, 70]. Children with advanced cancer experience pain and other highly distressing symptoms that persist over the course of their terminal illness [34, 76, 85, 86, 102].

Symptom distress has been linked to changes in several other dimensions of children's and parents' experience with cancer treatment. Higher levels of symptom frequency, intensity, and distress have been found to lead to decreases in health-related quality of life and functional status [66, 70, 74]. In particular, children who reported higher total number of symptoms had significantly lower measures of physical and emotional health-related quality of life and poorer functional status [66, 70]. Arslan [42] found that children who endorsed lack of energy, constipation, and sweating had significantly lower physical HRQOL scores. Nervousness, sadness, pain, worry, drowsiness, irritability, and changes in appearance were significantly related to lower emotional HRQOL. Lastly, the combination of sadness, worry, and irritability resulted in lower overall HRQOL.

Symptom burden has also been found to persist well into survivorship. Lack of energy, difficulty sleeping, headaches, pain, and lack of concentration were the most frequent, severe, and distressing symptoms reported and are often associated with functional difficulties [103–107]. Increased symptom burden and physical changes such as persistent hair loss, scars, and disfigurement have all been associated with decreased quality of life [2, 104, 108, 109]. Female cancer survivors of acute lymphoblastic leukemia (ALL) with greater levels of sleep dysfunction reported greater inattention, hyperactivity, and aggression as well as worse executive function, processing speed, and behavioral symptoms than male ALL survivors [110]. Psychosocial and mental health symptoms such as anxiety, depression, social withdrawal, peer conflict, and attention deficits have been found to co-occur and have been linked to treatment exposure and physical symptoms in survivors [111–113].

Symptom Clusters

Growing evidence of multidimensional and interrelated co-occurring symptoms reported by children with cancer has led researchers to explore the relationships among symptoms reported by patients [16, 28, 114–118]. Symptom clusters have been reported in a variety of adult [28] and childhood illnesses [115] and are generally considered as 2 or more co-occurring symptoms that are predictable and related to one another (i.e., pain and anxiety, sleep disturbance, fatigue, and irritability) [28, 118, 119].

Across studies, symptom clusters varied with regard to the specific symptoms included in the cluster; however symptoms generally clustered in logical groups. For example, a commonly occurring cluster that includes nausea/vomiting/sleep disturbance [1, 66, 68, 118, 120] varies across studies with regard to associated symptoms, such as pain [1, 68, 96] and loss of appetite [66, 68]. The cluster of fatigue, sleep disturbance, and nausea/vomiting was shown to increase depressive symptoms and behavioral changes in adolescents, while in younger children, fatigue

alone increased depression and behavior changes [96]. Yeh [68] described five symptom clusters and found that the presence of pain led to reports of significantly higher symptom distress in all clusters.

Symptom clusters have also been described based on the class of chemotherapy patients receive and their effect on quality of life [74]. Children receiving antimetabolites reported significantly more worry and irritability, whereas those receiving anthracyclines reported significantly more lack of energy and skin changes, leading to decreased quality of life. Lastly, Hockenberry [96] found that adolescents with solid tumors receiving chemotherapy who experienced the cluster of fatigue and sleep disturbance had higher levels of depression. Adolescents with solid tumors also experienced the cluster of nausea and vomiting and had greater sleep disruption and significantly less daytime activity compared to other children with cancer.

Two studies evaluated changes in symptom clusters over time. Atay [116] reported shifts in symptom clusters over the first 3 months, with emotional symptom clusters reported more frequently in the first and third month of treatment, while symptoms related to chemotherapy were more frequent in the second month of treatment. Hockenberry [19] evaluated symptoms in 236 children with leukemia over four time periods and identified three distinct symptom groups: mild symptoms (46%), moderate symptoms (52%), and severe symptoms (11%). Analysis of symptom change over time demonstrated that sleep disturbance and nausea changed little over time; however fatigue, pain, and depression decreased over the four time periods.

Lastly, Finnegan [103] described a cluster of eight symptoms in adult survivors of childhood cancer (ACC) and explored factors likely to predict subgroup membership according to presence of chronic health conditions (CHC), health-promoting lifestyle, and quality of life. Similar to Hockenberry, three distinct groups were identified as high symptom (21%), moderate symptom (45%), and low symptom (34%). ACC with at least one CHC were six times more likely to be in the high symptom group. Mean health-promoting lifestyle scores were lower in the high symptom group and highest in the low symptom group. Quality of life differences across subgroups were statistically significant with the high symptom group having the lowest quality of life. Quality of life in the moderate symptom group and low symptom group matched or exceeded quality of life scores of healthy young adults.

Symptom cluster research, while still in the early stages, is providing important insight into symptom interrelatedness and the consequent effect on function and quality of life. Evolving statistical modeling has expanded cluster research beyond describing symptoms that coexist, toward a better understanding of patients with similar symptom experiences. Understanding both the interrelatedness of symptoms within a cluster and the child's symptom experience with regard to their everyday life is important to creating an optimal symptom management plan to maximize comfort and quality of life over the course of treatment. Ongoing research into symptom clusters will advance our understanding of the global symptom experiences of children with cancer and provide opportunities for developing and evaluating symptom management interventions.

Immunomodulation and Sickness Behavior in Cancer-Related Symptoms

The interrelated symptom experience frequently reported by children receiving cancer treatment results from a complex physiologic and pathophysiologic milieu. There have been great gains in both pre-clinical and clinical research in the past 30 years leading to a deeper understanding of the relationship between the physical symptom experience and the cognitive and emotional responses to cancer symptoms [121–126].

There is an increasing body of evidence that cancer-related pain and symptoms are initiated and in some cases amplified by key mediators within the peripheral immune system inflammatory cascade that interact with cytokines and glial cells in the central nervous system, prompting a process of neuroinflammation [123, 124, 126, 127]. Circulating cytokines act on receptors via neurotransmitters in the CNS to stimulate the release of pro-inflammatory cytokines that affect the brain creating symptoms such as fatigue, fever, anorexia, and cognitive dysfunction. These symptoms are consistent with infectious illnesses and serve to motivate energy conservation to facilitate healing [123, 125, 128].

Cytokine-induced "sickness behavior" is a cluster of symptoms that includes lethargy, anorexia, depression, anxiety, fatigue, and hyperalgesia and is promoted by changes in cytokines that are abnormally produced by cancer cells as well as various phagocytic cells [122–124]. Neuroinflammatory symptoms can become pathologic if there are high levels or prolonged duration of pro-inflammatory cytokine production, if there are defective down-regulation of molecules and cellular components, or if neuronal circuits become sensitized [123, 129]. Lastly, subtle genetic variations of cytokines have been associated with depression in adult cancer patients [121, 124, 130], pain sensitization [124, 131, 132], and higher levels of fatigue, sleep disturbance, and cognitive impairment [122, 124, 132, 133] .

Relationships between symptom clusters in adults and children at risk for higher symptom burden have been linked to cytokine-mediated inflammatory processes that promote the development and perpetuation of sickness behavior. Hockenberry [118] identified two symptom clusters in children receiving chemotherapy and noted that they corresponded to the symptoms commonly associated with sickness behavior. The symptom cluster of fatigue/depression is related to emotional sickness behavior symptoms, while the nausea-vomiting/performance status/sleep disturbance cluster is related to physical sickness behavior symptoms. In a similar study, Cheung [110] evaluated the role of sleep, fatigue, and systemic inflammation and found that female survivors of acute lymphoblastic leukemia (ALL) had greater levels of sleep dysfunction and experienced more inattention, hyperactivity, and aggression. Fatigue, in combination with higher levels of IL6, IL1B, and C-reactive protein, was also associated with worse executive function, processing speed, and behavioral symptoms in female survivors of childhood cancer.

Genetic polymorphisms have also been linked to cytokine-induced sickness behavior in cancer as well as other chronic illnesses [124]. In a study of adult cancer patients, Illi [121] compared cytokine genes with patient-reported measures of pain, fatigue, sleep disturbance, and depressive symptoms in adult patients with breast,

prostate, lung, or brain cancer. Three distinct classes of patients were identified based on similar symptom experiences. Findings indicated significant differences between the classes, with the high depression/high pain group (12%) being significantly younger and female, having higher co-morbid conditions and lower functional status. Additionally, having a minor allele for IL4 was associated with membership in the all high group.

These studies provide further areas of exploration as to the role of inflammatory cytokines and genetic alterations in patients exhibiting high symptom burden during cancer treatment. Identifying clear biochemical and genetic markers of risk for high symptom burden would provide opportunities to more closely monitor and manage symptoms and increase the likelihood of improved quality of life and treatment outcomes.

Symptom Management in Childhood Cancer

Research in symptom management is limited, with very few outcomes studied to provide evidence-based guidance in childhood cancer symptom management. Following is a discussion of the most commonly experienced symptoms and research-based non-pharmacologic and pharmacologic interventions.

Sleep Disturbance and Fatigue

Sleep disturbance underlies several frequently reported symptoms, such as lack of energy, fatigue, and difficulty concentrating. Fatigue in children has been defined as a "profound state of being physically tired or having difficulty with bodily movements," while adolescents experience fatigue as a "changing state of exhaustion that can include physical, mental, and emotional tiredness [134]." Sleep is a biologically necessary process of disengagement from external stimuli, and disturbance of restful sleep is detrimental to a child's mood, cognitive and physical functioning, and behavior [135–137]. There are numerous types of sleep disturbance experienced by children being treated for cancer that exert substantial effect on overall quality of life [107, 136, 137], with excessive daytime sleepiness (EDS) being the most frequently reported [135, 136].

Non-pharmacologic Interventions Increased physical activity is the most frequently studied intervention aimed at improving sleep and fatigue in children receiving chemotherapy [138–141]. Studies of physical activity monitored either by wrist fitness tracker or by actigraph suggest that patients with increased physical activity have significantly lower fatigue [140, 141], improved sleep [139], and improved physical endurance [142]. Similarly, nursing educational interventions with patients and parents that focus on cancer-related sleep disturbance and fatigue

found that instruction on sleep hygiene, nutrition, and scheduled walking activities decreased fatigue [143], while use of relaxation techniques increased sleep time and decreased sleep disruption [144]. Home-based exercise, healing touch, and yoga interventions have also been associated with lower fatigue and/or improved sleep [141, 145, 146]. However, these findings are tempered by a stationary bicycle exercise [147], massage therapy [148], and yoga interventions [149] that did not demonstrate improvement in fatigue symptoms. Numerous other self-help strategies aimed at managing sleep disturbance and fatigue such as engaging in relaxing activities, warm baths, availability of comfort items, and sleeping with parent/friend have also been reported [137, 150].

Pharmacological/Interventional There are no published clinical outcome trials on the efficacy and safety of pharmacologic agents to manage sleep disturbance or fatigue in children with cancer. Stimulant medications, growth hormone, and scheduled naps have been prescribed to manage fatigue in children experiencing EDS [135–137, 150]. Pharmacologic management of underlying pain and sedatives and melatonin have been used to address insomnia, and anticonvulsants prescribed for parasomnias [137, 150]. Lastly, for children with cancer who were diagnosed with either central or obstructive sleep apnea in a pediatric sleep center, use of noninvasive ventilation (continuous or biphasic positive airway pressure) and supplemental oxygen have provided relief [136, 151].

Pain

Pain is one of the most frequent symptoms reported by children with cancer and their parents [80, 82, 152]. Studies of parents' experiences of pain provide a conflictual attitude toward pain management, as they prefer to limit strong analgesics such as morphine and other opioids due to concerns about side effects and addiction, while also advocating for appropriate pain management for their child [36, 80, 82, 153].

Parents report managing their child's pain primarily with physical and psychological strategies rather than pharmacological agents [80]. In general, there is evidence that parents believe that their child's comfort is their responsibility and that they would benefit from pain education and clear pain management instructions from their health-care team to help them achieve those goals [6, 18, 82]. While a comprehensive discussion of cancer pain management in children is beyond the scope of this chapter, following are summaries of research related to non-pharmacologic and pharmacologic pain management strategies.

Non-pharmacologic Interventions Several randomized trials have demonstrated that distraction is an effective form of non-pharmacologic management for procedural pain [154]. Distraction with and without medications is also the most common intervention used by parents to manage their child's pain at home [80, 82]. In

addition to distraction techniques, several complementary/alternative and integrative medicine techniques such as hypnosis, guided imagery, healing touch, and cognitive-behavioral therapy have been shown to improve pain and quality of life in children with cancer [155–158]. Lastly, recent studies evaluating animal-assisted activities (pet therapy) reported pain and other distressing symptoms improved significantly in patients who had animal visits [159, 160].

Pharmacologic/Interventional Although nearly all children with cancer will report some level of pain during their treatment, with 60% reporting clinically significant pain [80, 161] there are no controlled trials of pharmacological approaches to cancer pain management [162–164]. This lack of evidence-based management contributes to substantial variability across health-care settings and providers, increasing the risk of inadequate pain relief and complications related to opioid therapy. In busy oncology clinics where multiple providers see patients, there is an increased risk that patients may receive multiple prescriptions of various pain medications. Persistent myths regarding the safety of opioids and other analgesic and adjuvant medications, the wide variety of pharmacologic options, and the risk of opioid overuse and abuse [165–167] further complicate effective pain management.

Opioids are the mainstay of pediatric cancer pain management [168] although little is known about the prevalence, indication, and duration of opioid use in this population of children. Getz [169] reviewed data from the national health service in Ireland and found that over 75% of children with acute myeloid leukemia (AML) were exposed to opioids over the course of their treatment, while children with cancer represented nearly 40% of patients receiving opioid infusions for more than 28 days in a US children's hospital [170]. A retrospective chart review of approximately 400 children treated at a US pediatric cancer center found that approximately 25% of children were prescribed outpatient opioid therapy for 7 or more days [166]. Additionally, there is evidence that chronic pain syndromes in childhood cancer survivors result in increased risk of receiving opioids up to 3 years post therapy [88].

Mu receptor agonists such as hydrocodone, morphine, and hydromorphone are the most frequently used opioids and are effective analgesics for moderate to severe acute and episodic cancer-related pain. Opioids are generally considered safe for use in children with cancer over the course of their care [171]; however there are undesirable effects that must be managed, such as constipation, development of tolerance, physiologic dependence, and, with chronic use, a risk of increased pain sensitivity (hyperalgesia) [168].

In recent years, methadone has played a role in chronic, neuropathic, and end-of-life cancer pain management. While methadone has utility in managing complicated cancer pain syndromes, it should be used with caution and in consultation with pain and/or palliative care professionals. Methadone has unique pharmacodynamics that include QTc prolongation, prolonged time to steady state (3–5 days), as well as a prolonged and variable half-life requiring caution in initiation, monitoring, and titration [172, 173].

Recent recommendations on methadone management [173] in adult chronic pain and addiction settings include routine electrocardiogram (ECG) prior to initiation and routinely while on therapy. The recommendation was extended to children as there were no available studies on methadone in children at the time. However, recent reviews of methadone use in two pediatric cancer centers found no correlation between methadone dose, duration of therapy, or concomitant QT prolonging medications and QT prolongation in children with cancer [174, 175], suggesting that methadone, when prescribed and monitored appropriately, is safe for use in children.

In addition to methadone, there are a number of adjuvant medications that have demonstrated utility in neuropathic and other complex pain syndromes [176–180]. Gabapentinoids are generally first-line agents for chemotherapy-related neuropathic pain, with agents such as tricyclic antidepressants, lidocaine, and alpha agonists also having utility in refractory neuropathy [84, 181, 182]. Complex, refractory pain interventional management includes peripheral nerve blocks and epidural infusions [176–178, 183].

In the face of the national crisis of opioid-related deaths, there is increasing concern regarding the widespread use of opioids as the primary remedy for cancer pain, and there are increased calls to develop policies and procedures related to opioid risk evaluation and mitigation strategies (REMS) [165–167]. Reports from two large US pediatric cancer centers using risk evaluation in adolescents with cancer reported high opioid risk in 34% [167] and 39% [166] of screened patients. While there are efforts to increase safe prescribing through standardized risk screening at initiation of opioid therapy in adolescent and young adult (AYA) cancer patients, the counter concern is that gains made in addressing pain in children and AYA may be lost out of fear of prescribing opioids despite a sound clinical indication. Healthcare provider's obligation to address suffering while minimizing exposure to opioids can be actualized by engaging in efforts to advocate for effective pain assessment and management policies and practice standards as well as expanding the availability of integrative health providers to provide a balanced approach to pharmacologic and patient-centered approaches to care.

Nausea/Vomiting

Anticipatory, acute, and delayed chemotherapy-induced nausea and vomiting (CINV) is a challenge in childhood cancer, particularly with regard to nausea management [184]. Nausea is generally reported by children with cancer and their parents as more distressing than vomiting [12, 15, 96, 185]. Parents, nurses, and children who were asked to score the child's nausea and vomiting before, during, and after chemotherapy found that parent, patient, and nurse reports of vomiting were similar at all time points; however nurses and parents underreported nausea in both the anticipatory and delayed phase of nausea/vomiting [186].

Non-pharmacologic Children have reported various active and passive coping strategies related to managing nausea and vomiting (CINV), with the most fre-

quent being distraction, wishful thinking, and emotional regulation [187–190]; however there was no assessment of the success of these strategies in reducing nausea and vomiting. Distraction with video games has been shown to reduce nausea in children with cancer as well as other cognitive-behavioral interventions such as guided imagery, story-telling, systematic desensitization, and hypnosis [191, 192]. Chan [193] reported on a psychoeducational intervention that evaluated the use of progressive muscle relaxation and guided imagery versus an educational program focused on risk assessment, antiemetic use, and meal planning with patients and parents. Patients in the intervention groups tended to use less antiemetics than controls and reported significantly less vomiting on day 3. Parents in both the relaxation and educational groups had significant decrease in anxiety levels, although children's anxiety did not change significantly.

A number of integrative medicine techniques aimed at managing CINV have been reported in both adult and pediatric cancer research. Acupuncture is the most frequently studied integrative technique and successful in controlling nausea and vomiting, with the most common side effect being localized redness at the site [192, 194]. Reindl [195] reported on a multicenter crossover trial of antiemetics with and without acupuncture. Recruitment was a challenge as nearly half of eligible patients declined, and another 11 could not receive acupuncture at the appropriate start time. However, data from the 11 patients who did consent and participated in the acupuncture sessions suggested that acupuncture is feasible, particularly in adolescents, and that although there was not sufficient power to detect significant changes in antiemetic use, there was a decrease in use of sedative as-needed (PRN) antiemetics and increased alertness in the acupuncture group. Interestingly, there was no significant difference in subjective nausea reports despite the decrease in PRN antiemetics.

Acupressure has also been evaluated as an integrative approach to CINV in adults and children and has been found most useful in combination with antiemetics in decreasing acute nausea severity, but less effective in reducing vomiting or controlling delayed nausea and vomiting [192]. Yeh [194] utilized auricular acupressure on a group of Taiwanese children and adolescents with cancer and reported a significant decrease in both the frequency and severity of nausea and vomiting when compared to a control group. However, a study on the use of acupressure bands versus placebo bands in 21 patients in a US cancer center found no significant effect on nausea or vomiting between the groups, although surveys of patient's expectations of acupressure to improve their nausea and vomiting demonstrated only a moderate expectation of benefit [196].

Sensory interventions using essential oils and popsicles/lollipops have also been reported in adult stem cell transplant patients, with orange popsicles, as well as orange scent and taste demonstrating significant reduction in nausea intensity and retching over deep breathing and aromatherapy massage interventions [192].

However, in a double-blind placebo-controlled study, Ndao [197] found that children exposed to bergamot aroma therapy during stem cell transplant had greater anxiety after cell infusion, while parent anxiety declined in both treatment and control groups.

Although the research on integrative management of nausea and vomiting is limited, there is increasing interest in the use of integrative techniques in clinical settings, particularly in persistent or refractory symptoms. Clinicians should carefully assess patients and consult with integrative medicine and palliative care colleagues to determine the appropriate techniques and tailor an integrative symptom management plan to the individual child.

Pharmacologic Control of chemotherapy-induced nausea and vomiting has improved substantially in the past two decades with the development of several agents that specifically target key emetic receptor pathways in the brain. Agents such as ondansetron, granisetron, and palonosetron target 5-hydroxytryptamine 3 (5-HT3) receptors [198], while aprepitant targets substance P and neurokinin 1 receptors [199]. The emetic potential of a given chemotherapeutic agent can range from low (10–30% frequency of emesis) for common agents such as etoposide, doxorubicin, low-dose methotrexate, and topotecan to high (> 90% frequency of emesis) for agents such as cisplatin, high-dose cyclophosphamide, and high-dose methotrexate [186].

There are a number of evidence-based guidelines by the Pediatric Oncology Group of Ontario (POGO) Guideline Development Committee on the pharmacologic management of anticipatory, acute, and delayed nausea and vomiting that have been published in recent years [200–204]. Pharmacologic control of anticipatory nausea and vomiting (ANV) is based on the need to prevent acute and breakthrough NV, and guidelines recommend lorazepam at bedtime the night before and morning of chemotherapy for children with persistent ANV [200]. Acute CINV prophylaxis recommendations provide suggestions for various agents, based on detailed and well-supported evidence that considers the patient's age, potential contraindications, and emetogenicity of the chemotherapy received [202]. Breakthrough NV recommendations include escalating acute CINV prophylaxis and addition of olanzapine for highly emetic chemotherapy [202]. For children with refractory CINV, the guidelines provide several suggestions for antiemetic rotation as well as additions to aggressively manage refractory NV [202].

In addition to 5-HT3 and NK 1 receptor antagonists, there are a number of adjuvant medications that can be incorporated into a patient's CINV regimen to maximize control. Dexamethasone is the most frequently used adjuvant to manage CINV; however it is contraindicated in some children, particularly those with leukemia. Benzodiazepines such as lorazepam are useful in anticipatory NV based on adult studies [200], and in a retrospective review of 60 children receiving chemotherapy, the atypical antipsychotic olanzapine was found to be effective for acute phase chemotherapy-induced vomiting [205].

Psychosocial Symptoms

Anxiety, worry, and depression are reported less frequently than physical symptoms, which is consistent with a number of studies that report children with cancer generally function as well as or at times better than healthy peers [206–208]. A longitudinal study of children in the first year of treatment for leukemia found that overall experience of anxiety and depression were similar to same-age peers; however approximately 25% of children experienced higher levels of anxiety and depression, with anxiety levels returning to normal while depression persisted throughout the first year [209].

Anxiety in childhood cancer is generally related to treatment and procedures, particularly those that entail some level of pain, as well as anticipatory nausea and vomiting [185, 208]. Depression has been linked with higher levels of cancer symptom frequency and severity, severe medical complications from treatment, and neurologic sequelae from disease and treatment [96, 208, 210, 211].

There are a number of risk factors that contribute to poorer psychosocial functioning for children that require ongoing assessment and management [207–209, 212]. Family functioning and individual dispositional traits of children have been consistently identified as primary risk factors for anxiety and depression during childhood cancer therapy [206, 208, 209, 211, 213]. Families with unhealthy patterns of functioning and poor social support have significantly increased risk for children to experience anxiety and depression [206, 209, 211, 214]. Children who demonstrate higher levels of worry and difficulties distracting themselves during stressful treatment and procedures experience higher levels of treatment-related anxiety and distress [209, 213].

Risk factors for development of anxiety and depressive disorders in survivors of childhood cancers include being female, unmarried, lower economic and educational status, presence of physical late effects and chronic health conditions, and lack of health insurance [207]. There is also emerging evidence that there is a small subset of survivors with chronic complications such as poor physical health, chronic pain, and emotional difficulties that are at risk for suicidal ideation [5, 207].

Supportive Management Interventions aimed at managing treatment-related anxiety and depression should begin at diagnosis with a thorough assessment of known risk factors followed by tailored educational and psychosocial interventions (psychoeducation) based on individual patient and family needs [215, 216]. Psychoeducational interventions focus on guidance around a variety of topics such as developmentally based disease education, family coping, treatment management, procedures and symptoms, fertility, medical decision making, and numerous other topics unique to each family. Children and families who receive psychoeducational interventions have been found to have increased health locus of control and improved symptom management outcomes [217, 218]. Psychological support through individual, marital, and family therapy can assist children and families with adjusting to the life-altering experience of childhood cancer. Cognitive behavioral therapy and problem-solving skills training are effective psychological interventions for

reducing stress in parents and children with cancer [219]. Creative arts and expressive therapies [220–222] have also demonstrated a role in relieving anxiety and depression in children and adolescents.

Pharmacologic Management Studies of oncologists prescribing habits have found that prescriptions for antidepressants and anxiolytics in children with cancer exceed that of general population of children [223, 224]. Similarly, survivors of childhood cancers had nearly 5 times the risk for antidepressant use and up to 7 times that risk for anxiolytic use up to 3 years post-treatment compared to non-cancer controls [88]. Many of the symptoms of anxiety and depression in particular overlap with common treatment-related symptoms and clusters such as sleep disruption, fatigue, difficulty concentrating, and irritability, suggesting that it may be difficult for clinicians and parents to distinguish depressive symptomatology from known cancer-related symptoms, leading to overprescribing [224].

Supportive interventions discussed above should be the first line of management of depression and anxiety; however there may be a role for adding pharmacologic management in certain circumstances, particularly in children and adolescents with pre-diagnosis history of depression, anxiety, or other mental health disorders [208, 225]. The most common class of antidepressant prescribed by oncologists is selective serotonin re-uptake inhibitors (SSRI) [208]. However in a survey of pediatric oncologists in nine US cancer centers [224], consultation with psychology or psychiatry colleagues was low, with less than 20% always consulting mental health professionals, while three-quarters of oncologists reported not adhering to black box guidelines for monitoring of SSRIs and just 9% assessed for suicide risk.

Symptom Management in Advanced Disease and at End of Life

While most symptoms experienced during cancer care are generally related to treatment, symptoms in advanced disease and at the end of life (EOL) are related to both the cumulative effects of disease treatment and progression of the disease itself [76, 226–228]. Symptoms in advanced cancer are similar to those experienced throughout treatment, with pain, fatigue/drowsiness, dyspnea, nausea and lack of appetite, loss of mobility, communication, and breathing changes being the most prevalent EOL symptoms [229]. Symptom burden increases over time from progression to death, with prevalence and distress levels increasing in the weeks before death, leading to substantial decrease in quality of life [3, 76, 86, 228].

Interviews with bereaved parents suggest that as disease progresses, symptoms of most concern to parents are those which were unexpected or they were not prepared for, occur suddenly, or caused fear to the child or parent [85]. In particular, unrelieved pain and other symptoms, as well as difficulties at the time of death, have been shown to affect parents for several years after their child's death [34, 230, 231].

Parents of children with advanced, incurable cancer find themselves faced with witnessing the toll that the disease and treatment is taking on their child. The utmost attention should be given to addressing symptoms as disease progresses. Symptoms should be routinely assessed and managed across all care settings (home, clinic, and hospital) to maximize comfort.

Symptom management interventions should be balanced with the overall condition of the child to assure that the benefit outweighs any burden of the intervention. Parents should be provided with a point person to call if there is any worsening of pain or other symptoms so they can be addressed quickly to avoid intractable discomfort. Specialty community-based hospice and palliative care experts [232–237] can assist by providing home visits to assess pain and symptoms and coordinate with the primary oncology team to adjust medications as needed.

Symptom Management at End of Life

Unfortunately, there is a significant dearth of clinical outcome research on pain and symptom management interventions in advanced and terminal care of children with cancer [162, 163, 238]. Generally, symptom management at end of life is a continuation and at times escalation of previously discussed symptom management strategies to address global symptoms at end of life.

In addition to the global symptoms that most parents report across all diseases, there may also be disease-specific management needs. Children with central nervous system (CNS) tumors experience substantial symptom burden related to focal neurological deficits [239, 240] such as impaired mobility, altered levels of consciousness, and dysarthria/dysphagia in the months prior to death. The most prevalent medications aimed at management include analgesics, laxatives/steroids, sedatives, antiepileptic agents, and antisecretory medications as well as low-dose chemotherapy and palliative radiation therapy [239, 240].

Children with hematologic cancers may have symptoms such as pallor, petechiae, and fatigue [235]that are related to pancytopenia in advanced disease. Blood and platelet transfusions may be helpful over the course of disease progression [241]; however these may be less effective as disease worsens. Consideration should be given to the child's overall clinical condition and history of major bleeding complications when considering the risks and benefits of transfusions at the end of life.

Lastly, children with solid tumors may experience wound care issues and intractable pain related to tumor growth. Consultation with wound care specialists for open and/or fungating tumors can be extremely helpful and mitigate parent/child distress related to odor and appearance concerns. Targeted palliative radiation [242–245] has been shown to provide pain relief with minimal toxicity in children with advanced tumors. Children with intractable pain may require rapid escalation of opioids and the addition of adjuvant agents such as ketamine [246–248] and methadone [249, 250] to maximize analgesia.

Managing symptoms in children at end of life is challenging for all members of the treatment team as they bear witness to the physical, emotional, and spiritual suf-

fering of the child and family. In the rare cases where significant pain or other symptoms such as severe anxiety, profound restlessness, or delirium persist despite ongoing attempts to manage the symptoms, palliative sedation may be considered as an intervention of last resort [251–254].

In the setting of intractable symptoms, physicians and nurses often worry that escalation of opioids and other sedating medications aimed at optimizing comfort will lead to the patient's death. Families and the treatment team are left with no "good" options and therefore may feel culpable in hastening the child's death [255]. It is imperative that the team pauses with the family to review the care provided over time and the level of perceived suffering of the child and acknowledge that death is now the expected outcome and the intention of care is to minimize suffering.

Palliative sedation has an ethical basis in the principle of beneficence, where the intent of sedation is to alleviate suffering and should not be conflated with euthanasia or assisted suicide. The principle of double effect has been used to address this dilemma by focusing on the intent of the actions taken, such that those interventions purely intended to provide comfort are considered ethically sound, even if there is a risk that they may have known but unintended consequences that may be perceived to hasten death [256–258]. While this principle is well established in palliative care, concerns regarding clinicians interpretation of intent and foresight as well as a clear understanding of the moral basis of the actions being contemplated are best reasoned out with the assistance of an experienced clinical ethicist [256–258].

Palliative sedation therapy should be managed by experienced pain and palliative care professionals after consensus by family and interdisciplinary team members that the child is imminently dying and all available attempts to manage suffering have been exhausted [251–253, 259]. Implementation of palliative sedation should include having a do not resuscitate order in place, reviewing goals for comfort care (hydration, antibiotics, transfusions) during the period of sedation, and define outcome measures for assessing comfort and when to titrate or discontinue sedation [254].

The explicit goal of palliative sedation therapy is to achieve a satisfactory level of unconsciousness that minimizes suffering. The choice of sedative agents should be determined based on the goals. Midazolam is a common agent for moderate to deep sedation due to its short half-life, allowing for easy reversal in situations where sedation may be time limited to allow rest or re-evaluation of symptom control. Other agents that provide deeper sedation are commonly used include barbiturates, ketamine, and propofol [260].

Psychosocial/Spiritual Support

Even in terminal stages of disease, children and adolescents can have periods of reasonably good quality of life and functional ability if symptoms are managed and treatment-related side effects are minimized to the extent possible. The strategies to manage symptom distress using supportive, complementary, and integrative interventions discussed earlier can be equally effective during advancing disease and at end of life.

Supportive activities that are particularly important during EOL care involve helping children and families maximize family and peer interactions and engage in legacy building and meaning making [261–264]. Studies focused on legacy building have demonstrated that children as young as 2 years old have an awareness of their impending death and intentionally leave items for special people or share their wishes for remembrance. These intimate activities between children and families provide a sense of the sacred and bring comfort to parents, siblings, and others who were touched by the child long after the child's death [261–264].

Spiritual support and exploration is important across the cancer trajectory, but is increasingly important in advanced disease and end-of-life care [265–269]. Consultation with a hospital chaplain who is experienced with caring for children with cancer and their families can provide a through spiritual assessment and coordinate care with community spiritual providers to maximize coping and bereavement outcomes after the child's death. Spiritual well-being in parents has been associated with positive outcomes such as feelings of comfort and hope, acceptance of limits within disease, and emotional support and guidance in contending with their child's illness and the difficult decisions they faced [265]. Spiritual development in children evolves as they move through the cognitive stages of development first from their connection to their parents' beliefs as a child, through experiences of spiritual questioning and disappointments in the school age years, to adolescence searching for understanding and answers in various religious frameworks [270, 271]. Children's spiritual beliefs can provide comfort, strengthen bonds to family and friends, elicit desires to be remembered and leave a legacy, and provide opportunities for expression of feelings, finding meaning and transition of hope from a focus on cure to acceptance and hope for comfort, desired activities, and anticipation of an afterlife [266]. While spiritual connection is generally reported to be protective and supportive, for some parents and children, cultural experiences of spirituality can also be a source of distress from a sense of punishment through illness and suffering as a requirement for entrance to heaven [267, 268].

Health-care providers can optimize spiritual well-being by assessing parent and child beliefs [266, 272]. Providing opportunities for children to express feelings and concerns through empathic listening and exploring their spiritual experiences and journey using interventions such as creative and expressive arts, story-telling, and prayer can help the child manage strong emotions related to dying [273].

Ethical Imperatives in Symptom Assessment and Management

Resolving the Ethical Dilemma in Pain and Symptom Management

While the impressive gains in overall survival in childhood cancer should be celebrated and advanced in the coming decades, it is clear from the growing body of symptom research that there is a substantial treatment-related symptom burden over the course of therapy that has substantial effects for roughly half of children and

adolescents with cancer. Symptom researchers have poignantly captured what children and parents have elucidated through interviews and surveys, the outward face of strength and coping that many families put forward as they fight for survival, while within they harbor the belief that symptoms are an accepted, tolerated, and even necessary part of surviving the disease [6, 29, 267], contributing to underreporting, inadequate assessment, and suboptimal management of symptom distress [17, 18, 55]. To achieve ethically sound symptom assessment and management, there is a need for further research and clinical efforts toward understanding child and family symptom experiences as well as increasing provider knowledge in symptom assessment and management.

Standardized Symptom Assessment

To maximize well-being across the childhood cancer continuum, the starting point is systematic assessment of symptoms across the trajectory of care using patient-reported outcome measures (PROM). Symptom research to date has been focused on using symptom PROM to describe the prevalence, severity, and distress of cancer symptom experience as it relates to quality of life and functional and emotional outcomes of cancer treatment. Attention now should shift to the clinical application of symptom assessment PROM instruments. Wolfe [53] reported on the results of a randomized, controlled trial evaluating the use of a symptom screening tool in children with advanced cancer that included feedback of symptom reports to oncologists. Children and parents completed a standardized symptom assessment scale as frequently as once a week, and results were emailed to the provider when predetermined symptom scores were exceeded; however feedback did not significantly affect symptom trends. There are a number of questions to explore when moving a research measure into a clinical setting. How will the instrument be distributed? How frequently should it be given? Who reviews the instrument with the family? What do symptom scores mean clinically? Further research and quality initiatives focused on the implementation of symptom assessment instruments in clinical care and their effect on symptom management will go a long way toward improving child and family quality of life.

Symptom Management

As with assessment, efforts to improve symptom management should be a priority area in pediatric oncology research. Pain is the most commonly managed symptom in children, with opioids being the most frequently prescribed. Despite this fact, there are no randomized trials of opioid pain management outcomes in children with cancer [162]. Similarly, the incidence of opioid misuse in children and adolescents with cancer is currently unknown [274]. The current regulatory climate regarding opioids in pain management requires substantial assessment and monitoring of pain and a desire to reduce opioid exposure by increasing availability of integrative medicine and other non-pharmacological interventions [275, 276]. Pediatric cancer research institutions should take the lead in supporting comparative

effectiveness trials of opioid management strategies in children with cancer to assure pain is managed effectively, safely, and consistently across institutions.

Another area of improvement with regard to symptom management is the creation of multimodal management plans. Symptoms are often intertwined and it is difficult to determine what symptom is inciting other symptoms. Including non-pharmacologic (i.e., distraction or guided meditation) and pharmacologic interventions in symptom management plans may lead to lower overall doses of analgesics and adjuvant medications. Again, studies on the use of multimodal and integrative medicine interventions and their effect on symptom burden would provide valuable evidence for symptom management planning.

The Ethical Imperative in Symptom Management

The continued strive for cure in childhood cancer certainly meets the ethical requirement of beneficence, to do the right thing by children with cancer through systematic clinical research aimed at improved survival and ultimately cure rates for the leading disease-related cause of death in childhood [277–280].

However, if the scale is tipped solely to the beneficence of cure, there is a breach of the ethical requirement of non-maleficence, to do no harm, if we do not simultaneously seek to develop and integrate symptom and quality of life outcomes in treatment protocols and clinical practice across the cancer trajectory. The current body of symptom research has clearly demonstrated the presence of a complex symptom experience over the course of cancer treatment and into survivorship and end-of-life care. Increasing symptom management outcomes research and implementing standardized symptom assessment and management within cancer treatment protocols address both high-quality cancer care and minimization of harm to patients and families.

Lastly, the principle of justice in childhood cancer requires equal access to care that is appropriate to the child's health-care needs. The relative lack of symptom and psychosocial outcomes research as well as evidence-based guidelines in cancer symptom management leads to wide variability in symptom management across care providers and settings, quite possibly affecting overall survival outcomes [281].

An ethical dilemma exists in the reality that childhood cancer cannot be cured without incurring suffering related to risks of symptoms [53, 282], which patients and parents accept as the price to pay for cure. Few standardized symptom management processes exist for children receiving treatment to maximize quality of life across the trajectory of care regardless of disease or location of care [162]. Recent findings from an expert panel on pediatric oncology care recognized this dilemma and proposed that in addition to efforts aimed at new therapeutic options for cancer treatment, there should be an equal focus on integration of psychosocial and palliative care with disease-directed therapy to ensure patient and family well-being across the continuum of care [53]. The remedy then, for the dilemma of children and families suffering as a reality of cancer care, is to hold both disease treatment and symptom management equally important in cancer research and clinical manage-

ment by advancing comprehensive cancer care as the gold standard [53, 283]. Parent and provider engagement in shaping symptom reporting, and improving management of the child and family's symptom experience and quality of life over the course of care is an important first step toward achieving comprehensive, high-quality patient- and family-centered symptom assessment and management [51] that will minimize suffering and potentially avoidable harms.

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Chapter 10
Intercultural Competence and Communication over Language Barriers

Pernilla Pergert and Elisabet Tiselius

Introduction to Intercultural Healthcare

Intercultural healthcare refers to when people of different cultures and languages communicate and interact with each other in healthcare [36].

In this chapter, we will discuss intercultural competence. We prefer the term *intercultural* as it stresses that at least two different cultures are involved in the interactive process. Many authors, some of them referred to in our text, use the term *cultural*. In our opinion, there is a risk that the focus will then only be on the other person's culture and not all the different cultures involved in the process.

In our text, we will use *intercultural* when we discuss our own model, but we will retain *cultural* when we refer to authors who use that term.

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A *culture* is the rules and values that we learn and share in a group; cultural values are passed on to coming generations but are also dynamic over time [32]. The features that a cultural group have in common vary: for example, the group could share a place (a country, region, or workplace) or a professional area (nursing or medical). Thus, we all belong to various cultural groupings, and all healthcare could be considered intercultural. An individual's culture must be understood in terms of his/her interactions in various groups and as a process of shared values [28]. However, the literature on cultural care has had a tendency to equate culture and ethnicity and has thus failed to identify other cultural aspects that might be even more crucial for the formation of values, such as education and the socio-economic situation.

There has been a tendency to acknowledge the cultural identity of the other, especially of people belonging to minority ethnic groups and failing to recognize one's own culture or the healthcare culture [15]. In a small study performed in paediatric care in Sweden, nurses were asked if they believed that their communication with the caregiver was influenced by their own culture [27]. The results show that the majority of nurses (n = 32/36) perceived that their own culture did not ("not at all"/"fairly little") affect their communication. If there is little awareness about how one's own culture and the culture of the healthcare system influence intercultural interaction, there is a risk of cultural imposition [12].

Our cultural rules define how we ought to act in healthcare interactions. They affect for instance our views of the disease/illness, our expectations of the healthcare system and healthcare professionals' roles, our views and practices of child-rearing, and how the body is cared for after death, as well as the language we use to talk about illness and death, the family's decision-making process, and the appropriate expression of pain and grief. Cultural diversity can constitute obstacles in intercultural interactions [42] especially if there are major differences in rules and values, for example, when there are major differences in emotional expressions of anger or grief [42, 44]. Even though all encounters in healthcare are intercultural, some encounters entail greater cultural disparities than others.

Intercultural Encounters in Healthcare

There are various conditions and actions that can influence the quality of intercultural encounters in healthcare. Potential obstacles to communication and interaction include linguistic, cultural, religious, social, and organizational ones [42]. These obstacles could be present in any intercultural encounter. For example, families entering paediatric cancer care are likely to experience linguistic obstacles related to the medical terminology used; however, if families do not at all speak the same language as healthcare professionals, this could be considered a greater linguistic obstacle [42]. Thus, some intercultural encounters will include extensive obstacles related to major differences between the parties, for example, if a family comes from a rural area in a foreign country, has another religion, speaks another

language, and has a lower level of education compared to the healthcare professionals from the majority population in an urban area of the new country. Furthermore, though cultural values and rules influence all interactions in healthcare, in some situations, critical values are at stake and can differ, for example, in regard to the child's growing autonomy, pain relief, and truth-telling about diagnosis, treatment, and prognosis [5].

In all interactions, including intercultural care encounters, we show or present an outer appearance in an act of facading [39]. Other people's interpretations will be influenced by our facading, and in intercultural care, this interpretation might be difficult and can possibly lead to misunderstandings. Facading is a conscious or unconscious strategy used not only to present oneself but also to protect oneself and others in care. Facading includes showing roles, social identities, and affiliations to groups by using different attributes such as religious or professional attributes and clothing [39]. Facading is used to protect oneself and others in emotionally demanding situations [39]. For example, parents with a foreign background have been found to hide vulnerability and sadness through strength facading, while nurses have been found to present a professional facade in order to protect professional composure when they meet overwhelming emotional expressions in paediatric care [44].

Cultural rules and values influence how we think and act in specific situations and guide our social interactions including facading and façade interpreting. Furthermore, Pergert et al. [40] showed that culture influenced what approaches families used in their interaction with healthcare professionals in paediatric cancer care and how they understood and dealt with paediatric cancer (cf. [55]). Thus, to provide culturally congruent and meaningful care, intercultural competence is essential.

Intercultural Competence in Healthcare

Campinha-Bacote [14] described cultural competence as a process in healthcare interactions and systems, aiming to increase equity and reduce disparities in care (cf. also [47]). There has been a discussion on whether cultural competence could be negative in the sense that it gives more power to healthcare professionals and "risks reifying appropriating rather than respecting and engaging the other's life-world" [28, p. 157]. For example, randomly assuming, rather than asking, that patients with a Muslim background do not eat pork can result in us not making an effort to find out the practices and beliefs of the individual patient. We would argue, contrary to Kirmayer [28], that in the same way as it is desirable that healthcare professionals have ethical, medical, and/or nursing competence, it is also desirable with intercultural competence since it is a crucial condition for increased equity in care.

Cultural competence shares core components with patient-centred care because both aim to see the patient as a unique person and to provide care congruent with the individual patients' preferences [47]. Furthermore, some strategies are shared; thus

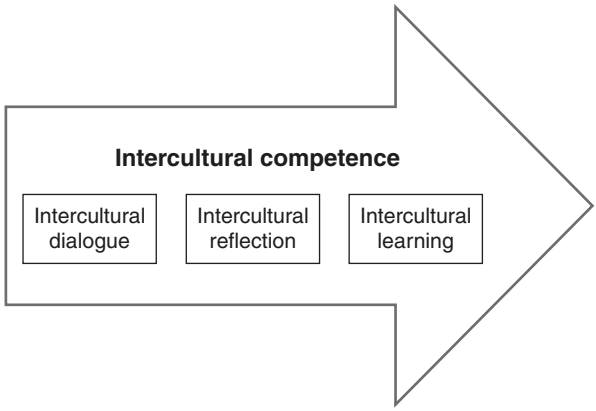

Fig. 10.1 The process, shown with the arrow, of intercultural competence with a relational ethics approach includes three stages

operationalizing patient-centred care will result in a more culturally congruent care [16]. Healthcare organizations focus more strongly on patient-centred care and on safety and quality than on cultural competence [16]. However, patient-centred care needs to be combined with a focus on cultural and linguistic differences to achieve a more equal care and to reduce disparities in care [47]. Campinha-Bacote [14] argues that cultural competence is essential to provide patient-centred care but that patient-centred care is difficult when the values of patients are in conflict with the values of the healthcare professionals and systems.

Cultural diversity can lead to conflicts concerning fundamental values; for example, regarding the patients'/families' right to information and views on truth-telling [42]. Thus, intercultural healthcare requires that professionals have opportunities and skills to deal with value conflicts. Cultural competence with a reflective praxis can assist in the development of knowledge about how to reduce inequalities in healthcare [10].

There are many different descriptions of cultural competence but most of them include cultural sensitivity, knowledge, and skills. Instead of these different approaches, we present a relational ethics approach to intercultural competence (Fig. 10.1), which stresses the importance of an interactive process for achieving an interculturally congruent healthcare.

A Relational Ethics Approach to Intercultural Competence

The basic ideas of relational ethics are that ethical practices exist in relationships [4], the context is important, and true dialogue is the core [3]. The same is true for the process of achieving intercultural competence, which includes intercultural dialogue, intercultural reflection, and intercultural learning (Fig. 10.1).

Relationships, including intercultural relationships in healthcare, depend on trust, which is built in relationships from a desire and a motivation to understand

and know the other [42]. The concept of cultural desire has been suggested as the most basic part on which cultural competence is built [13], and we would argue for the relevance of desire to know and understand the other, to build trust, and to create space for dialogue.

Intercultural Dialogue

Through dialogue, ethical issues in the care situation are addressed with the patient and the family. It is not only the patient's and the family's cultural views that are explored and taken into account but also those of the healthcare professionals. The dialogue should aim for a shared view and some kind of agreement. A shared view does not mean that we have the same view but that we are aware of and can see each other's views. Thus, the agreement could include a way to deal with the different views or opinion. Furthermore, respect should be shown to both reason and emotion as communicated by the involved persons [3]. Space for dialogue is essential and needs to be facilitated in the healthcare organization to create partnerships in care and through dialogue, perspectives can be enriched when striving for common meanings. The enrichment lies in having a fuller understanding of the situation and the different views, although it does not necessarily lead to the same perspectives or views.

The dialogue of relational ethics has many similarities with the four steps that have been described by Kleinman et al. [30], as presented in Box 10.1. In the first step, the patient's explanatory model and expectations are explored using open questions. Examples of questions for exploring the explanatory model of patients according to Kleinman et al. [30], adapted to the paediatric context and the exploration of the parents model, are presented in Box 10.2. These questions could also be adapted and used when, for example, the child suffers from nutritional problems or other side effects from the treatment. In the second step, the model of the healthcare professionals is articulated, before both these models are compared to find similarities and differences. Finally, the models are negotiated with the aim of finding shared models and common understanding. According to Kleinman et al. [30], this last step could be the most important one to promote trust, compliance, and patient satisfaction. Furthermore, in the case of language barriers, a dialogue with the family on how to best manage these barriers is needed.

Box 10.1 Steps in the dialogue [30]

1. The patient's explanatory model is explored.
2. The healthcare professionals' explanatory model is articulated.
3. The two models are compared.
4. Negotiation of models with the aim of finding shared models and common understanding.

Box 10.2 Open questions adapted from Kleinman et al. [30]

1. What do you think has caused the problem (sickness or side effect) that your child has?
2. Why do you think the problem started when it did?
3. What do you think the problem does to your child?
4. How severe is your child's problem?
5. What kind of treatment do you think your child should receive?
6. What are the most important results you hope that your child receives from this treatment?
7. What do you fear the most about your child's problem?

There is a tendency in intercultural healthcare to accept and tolerate cultural arguments without entering a true dialogue with the family, even though professionals may think that these arguments are immoral [45]. Reasons for this could be that healthcare professionals are afraid to be seen as racists with prejudice and intolerance of other cultures [42]. For example, when parents say that they do not want healthcare professionals to speak with their sick child about the diagnosis or their dying child about prognosis/dying because of cultural values and rules, healthcare professionals may tolerate this and end up in a situation of acting against their own values, or they may enter into a dialogue with the parents [45]. In the dialogue, the cultural values and beliefs of the family are further explored, for example, by asking the family what they think that their child already knows. After that, healthcare professionals need to be brave enough to articulate their evidence-based knowledge, experience and beliefs that are relevant to the situation. They might find both similarities and differences when comparing the different beliefs, and in the dialogue they can negotiate a common understanding so that they can agree on actions that are congruent and meaningful to all.

An intercultural dialogue with the patient/family is an essential process for intercultural competence in social interactions; however, ethical issues in the care situation also need to be addressed in a dialogue with oneself and/or co-workers through intercultural reflection.

Intercultural Reflection

Intercultural reflection is an ongoing process of trying to understand one's own values and cultural beliefs and the values of the other [43]. Such reflection also includes trying to understand and question the values of the healthcare context and the norms that prevail. The aim of this critical reflection is to improve care and achieve equality in healthcare [10].

Box 10.3 The modified version of the Karolinska model for ethical analysis [7]

1. Briefly present the case by describing the present situation.
2. Identify the ethical problem in the case – formulate the problem as a question beginning with "Should we …".
3. Present the relevant facts, whether medical, nursing, legal, cultural, religious, existential/spiritual, and/or psychosocial.
4. Identify the parties involved, including the patient, parents, siblings, relatives, and healthcare professionals.
5. Identify what is at stake: interests, values, and moral principles.
6. Identify available action alternatives and find different solutions.
7. Evaluate each alternative action by determining their strengths and weaknesses.
8. Carry out the ethical argumentation: weigh the different interests, values, and moral principles and try to reach an agreement.

Healthcare professionals can reflect by themselves but have been found to want inter-professional consideration, including teamwork and reflection, to deal with ethical concerns in paediatric care [5]. A reflective practice in the organization could be facilitated by implementing regular sessions of ethics case reflection (ECR) in the inter-professional team [7]. These sessions aim to explore an ethical problem in a case and the values that are important in that specific case. An ethicist could facilitate the session, or a communicational model for ethical analysis could be used to explore the problem. One example of these models is the Karolinska model [7]. A short description of each of the eight steps in the modified version of the Karolinska model for ethical analysis is presented in Box 10.3 [7, pp. 89–90]. Ethical and intercultural learning can be achieved when healthcare professionals listen to others articulating their moral arguments in a case, but also from having the opportunity to formulate their own values and arguments of importance in the case [6]. When perspectives are clarified, care can be consolidated, and a shared view created [6].

ECR sessions should be used to challenge perspectives and explore situations with intercultural differences because that will lead to intercultural learning in the relevant context [10]. A situation laden with intercultural differences might, for example, be the time of diagnosis, where cultural values influence the way cancer is understood. The biomedical view is that paediatric cancers most often are treatable diseases, that is, biologically defined abnormalities of the body, while the patient might understand it as an illness, that is, a socially and culturally influenced experience of sickness that the patient is suffering from and that others have died from [30].

An effect of intercultural dialogue and intercultural reflection is intercultural learning.

Intercultural Learning

Intercultural learning is an ongoing process and includes learning about one's own values and practices as well as the other's cultural rules and beliefs [43]. Intercultural learning will change the learner and also the context [10], leading to new learning opportunities. In the literature on cultural competence and cultural knowledge, cultures are portrayed as dynamic, but the knowledge about different cultural groups is still presented as if they were static. Knowledge about cultural values and value systems is essential [31] in intercultural care: for example, healthcare professionals need to be aware of various views on facading-sensitive issues and emotional facading [39]. However, a general knowledge of cultures may lead to stereotyping and objectification of the other and may preclude an authentic dialogue and opportunity to get to know the other [61].

Learning about one's own values is similar to cultural awareness, as defined by Campinha-Bacote [12], which includes exploring one's own values, prejudice, and beliefs. Learning about one's own practices includes learning about one's own facading and possible interpretations [39]. Because one's own cultural identity is dynamic, influenced by interactions and experienced situations, a process of learning is needed.

Not only does the individual healthcare professional need to engage in intercultural learning, but also the healthcare organization needs to facilitate intercultural learning, for example, by using organizational tools such as allocating time for intercultural care encounters [43]. Healthcare organizations need to provide opportunities for intercultural learning and become learning organizations. Five practices have been described as the core of learning organizations, including personal mastery, mental model, shared vision, team learning, and systems thinking [50]. Mental model, team learning, and shared vision could all be achieved through intercultural reflection in the inter-professional team. Every organization is a result of how its members think and interact, and such patterns of interaction can be changed when the team learns together and reaches a shared vision [50].

As described above, the process of intercultural competence requires not only intercultural reflection and learning but also authentic dialogue. To be able to enter into a dialogue with families, interaction and communication needs to be tailored to the individual family's needs and circumstances. When the family has limited language proficiency in the majority language, tools to communicate over language barriers are needed.

Intercultural Encounters in Healthcare with Language Barriers

> I met a family, and I interpreted for them for almost one whole year, until the child died. I was there from the beginning, all the way to the end. Sometimes I distanced myself from the family, because they became like my family. In the end, I did not know what role I had.

> I wanted distance, but at the same time it was about a child. I have children the same age. Sometimes I tried to create a distance, but I became like a family member. I also became part of their family because we come from the same country and speak the same language and I liked helping them. I felt that it was my duty, my cultural duty, too. (Interpreter in interview)

This narrative is from one of our interviews with interpreters in paediatric cancer care [20]. The narrative has many layers and questions. What can you expect from an interpreter? What can a family expect from an interpreter? Do interpreters have a cultural duty? The interpreter is caught in the cross-fire of intercultural communication, and this section will discuss such intercultural communication in both healthcare in general and childhood cancer care in particular. Part of intercultural learning is communicating over language barriers via interpreters; we will discuss intercultural communication using such interpreters as a tool in intercultural dialogue. The concept of intercultural communication is not confined to communication over language barriers; on the contrary, it includes all types of communication with other cultures, whether from another country or from another professional area such as the medical area. This section will, however, deal with the language part of intercultural communication, more specifically interpretation.

Intercultural communication theory focuses on the interactive side of communication and on information sharing between different cultures and/or social groups [21]. Scollon and Scollon [49] posit intercultural communication as cultural differences between distinct cultural groups. Researchers in intercultural communication investigate the communicative practices of groups in interaction with other groups. The responsibility for the act of communication and meeting over language barriers thus lies on all the parties in the intercultural encounter. An important aspect of intercultural communication is the process of understanding and adapting to the other in order to enable communication between cultures, as described above in Box 10.1 in section "Intercultural Dialogue". Intercultural communication has been criticized for being divisive, assuming that distinct cultures are related to nation states and national languages [46]. In the present chapter, intercultural communication is defined as the type of communication that must occur when a patient and his or her family, with limited proficiency in the majority language, enter the hospital system and thus enter a generally unilingual and unicultural context.

Introduction to Intercultural Communication over Language Barriers

Today's globalization has an impact on all parts of society, the healthcare sector being no exception. Consequently, there is a growing field of literature and research on language barriers and their implications on healthcare. The literature shows that language barriers are perceived as a major challenge both for healthcare professionals and for patients/families who do not share a common language [24, 34, 35, 41, 42, 52].

In many countries, healthcare professionals are under, not only professional and moral, but also legal obligation to give the patients and their family adequate information about their illness and treatment. It is also common to provide as adequate information as possible to be able to obtain informed consent, as is for example often the case in Australia, Norway, and Sweden (cf. [23, 51, 53]). In the United States, informed consent is regulated on the state level. The obligation to provide information and receive informed consent can be traced to article 19 of the Universal Declaration of Human Rights [57], concerning the right to freedom of expression.

Linguistic and cultural differences create difficulties for healthcare professionals when they communicate with patients and families to give adequate information about the patient's condition, treatment, and prognosis [17]. This means that it is important from the perspective of both informed consent and family- and child-centred care to overcome such language barriers. One of the interpreters in our study said that "when the doctor has to ask, 'What don't you understand?' they don't have anything to say, they don't have any questions … nothing [!] because they don't know how to ask" [20, p. 142]. This is also confirmed by Davies et al. [17], who found that parents with low proficiency in the majority language are unable to participate in their child's care because they cannot communicate their needs, questions, and concerns. In addition, Gulati et al. [22] show that communication challenges make it difficult for parents to learn complex medical terminology and to participate in the care for their children. Similarly, Klassen et al. [29] found in a study from Canada that learning about paediatric cancer is hard for parents with limited proficiency in the majority language, due to complex medical terms and complicated treatment protocols.

Several researchers suggest that in order to improve healthcare quality and safety for patients with limited proficiency in the majority language, a dialogue with the family on how to best manage language barriers is critical – in fact, that it is just as important as the dialogue on the health problem itself [25, 52]. This can be seen as part of the process of the intercultural dialogue described in section "Intercultural Dialogue".

Intercultural Communication as a Strategy for Intercultural Competence

In a study by Pergert et al. [43], healthcare professionals mentioned four different tools for bridging barriers in the caring relationship with patients with low proficiency in the majority language: using non-verbal communication, using relatives as language mediators, using bilingual co-workers as language mediators, or using professional interpreters. Tate et al. [54] report almost the same strategies among prehospital professionals; the participants in that study reported that when dealing with emergency situations, they developed strategies such as using non-verbal communication or using either bystanders or multilingual co-workers as language mediators.

Coping with language barriers for healthcare professionals requires training, planning, and intercultural competence. Falling ill is something that neither patients nor their families decide to do, and patients cannot postpone their illness until their linguistic proficiency is high enough. It is thus the responsibility of the healthcare professionals to handle these types of situations. This is not an easy task, however. Jirwe et al. [26] found that although nurse students in Sweden take a course in "transcultural nursing", they still experience that the lack of effective communication leads to dissatisfaction with the caring experience. They conclude that effective communication is fundamental to satisfactory intercultural care encounters.

The importance of effective communication is also supported by Hernandez et al. [24], whose research shows that paediatric healthcare professionals show low self-efficacy when they provide care to patients with low proficiency in the majority language. They suggest that a standardized best practice for working with interpreters should be implemented. Massimo et al. [35] add that meeting the challenges with health migration requires that healthcare professionals acquire the skills for proper intercultural communication.

In order to cope with language barriers, it is therefore important for healthcare professionals to receive proper training in the use of interpreters, but also for interpreter services to become an integrated part of the healthcare context. If finding and booking an interpreter is cumbersome and time-consuming and if the interpreter who shows up turns out to not be competent enough, it is highly likely that bilingual staff, relatives, or even children will continue to be the preferred language mediators in the healthcare sector. Intercultural competence is thus not only knowing how to handle patients from different cultural backgrounds, but also knowing when to hire and how to use an interpreter. Schenker et al. [48] have shown that interventions are needed to improve the use of interpreters and that issuing guidelines is not enough. They further argue that increased access to professional interpreters, together with education for healthcare professionals about the interpreter-mediated event, might improve the quality and safety of care in clinical settings.

Interpreters and Interpreting Services

The term *interpreter* should be understood as a bilingual individual with training and (if available) certification to mediate between speakers of different languages. Interpreters work in the oral mode, meaning they are not trained or certified to translate written texts, unless they have specific qualifications for that. Interpreters in the healthcare context can work in *dialogue mode* (also called short consecutive) or *monologue mode* (also called whispered simultaneous interpreting). In dialogue mode, the interpreter will interpret short sequences (utterance by utterance) allowing the participants to converse with each other in a dialogue format. If one of the participants has a longer monologue – for example, the patient describing an anamnesis or the physician or nurse explaining a procedure – the interpreter may switch to monologue mode and render the monologue in a low voice immediately to the listening participant. Although this mode is time efficient, one should not always

expect the interpreter, or indeed the other participants, to be able to handle it. Simultaneous interpreting is a highly complex linguistic task, difficult to perform, and sometimes difficult to listen to and understand, and parties who find it hard to follow the interpreting in monologue mode can ask the interpreter to go back to dialogue interpreting.

There is strong evidence that professional interpreters improve communication, but with an increased migrant population, there is an increasing need for other ways of consulting interpreters. Interpreters cannot be expected to be on-site in every possible context [33], but other options are available, such as interpreting via telephone or video. Especially video interpreting is almost as reliable, in terms of patient safety, as an interpreter on-site, but it is important to note that conversations must be managed differently when the interpreter is not on-site, as the interpreter does not have access to the whole event. It is also important to understand that interpreting is not only about translating the words but also about understanding the context and bridging cultural differences [20]. Flores [19] found that optimal communication, the highest patient satisfaction, the best outcomes, and the fewest errors of potential clinical consequence occur when patients with low proficiency in the majority language have access to trained professional interpreters or bilingual healthcare providers. Lion et al. [33] found that video relay interpreting leads to better parent comprehension and decreases the risk of communication-related safety events as compared to telephone interpreting [33]. Given Flores's [19] findings, one can assume that if on-site interpreting had been part of Lion's study [33], that context would have even higher figures of parent comprehension as well as a decreased risk of communication-related safety events. However, as we argued above, Bischoff and Hudelson [9] found that it is not enough to have professional interpreters available to healthcare professionals to guarantee the use of professional interpreters. There seems to be a disposition among healthcare professionals to use professional interpreters only in the absence of other available options. This means that ad hoc language mediators are judged to be "good enough" even when the quality difference between trained interpreters and untrained language mediators is recognized [9].

Unfortunately, as shown by Abbe et al. [1] and Butow et al. [11], the quality of interpreted medical consultations differs greatly. Interpreters also experience dilemmas in the interpreted medical consultation. Those dilemmas consist of situations where the interpreters must choose between delivering accuracy versus assuring understanding between the parties, "only" translating versus choosing different types of cultural advocacy, and staying in a strictly professional role versus showing empathy or providing support [11, 20]. These dilemmas are similar to those of the healthcare professionals, but unlike the latter, interpreters are seldom trained in ethics and do not have professional supervision or support groups.

When reviewing the research on interpreting in healthcare, it becomes clear that healthcare professionals need training in using interpreters, in order to both create the most efficient intercultural communicative event and to ensure that they can handle the situation in the unfortunate event of the interpreter not living up to expectations.

How to Use Interpreters and What to Expect

The following section will provide practical information on the interpreted healthcare consultation (for a short list of the different steps, see Box 10.4). Different countries and healthcare systems have different ways of providing interpreters: for example, at some hospitals interpreters work in-house, whereas in many other contexts interpreters are booked via language service providers (cf. [2]).

The first question to ask is perhaps when you need an interpreter. The rule of thumb is that you will need an interpreter if you are not fluent in the patient's/family's language. You may notice that we stress that it is the healthcare professionals who need an interpreter – and indeed, you will need an interpreter to understand the patient/family just as much as they do to understand you. Unlike the patient/family, however, you are legally accountable for providing correct information and getting informed consent, and you will only be able to do that if you share the patient's/family's language or use an interpreter. Furthermore, you will need an interpreter for all types of different consultations, not only the physician's consultation with the patient. Pergert et al. [42] found that nurses' healthcare communication and information work is often done while performing other procedures such as changing an infusion. Unless interpreters are used to communicate with patients/families with low language proficiency in the majority language, the patients/families will lose this often crucial information.

Box 10.4 Steps in the interpreted healthcare consultation
Before the consultation

- Book the interpreter and inform him/her that she/he will be working at the paediatric oncology ward.
- Let the interpreter wait separately from the family.
- Brief the interpreter on terminology and possible emotional difficulties.

During the consultation

- Think about placement.
- Let the interpreter introduce himself/herself (see Box 10.5).
- Check that the language match is right.
- Everything uttered in the room must be interpreted.
- Remember that you are responsible for the conversation, while the interpreter is responsible for the communication.
- Do not pack one session with too much information; it's better to book an interpreter twice.
- Check that all parties have understood – ask the patient/family to summarize the conversation.

Whether the interpreter works in-house, remotely, or arrives for the interpreted event on-site, all interpreters need briefing. No matter how well educated or experienced the interpreter is, she/he will not know every word or every illness or every treatment, but after a quick briefing the interpreter will be able to provide much better service. It is also crucial for the interpreter to know whether the medical consultation is going to include bad news. The interpreter's time management as well as self-control will work much better if she/he is prepared for emotional challenges. Before the consultation the interpreter should not wait with the family/patient. Having to wait with the family/patient puts the interpreter at risk of not being able to keep the necessary professional distance during the medical encounter [20]. Furthermore, some cultural and language communities are small, and having interpreters and families meet before the medical consultation puts the interpreters in an awkward situation and compromises neutrality.

Professional interpreters will always introduce themselves in both languages and inform all parties that all communication is confidential. If the interpreter does not do that, ask him or her to do so as it puts the patient at ease, and you can also check whether the patient and interpreter understand each other well. You should always address the patient/family directly: do not say "Ask him if he would like to …?", but ask instead directly (while facing the intended recipient) "Would you like to …?". Remember that the interpreter should interpret everything uttered in the room. If you do not want it interpreted, you should not say it – this goes for everything from consultation with your colleague to a private phone call. Furthermore, if the interpreter does not interpret what a family member or the child says, you should ask him/her to do so. See Box 10.5 for an example of an interpreter introduction and a check on the parties' language match.

When you speak to the patient/family, you must keep your eye contact with them, and the interpreter should be placed so that she/he can make eye contact with either you or them. If for instance the interpreter needs to interrupt, eye contact will be the first tool the interpreter uses. Placement may seem unimportant, but it slightly shifts the power balance of the interpreted event (cf. [58]). For example, if the interpreter is placed as in placement 1 in Fig. 10.2, she/he will be placed alongside neither the family/patient nor the healthcare professionals, underlining the interpreter's impar-

Box 10.5 Example of an interpreter introduction

- *Interpreter:* Let me introduce myself. I am John Doe, your interpreter. I am impartial, and all communication is confidential. I will use first person singular (the "I" form) when I interpret. If I talk about myself, I will say "the interpreter". You should speak directly to each other. I will interpret everything that is uttered in the room, including phone calls and the like. I may take notes, but I will destroy them before I leave the room. Thank you.
- *Healthcare professional:* [To the interpreter] Thank you. [To the family/patient] Let me first ask you if you can understand the interpreter's language and accent.

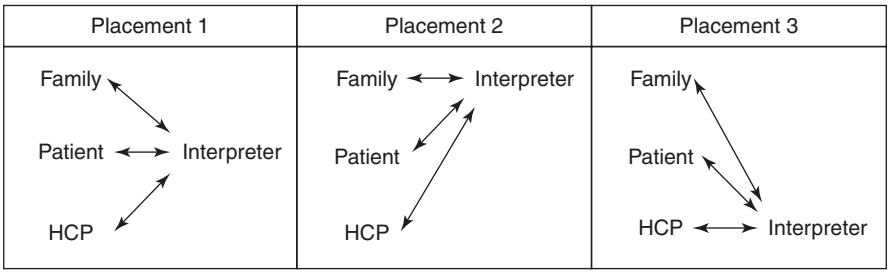

Fig. 10.2 Different placements of the interpreter in the interpreted healthcare consultation

tial position. Conversely, placing the interpreter as in placement 2 or 3 in Fig. 10.2 may indicate to the patient that the interpreter is either loyal to the patient or loyal to the healthcare professional or system.

Normally, you will speak one utterance at a time and let the interpreter interpret, but if the interpreter needs to interrupt you or the patient/family, she/he will do so by using eye contact as a first action. You do not have to change the way you are speaking, but do not whisper or speak in a very low voice, as the interpreter needs to hear you clearly. Also, if you have a dialect or accent, remember that it may be difficult for the interpreter, who has often learned your language as an adult. As healthcare professionals, you are used to jargon and highly advanced medical terms; when the family/patient has been in treatment for a while, they will also know that terminology. Nevertheless, you must still brief a new interpreter about the terminology, even if both you and the patient know this terminology, as the understanding will suffer otherwise since the interpreter may get unfamiliar terminology wrong. On the same note, if the interpreter asks you to explain or clarify, it does not mean that the interpreter has not understood: normally, the interpreter asks for clarification because she/he has an indication that the family/patient has not understood. Depending on the patient's academic and cultural background, you may have to explain basic terms, procedures, or conditions at a pre-school level. If the patient comes from a culture where internal organs are not talked about, for example, then it may be very difficult to understand the importance of a liver or getting biopsies from the bone marrow.

Always ask your patient/family if they have understood. You can find out how much they have understood by asking them to tell you, via the interpreter, about their child's/their own illness or treatment. The interpreter is responsible for the intercultural communication, but you are responsible for the healthcare consultation. This means that in situations where, for instance, the interpreter and the family seem to talk among themselves, you should ask for an interpretation. Sometimes healthcare professionals feel that they cannot control the information given to the patient [42]. If you feel that you lose control of the information flow or the communication, stop the conversation, go back to the information where you lost control, and ask for an interpretation. You should also be careful to not discuss the patient/family with the interpreter outside of the room; such a discussion would exclude the patient/family and challenge the interpreter's neutrality and confidentiality. It is also important to remember that there is often at least one person, other than the interpreter,

who understands everything being said in the room, and that is often the child [59]. Furthermore, it is not unusual that the child is asked by the parents to check the quality of the interpreter and help remember what was being said. This means that even with an interpreter present, the subsequent understanding of the interpreted healthcare event may heavily rely on how the child understood it. We would therefore stress the importance of booking an interpreter for follow-up consultations.

In addition to the two interpreting modes (dialogue or monologue), the interpreter should be able to interpret orally from a written text (known as "on-sight" translation), but you should never ask the interpreter to for instance help the family to fill out a form or read a text and then you yourself leave the room; if you do that, you will not know whether the family has understood what was read or filled out.

Using interpreters may take a little longer than consultations without interpreters, but Bischoff and Denhaerynck [8] found that interpreters help healthcare professionals better understand the patient's condition, making it possible to reach effective solutions and thereby limiting visits. When it comes to life-threatening illnesses or conditions, it is fair to assume that access to interpreters as intercultural communication tools is also likely to reduce life-threatening risks caused by language barriers [18].

As it may be difficult to get an appointment with an interpreter, or simply due to a lack of planning, there is a tendency that several different healthcare professionals take the opportunity to use the interpreter and inform the patient/family on a wide variety of topics [42]. This should be done with caution, though, as earlier research on monolingual patients has found that depending on the seriousness of the initial message, the family/patient will not be able to digest subsequent information. Once again, we would therefore like to stress that it is better to book an interpreter on several different occasions.

Other Tools for Communication over Language Barriers

Since qualified interpreters may be scarce, and as some situations may occur when no interpreter is available, it may also be important to go through other tools for communication over language barriers. It cannot be stressed enough that these other tools should be used as a final, ad hoc option, not as the standard go-to solution. Other tools for communication over language barriers may be to use digital tools like animated or spoken instructions or translations tools [60]. Digital tools are most ideal when they are tailored to the exact healthcare context, in this case paediatric oncology. They can then be used by patients/families to understand specific terminology or treatment and used as a prompt for follow-up questions or explanations. Online translation tools should be used with caution, however; Patil and Davies [38] found, for example, that only 57.7% of the translations of different diagnoses using Google Translate were correct.

Other tools that can be used to overcome language barriers include providing families with materials aimed at helping them understand key medical terms and concepts in paediatric oncology [1]. If such materials are developed, it is important

to remember that literacy may differ even within a family, and not all adult members of a family may be able to read in their mother tongue. Further, many languages do not have a standardized written form, which means that understanding may be hampered. Pictures may also be a way to describe different organs, body parts, procedures, or illnesses. Once again, it is critical to remember that different cultures may know and understand the body in different ways.

A final point concerns using colleagues or a member of the patient's family members as ad hoc language mediators. If you are using other healthcare professionals as interpreters or rely on them to handle all the communication with the family/patient, you put your colleague in a difficult position and risk giving him or her a responsibility she/he is not qualified for. There is a high risk that the family/patient will consider your colleague as their advocate and count on him/her to be their spokesperson. You also risk excluding the family/patient from having contact with your other colleagues.

Likewise, using family members as ad hoc language mediators challenges communication on many different levels. If a child acts as an interpreter, the power balance of the family is shifted, and the child takes the role of an adjunct adult, which risks putting the child in an even more vulnerable situation [37, 56, 59]. If one of the adults in the family translates, there is a risk that information is filtered and that the primary caregiver (often the mother) does not get all the necessary information. This is often because the ad hoc language mediator (perhaps the father) does not fully understand the information, does not deem the information important enough to pass on, or believes that the primary caregiver (for example, the mother) does not need the information.

Summary

Cultural diversity can lead to conflicts concerning our most fundamental values. Thus, intercultural healthcare requires that professionals have opportunities and skills to deal with value conflicts. Intercultural competence with a reflective praxis can assist in the development of knowledge about how to reduce inequalities in healthcare. A relational ethics approach for intercultural competence has been presented in this chapter. The basic ideas are that intercultural competence exists in relationships, the context is of importance, and true dialogue is the core. The components of intercultural competence include intercultural dialogue, intercultural reflection, and intercultural learning. Furthermore, intercultural communication is key for enabling intercultural dialogue and should continuously be developed through intercultural learning in the process of understanding the other. Healthcare professionals need to learn effective interpreting use as part of intercultural competence because professional interpreters have an impact on cultural learning, true dialogue, and mutual understanding in the intercultural healthcare context.

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Correction to: Advance Care Planning

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The copyright statement in the figure had been missed inadvertently and the same has been included as below.

1. The copyright line:
   "Copyright Aging with Dignity. All rights reserved" has been included in Fig. 8.4 of Chapter 8.

The updated online version of this chapter can be found at
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