Ethically Navigating the Transition to the Precision Medicine Era in Pediatric Oncology

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Advances in precision medicine offer hope for a future of improved survival rates and decreased treatment-related toxicity for children with cancer. In order to achieve these substantial goods for children, however, there must be testing and clinical trials in actual children. Pediatric oncologists and clinical research organizations who are navigating this frontier therefore must carefully consider when it is ethically justifiable to present newly diagnosed families with the opportunity to participate in experimental trials from the beginning of treatment as an equal alternative to a reasonably effective standard of care. This matter is complicated by a few important factors: the inherent risk of serious harm, including death, of research to participating children; the concerns regarding a physician scientist's conflicts of interest between scientific and clinical goals; and protection of parents' autonomy despite their potentially reduced decision-making capabilities following an emotional diagnosis for their children. In this paper, I argue that despite these challenges, further expanding access to clinical research in the pediatric population by offering opportunities to participate in promising research at the start of treatment promotes and protects the ethical principles of respect for persons, beneficence, and justice by enabling the holistic flourishing of participating children. I also offer three considerations as a first approximation for how this change can be incorporated into current practice.

Introduction

Pediatric cancer is the leading cause of death by disease in children in the developed world (1). Every year in the United States alone, over 15,000 children and adolescents are diagnosed with pediatric cancer, and nearly 2,000 die from the disease (1). Fortunately, the combined 5-year survival rate for the more than 100 unique forms of childhood cancer has dramatically improved over the past fifty years, rising from just 10% in the 1970s to over 85% today (2). While this immense progress should be celebrated, these cures often require long and intense treatment regimens of chemotherapy, radiotherapy, and/or surgery (2). Such aggressive treatment protocols are frequently accompanied by significant and even life-threatening long-term effects such as heart damage, infertility, secondary cancers, and both physical and cognitive disabilities (3). As a result, there is an urgent need for less toxic and more effective front-line therapies for children who are newly diagnosed with cancer.

Acute Lymphoblastic Leukemia (ALL) exemplifies this tension between increased survival rates and increased toxicity of treatment and will therefore serve as the clinical example through which I explore this controversial topic. ALL is the most common form of pediatric cancer, accounting for over 30% of diagnoses, and just a few decades ago it was considered a terminal illness (1). However, decades of clinical trials have consistently pushed the survival rate higher through the refinement of an increasingly aggressive multi-drug cocktail (4). Today, the 5-year survival rate for ALL approaches 92% for children between the ages of 0 and 14 and 77% for adolescents ages 15-19 (1). The now standard treatment regimen involves two to three years of high-dose intravenous chemotherapy, intrathecal chemotherapy (injected directly into the cerebrospinal fluid), and corticosteroid treatments (4). High-risk patients may also be subjected to cranial radiation, stem cell transplant, or immunotherapy (4). On one hand, this rapid progress demonstrates the power of clinical research to improve outcomes both for the study participants themselves and for future children who will benefit from an improved standard of care. On the other hand, achieving such immense gains in survivorship has made it increasingly difficult to justify clinical research in newly diagnosed patients that involves any significant departures from this ubiquitously aggressive standard of care, despite the undeniable need for better treatments and the rise of promising potential alternatives (5). Modern pediatric oncologists are therefore left with a challenging situation: how can clinical research be ethically employed to improve outcomes for as many children as possible without recklessly wagering these hard-earned gains in survivorship?

In this paper, I argue that clinical research organizations are morally obligated to offer possibly superior but inherently risky clinical trials as equal alternatives to a reasonably effective standard of care for children who are newly diagnosed with cancer, because offering children opportunities to participate in promising research from the beginning of treatment

ultimately respects their human dignity, potentially promotes their holistic flourishing, and serves the common good of developing better pediatric cancer treatments. Since I have chosen to specifically focus on the implementation of CAR-T therapy into the frontline treatment for pediatric ALL, I begin by discussing CAR-T's promising outcomes in treating similar diseases, and I examine why the commonly accepted best practices in pediatric clinical research have limited CAR-T's expansion into the newly diagnosed patient population. I then explore three different arguments against expanding access to such clinical research, including the inevitability of a physician scientist's conflict of interest, a parent's inability to make truly informed, rational decisions in the highly emotional period following a child's new cancer diagnosis, and the potentially unacceptable risks of forgoing the known risks of a proven regimen for an ultimately experimental approach in the particularly vulnerable pediatric population. Through analysis of each of these ethical challenges, I demonstrate how the ethical principles of beneficence, justice, and respect for persons which underlie many of these concerns may in fact be best upheld by expanding access to clinical research for newly diagnosed patients. I conclude by offering a first approximation for how pediatric clinical research organizations can move forward with future clinical trial design in a way which promotes both scientific advancement at large and the best interests of every individual child with cancer.

CAR-T and Pediatric Clinical Research Policies

CAR-T Therapy

To investigate the larger issue of the implementation of experimental medicine into childhood cancer treatment, I will specifically focus on the potential integration of Chimeric Antigen Receptor-engineered T cell therapy (CAR-T) into the front-line treatment regimen for pediatric ALL. CAR-T involves conjugating a patient's killer T-cells with receptors engineered to recognize an antigen specific to their form of cancer. Reinfusing these cells back into the patient activates his or her immune system to recognize and destroy cancerous cells while minimizing the damage done to healthy cells. This revolutionary therapeutic has not yet been tested in newly diagnosed children, but CAR-T has proven effective for children with relapsed or refractory ALL, with 80-90% of these previously highly treatment-resistant patients now achieving complete and often lasting remissions (6). Admittedly, CAR-T does have its own share of side effects, including short-term neurotoxicity and a potentially severe immune reaction called cytokine release syndrome (7). However, improved knowledge of acute symptom management, the apparent rarity of the long-term side effects, and the reduced treatment duration compared to the standard years-long regimen for ALL make CAR-T's risk profile superior in many ways to the current standard of care (7).

Current Best Practices for Pediatric Clinical Research

Despite CAR-T's potential to revolutionize ALL treatment, its investigation in newly diagnosed children has been limited by the conventionally risk-averse interpretations of current best practices in ethical pediatric clinical research design. Notably, the widely accepted Belmont Report dictated that clinical research involving human subjects must always promote the three ethical principles of respect for persons, beneficence, and justice (8). In other words, clinical researchers must treat participating patients as ends in themselves above their role as experimental subjects. Additionally, the principle of beneficence requires that researchers both minimize potential harms (like long-term side-effects or higher chances of relapse) and actively promote the well-being of a participating subject. Lastly, researchers must carefully consider how the injustice of exploiting a child's vulnerability can be avoided while still promoting the justice of allowing children equal access to modern scientific advancements. Each of these basic principles are left intentionally vague in the Belmont report, but concerns about the difficulty of upholding them in the pediatric population have generally restricted the diversity of clinical research options available to children as compared to those available to adults.

The Children's Oncology Group (COG) has led the way in interpreting these basic ethical principles for children with cancer (9). As the world's largest clinical trials group of its kind, the COG requires that all proposed clinical trials undergo a series of external reviews by the NIH's National Cancer Institute, hospital-affiliated Institutional Review Boards, and Data Safety Monitoring Boards (10). This lengthy process ensures that any proposed research is designed in the scientifically and ethically rigorous fashion that this especially vulnerable patient population requires. Furthermore, the COG policy dictates that to minimize concerns of beneficence and nonmaleficence, all experimental drugs must first be tested in Phase I or II studies assessing dosage and efficacy in patients with treatment-resistant disease who are unlikely to be cured with conventional protocols (10). Before even considering opening a clinical trial to assess efficacy in newly diagnosed patients, there must be strong evidence to suggest that the proposed treatment will be at least as effective as the current standard of care (10).

Such well-meaning but strict limitations on clinical

research in newly diagnosed children have significantly hindered the implementation of twenty first century advances in precision medicine into frontline pediatric cancer treatment. Notably, there are currently only two therapeutic clinical trials open to children with standard-risk, newly diagnosed pediatric ALL in the US, both of which merely add a monoclonal antibody to the standard of care. While this approach of only adding drugs to an established regimen minimizes the chances of inadvertently decreasing survival outcomes through more radical protocol changes, it arguably inflicts more harm on children who must now suffer the side effects of multiple different medications. This precedent would suggest that the COG would only ever consider offering CAR-T to newly diagnosed children with ALL in combination with the standard treatment regimen, thereby potentially increasing survival rates but only amplifying the physical and emotional burden of an intensive frontline treatment. In order to reap the full toxicity-sparing benefits of modern clinical advances like CAR-T, the COG must reassess which of their policies are necessary protections for children and which are merely barriers in the development of safer, more effective cures.

Concerns of Respect for Persons: The Dual Duties of Clinical Researchers

Conflict of Interest as a Violation of Respect for Persons

An important source of concern involved with opening clinical trials involving CAR-T to newly diagnosed patients is the undeniable reality of a physician scientist's conflict of interest when enrolling patients in clinical research. Norbäck et al., for instance, note that due to the rarity of any particular type of childhood cancer diagnosis, there is often competition from several recruiting clinical trials to enroll patients (11). Consequently, physician scientists have professional motivations to persuade families to consent to research as a means to advancing their careers and gaining respect from other researchers, regardless of whether that trial is best suited for a particular child (11). Additionally, pharmaceutical companies have strong incentives to promote the widespread application of an expensive drug like CAR-T, which must be uniquely designed for every patient and would therefore cost families and insurance companies upwards of $620,500 in the first 90 days of treatment alone (12). The commonplace collaborations between researchers and industry may cause these corporate motivations to influence a physician-scientist's decisions to encourage enrollment in a clinical trial. Beyond these ulterior professional motives, many physician scientists simply wish to relieve children's suffering and use science to improve the offerings of modern medicine, which are generally positive aims but may obscure thoughtful consideration of what is best not just for all children, but for a unique patient. While it is generally accepted that research interests do not inherently conflict with a physicians' ability to provide excellent patient-centered care, one must wonder how effectively physician scientists could compartmentalize their distinct duties to their patients and to the greater scientific community when deciding whether to offer experimental therapeutics to newly diagnosed patients (13).

These concerns about how a physician scientist's conflicts of interest may infringe upon respect for persons are rooted in Kantian ethics. While consequentialist logic may be used to morally justify actions which promote the greatest good for the greatest number (such as offering an experimental therapy in hopes that it would advance survival rates, promote a scientist's career, and yield profits for the pharmaceutical industry, even if it potentially endangers some trial participants), Kant argued that acting in accordance with one's moral duty—rather than on the basis of an action's ultimate consequences—was the only way to make truly ethical decisions. He wrote that individuals must "act so that you treat humanity, whether in your own person or in that of another, always as an end and never as a means only" (14). In other words, even if researchers understand that some newly diagnosed patients must participate in clinical research if we are ever to dramatically improve the standard of care for future children, Kantianism would dictate that the interests of a researcher must always be secondary to the interests of a patient as an end in themself. Therefore, if there is any question as to whether a physician scientist could ever completely compartmentalize their professional interests as a researcher from their duty as a physician, then Kantian moral theory may be used to argue that even offering this type of research treats children (or at least highly risks treating children) merely as means to the end of scientific progress and is thereby unethical in all circumstances.

Natural law theory offers another framework from which to understand this argument about the potential for clinical research to degrade the dignity of the human person. Like Kantian ethics, natural law theory takes a strong position against strictly consequentialist moral theory, noting the potential for injustice for individual persons when striving for the greatest good and the difficulty of determining what exactly that would be. According to this approach, "if the action itself is unjust, it would be morally wrong to perform it even if it were conducive to the greatest pleasure or happiness of the greatest number" (15). Alternatively, natural law theory dictates that just actions must respect each individual as

possessing inherent human dignity (15). Regardless of a child's age or ability, their mere personhood dictates that any action affecting them must honor their dignity by promoting their basic human goods (15). In other words, even if a physician had professional motivations to offer enrollment in a clinical trial and truly believed that this research would eventually lead to the best outcomes for the most children, he or she could not uphold the respect for persons principle by offering this research as a therapeutic alternative if any given child subject's potential risk or benefit is unknown.

Clinical Research as a Vehicle for Promoting Respect for Persons

While this principle of respecting the wholeness of an individual is indeed of utmost importance in conducting ethical clinical research in children, I argue that the goal of advancing science is not mutually exclusive with the duty to provide the best possible patient care. Notably, the same ethical concerns of conflict of interest also apply in adult populations, but due to looser restrictions about clinical trial design for consenting adults, researchers have been able to enroll newly diagnosed adult patients on CAR-T trials with extremely promising results. A recent clinical trial in adult patients with newly diagnosed Diffuse Large B-Cell Lymphoma, for example, found that survival rates significantly increased from 40% with standard chemo-immunotherapy to 78% with CAR-T alone (16). This result suggests that reducing or even eliminating chemotherapy in exchange for CAR-T as part of front-line ALL treatment could also improve survival outcomes and spare toxicities for newly diagnosed children. Therefore, expanding clinical research opportunities to children does not violate the Kantian position on respect for persons, because the potential benefits to a participating child mean that even when their health data is being used to promote the greater good of scientific advancement, they are not being treated as "means only." Rather, their participation would serve the two non-conflicting and equally valuable aims of advancing science through the means of clinical trial participation and respecting pediatric patients as ends in themselves by giving them access to what may in fact be the best possible care. Such research also promotes the natural law theory conception of respect for persons by acknowledging how children have the same moral worth as adults and are therefore entitled to the same opportunities to promote their basic human goods through clinical research. As long as clinical researchers are aware that their principal duty is to treat a given child, whether or not his or her parents consent to clinical research, concerns about respect for persons need not prevent pediatric oncologists from seeking better treatments for all patients by offering to enroll children as research subjects.

Concerns of Justice: Respecting Parental Autonomy

Inadequate Informed Consent as a Violation of Parental Autonomy

An additional limiting factor in the expansion of clinical opportunities for newly diagnosed children is the difficulty of obtaining informed parental consent in this population. In the past, the COG has mitigated this challenge by repeatedly emphasizing that the decision to enroll in a trial is completely up to the parents, even if physicians genuinely believe that trial participation would benefit the child (10). Emphasizing parental duty over physician expertise in this way reflects a Kantian understanding of parental duty. Specifically, Kant wrote that parents automatically "incur an obligation to make the child content with his condition so far as they can" (17). In other words, by virtue of having brought this new life into the world, parents gain an unbiased perspective and an irrevocable duty to promote their child's well-being (17). Still, parents cannot exercise this duty without being able to provide truly informed and purely rational consent, because as Kant would claim, "only a rational being has the capacity of acting according to the conception of laws'' (14). This idea has made the pediatric research community particularly mindful of how best to communicate information about clinical trials to parents who lack scientific expertise but who must serve as the final decision-makers regarding their child's participation due to their intimate knowledge of what is best for their child.

In reality, however, attempts to instill complete parental understanding of basic research principles often fail. Alahmad, for example, noted how the deeply emotional state immediately following a child's cancer diagnosis may impair the rationality of parental reasoning about the risks and benefits of clinical trials (18). For example, researchers have described the prevalent issue of therapeutic misconception, in which parents fail to understand the important distinctions between an approved course of therapy and an experimental treatment (18). Furthermore, parents often struggle to grasp basic research principles like randomization into experimental versus control groups, and they often forget even being given the choice to not participate in a proposed study (18). Such persistent difficulties in obtaining truly informed consent have traditionally been accepted as unfortunate but ultimately relatively minor risks when enrolling pediatric patients on trials with a similar risk profile to the standard of care. However,

if clinical research groups considering offering CAR-T as a front-line therapeutic alternative cannot even fully ascertain the risks of offering this treatment to a new patient population, then how could non-expert parents ever be expected to do so? As a result, one could argue that presenting high-risk experimental therapies like CAR-T to newly diagnosed patients who are likely to survive with standard treatment would be unethical due to the injustice of violating a parent's autonomy by pressing them to make life-changing decisions in the vulnerable period following their child's diagnosis.

Expanded Therapeutic Offerings Can Promote Parental Autonomy

I argue, however, that this practice of withholding clinical trials out of fear that parents cannot rationally provide informed consent only infringes upon the parental autonomy to make these choices at all. Instead, clinical research organizations can allay these concerns through proven methodologies of maximizing parental understanding. A meta-analysis investigating informed consent in pediatric surgery research, for instance, demonstrated how holding multiple conversations, tailoring information to a given family, and including the child involved in discussions regarding their care can improve both parents' and physicians' satisfaction with the informed consent process (19). Additionally, a group of parents of children with leukemia suggested that providing families with as much time as possible to make critical decisions, taking extra care to clearly explain the differences between the proposed trial and the standard of care, and tailoring the content and communication styles of each informed consent conference to a particular family's needs would have made them more comfortable with the decision-making process (20). While ensuring informed consent in the stressful period directly following diagnosis will always be challenging for pediatric oncology teams, the knowledge that there are multiple actionable steps for clinical research teams to employ to facilitate this process should comfort those who fear it to be an impossible task. Even these efforts may never guarantee completely rational decision-making given the difficult circumstances, but depriving parents of the opportunity to make this choice in the first place ubiquitously violates their autonomy and should therefore never be considered as the more just alternative.

One must also consider how parents can in some circumstances best exercise their autonomy by choosing to provide trust-based rather than informed consent. A Swedish study, for instance, reported that distressed parents of newly diagnosed children are easily convinced to provide consent for clinical research (11). Many parents choose to put their full faith in the medical team's expertise and request to not even to be told the often overwhelming details of what their decision entails (11). While this dismissal of relevant information conflicts with an interpretation of autonomy resting upon informed decision-making, Kongsholm and Kappel note that trust-based consent can also be a perfectly valid form of rationality (21). A parent should not be expected to understand a doctoral degree's worth of scientific information in the days following their child's tragic cancer diagnosis in order for their rationality to be respected. Consequently, as long as all relevant information is made available to those parents who desire it, physicians may accept that a parent's choice to put their trust in an expert exemplifies rather than degrades a Kantian conception of parental autonomy. Therefore, clinical research organizations can best address concerns of justice in pediatric research by recognizing that parents always deserve the opportunity to be involved in the decision-making process during their child's treatment, even if that means providing them with the opportunity to offer trust-based consent to research that they cannot fully comprehend.

Concerns of Beneficence: Promoting the Flourishing of the Child

Double Effect Arguments against Risky Clinical Research

A final argument against presenting CAR-T research to newly diagnosed patients may focus on the question of whether CAR-T truly promotes the flourishing of the child through beneficence and nonmaleficence. While it is difficult to compare the risks and benefits of the two very different treatment approaches of CAR-T and conventional chemotherapy, one could argue that natural law theory's double-effect reasoning would not permit the fundamentally risky nature of this research. Specifically, double-effect has four conditions: "the action is not morally incorrect," "the good effect … is not achieved through the bad effect," "the bad effect is not intended by the agent but only foreseen and tolerated," and "there is proportionality between the good effect and the bad one" (15). Given the aforementioned arguments about how this research would align with the ethical principles of respect-for-persons and autonomy of rational beings, it seems reasonable to conclude that "the action [of CAR-T treatment] is not morally incorrect" (15). Furthermore, the good effect of improving survival rates and decreasing toxicities is achieved through CAR-T therapy, rather than through the bad effect of potentially increasing the chances of relapse or disease progression for some patients. Additionally, the risk

of decreasing an already high survival rate of around 92% through the more widespread application of a novel therapy is foreseen and accepted but not intended by CAR-T, which instead hopes to eventually improve survival rates even further. The most critical double effect argument against this type of research, however, may be the argument that there is not "proportionality between the good effect and the bad one" (15). A natural law theorist applying this line of reasoning may argue that accepting any potentially decreased chance of initially responding to treatment in hopes of improving survival outcomes and decreasing treatment-related side effects would be a disproportionate risk to the mere 8% chance that a newly diagnosed child will ultimately die from ALL.

Clinical Research Promotes Holistic Human Flourishing

From a scientific perspective, one could lessen these concerns by noting that decreased initial response to a chosen front-line treatment approach (either the therapeutic standard of care or front-line experimental CAR-T research) does not necessarily decrease the chances of survival, especially for a cancer like ALL which has multiple potential secondary treatment regimens if frontline therapy fails. For instance, if a child were to initially only be treated with a brief period of chemotherapy to prepare their body for a potentially curative CAR-T infusion, he or she could feasibly start the standard treatment regimen from scratch if CAR-T failed to secure a durable response. Troublingly, the child would now be exposed to the risks of both the standard of care and a relatively novel therapeutic agent, thereby amplifying the bad effect without any clear good effect for that particular child. Worse, a child who is not cured by CAR-T may miss the window of opportunity when the standard treatment may have been most effective and consequently display a higher risk of relapsed or refractory cancer after trying both treatments. Although treatment-resistant disease typically has a worse prognosis, this unfortunate outcome would still not be a death sentence. Children with treatment-resistant ALL may respond to genetic therapies, monoclonal antibody treatments, radiation, stem cell transplant, or alternative combinations of existing chemotherapeutic agents (22). While any of these options would fall into the umbrella of the "bad effect" according to natural law reasoning, there is at least hope that additional risk-taking in front-line treatment would be limited in scope to exposing children to additional treatment-related toxicity, rather than inevitably decreasing survival outcomes.

Additionally, the concern that vulnerable children require additional protections when designing potentially risky therapies is understandable, but in reality, depriving them of the same clinical trials options available to adults fails to respect their personhood as equal to adults under natural law theory. Gómez-Lobo highlights how the capacity of children to develop into adults necessitates "the fundamental equality of all human beings" (15). In other words, parents should be given the choice to participate in clinical research that would provide children with the same opportunities afforded to adults with cancer. Furthermore, one must consider how in addition to promoting biological life through superior cancer treatment, participation in CAR-T trials from the start of diagnosis may promote a patient and family's emotional flourishing by sparing them from the psychological burden of undergoing years of chemotherapy (5). It also may promote their rational flourishing through the knowledge that they are taking control of a terrible situation by allowing their treatment to benefit scientific progress (11). While not all families may be equally motivated by such altruistic principles, Norbäck et al. noted how when asked why they chose to enroll their child on clinical research, parents often reported that their gratitude for their healthcare teams and their desire to give back to future families were central motivators (11). Therefore, clinical researchers applying natural law theory to trial design must consider how the equal moral status of children dictates that they must be given the same opportunities for holistic biological, emotional, and rational flourishing that we provide to adults, including when that means allowing families to take physician-approved and rationally-evaluated risks at the beginning of treatment.

Proposed Changes to the COG's Approach to Clinical Trial Design

While I have demonstrated how expanding access to research for newly diagnosed patients may promote respect for persons, justice, and beneficence, the ethical concerns of physician conflict of interest, lack of informed consent, and disproportionate risks remain important considerations in determining under what conditions such clinical trials would be ethically justifiable. With these concerns in mind, I have three main propositions for the pediatric oncology community moving forward.

First, clinical research organizations must ensure that newly proposed trials respect children by strengthening existing review procedures and minimizing concerns regarding the conflicting interests of physician scientists. The COG should continue their practice of requiring several external reviews of any proposed research, thus ensuring that there is scientific evidence to suggest that research would benefit a particular child. Additionally, physician scientists must

be wary of how even their well-meaning intentions of advancing cures for all children must never impede their care of the patient in front of them. While hospitals or clinical research organizations may be tempted to eliminate this question of conflict of interest by not even allowing clinical researchers to personally present their research studies to patients, the scientific community must remember the invaluable perspective that these dual-trained experts bring to both the laboratory and clinical setting. As a result, the research community can serve the best interests of patients not by eliminating these invaluable professionals from a child's care team, but rather by minimizing questions of conflict of interest by promoting a collaborative research community and disincentivizing coercive medical counsel. For example, the COG may consider requiring physicians who raise their own study as a potential treatment option to give equal weight to all other potential trials, including those offered by their colleagues. Creating such a collaborative professional environment would allow the research community to continue to strive for the cures that children need without sacrificing the respect that they deserve.

To address the concern of parental autonomy, pediatric oncology teams should consider a multidisciplinary approach to conversations with parents of newly diagnosed children. Acknowledging how parents may perceive the offer of clinical trial participation as an expert's advice to enroll, the standard of care should always be presented simultaneously and directly alongside experimental research, preferably by a different physician and care team. Doing so would avoid the problem of therapeutic misconception by clearly differentiating between standard treatment and experimental therapy and would ensure that both options are truly presented as equal alternatives. This approach would also allow parents to individually weigh the risk and benefits of each treatment without worrying about how their decision may affect how the presenting physicians care for their child. Additionally, clinical research organizations must reconsider how concerns regarding the potential injustice of exploiting the vulnerability of understandably emotional parents may be doing more harm than good. While it will always be important to strive for informed consent whenever possible, clinical research organizations must recognize how in such a difficult time as the period following a child's cancer diagnosis, it might be perfectly rational for parents to offer trust-based, rather than informed consent.

Lastly and perhaps most importantly, clinical research organizations must do their due diligence of adequately weighing the risks and benefits of a proposed treatment before offering it to newly diagnosed patients in order to ensure that the ethical principle of beneficence is upheld. While it is true that studies in adults or children with treatment-resistant disease have limited utility when making assumptions of how a newly diagnosed child might respond, clinical research organizations must make every effort to gain the scientific backing required to make informed risk assessments before considering radical changes to the standard of care. While CAR-T may be an ideal frontline treatment alternative to chemotherapy for pediatric ALL because of its similar risk profile and potentially superior survival rate compared to the standard of care, such risk-taking for the sake of reduced long-term toxicity, diminished emotional burden, or the rational flourishing of a family would not be justified in cases where a proposed treatment alternative would likely decrease survival outcomes. Furthermore, such risk-taking in newly diagnosed patients may be the most ethical course of action when there are multiple back-up options, like with ALL; however, completely replacing front-line treatment to reduce treatment-related toxicity may not be an appropriate risk for children with diseases that would be unlikely to be cured if initial attempts at treatment failed. This kind of disease-specific calculus can only be properly performed by experts in the field, but in general, for a proposed experimental front-line treatment alternative to be ethically justifiable under this criterion, it must be equally or more likely to produce a cure, and it must be equally or less harmful to a child's physical or emotional health, both in the short-term and long-term.

Conclusion

As new immunotherapies and genetic therapies open the doors to a new era of precision medicine, the pediatric oncology community must wrestle with the question of how to pave the way for a future with improved survival rates and decreased treatment-related toxicity while providing the best care possible to the children of today. Any number of ethical arguments— including concerns about informed consent, respect-for-persons, and disproportionate risk— could relegate these potentially revolutionary therapeutics to a last line of defense reserved for children who fail the standard of care. Nevertheless, we must have the courage to examine these concerns closely and recognize how clinical research in newly diagnosed patients may actually promote rather than violate these ethical principles. While any new clinical trial designs will still require sound scientific rationale that only experts in the field could provide, I invite the pediatric research community to worry not only about the risks of presenting these trials to a vulnerable population, but of the risks of

withholding them. It is certainly easier to rationalize accepting the risks of the status quo by claiming that we are protecting children from unknown risks or shielding parents from malignant persuasion to consent to risky research. However, I would like to imagine a present in which the right of parents to rationally choose between two or more potentially curative options is respected. And I would like to have reason to hope for a future in which 100% of children with ALL or any other form of childhood cancer survive with as few acute and chronic side effects as possible. I therefore implore clinical research organizations to balance their current risk-averse policy of not infringing upon a patient's health with a newfound appreciation of a parent's liberty to determine what is best for their child, a renewed sense of duty to continue to strive for better cures, and a more holistic understanding of how experimental treatment can promote the human flourishing of a child with cancer.

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