Guidelines Perspective

Defining the whole of reproductive health in adolescent and young adult cancer populations: fertility is only one piece of the puzzle

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Practice Points

- The adolescent and young adults (AYA) group (ages 15–29 years) in oncology is often called 'the orphan cohort', as they have been understudied for a variety of reasons.
- AYA populations are in the distinct situation of dealing with a life-threatening illness alongside managing major developmental, personal, educational and occupational milestones.
- This review highlights National Comprehensive Cancer Network and American Academy of Pediatrics guidelines on issues within reproductive health, the influence of these guidelines in clinical practice and the impact of missing pieces of the reproductive health puzzle for AYAs.
- Largely, these organizations have not integrated the broad definitions of reproductive health into current policies, which leaves significant gaps in medical and ethical standards of care.
- The National Comprehensive Cancer Network AYA oncology guidelines offer a more comprehensive approach to care and integrate the UN Populations Fund's refined reproductive health definition more successfully than the American Academy of Pediatrics.
- A multidisciplinary approach is necessary to bridge the gaps among physician practice guidelines.

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SUMMARY Quality of life is an important but distinct issue for adolescent and young adults (AYA) compared with older adults. Reproductive health is a key aspect of health-related quality of life and spans across physiological and psychological domains. While fertility issues have had more attention in the past 5 years, there are other aspects of reproductive health requiring recognition by healthcare practitioners in AYA oncology. These include attention to human papillomavirus and sexually transmitted infection risk, contraception and sexual health in relation to late effects of cancer and treatment. Alkylating agents in chemotherapy, total-body radiation or external-beam radiation in a field that includes the ovaries, testes or endocrine system may cause long-term impairment to reproductive health functioning. We examine reproductive health in relation to National Comprehensive Cancer Network and American Academy of Pediatrics guidelines for AYA cancer survivors in the USA. While fertility preservation and issues related to fertility are present in the guidelines, contraception, human papillomavirus vaccine or other sexual health issues are incomplete.

Recently, the clinical community has acknowledged that adolescents and young adults (AYA) have unique needs in cancer survivorship that require attention separate from children and older adults, particularly as it relates to quality-of-life issues. While health-related quality of life does not have a universal definition, it is typically defined as a "broad dimensional concept including self reported measures of physical and mental health" [101].

In the USA, more than 69,000 AYAs are diagnosed with cancer each year [102]. The AYA population is comprised of people aged 15–39 years; an age group that has not seen an improvement in survival rates compared with those younger than 15 years and older than 39 years of age [1]. The AYA group in oncology is often called 'the orphan cohort' as they have been understudied for a variety of reasons, primarily the difficulty on the part of researchers and the population in creating protocols and methods that facilitate longitudinal and follow-up studies [2,3]. Furthermore, the biologic differences between types of childhood and AYA cancers were also left unattended to until the early 2000s [4]. AYA populations are in the distinct situation of dealing with a life-threatening illness alongside managing major developmental, personal, educational and occupational milestones. Therefore, in addition to having physiological and biological health issues that extend beyond routine medical care, AYAs may experience psychosocial issues such as neurocognitive problems from treatment, difficulty becoming independent, reduced social skills, difficulty establishing relationships, risk-taking behavior, body image dissatisfaction, sexual dysfunction, loss of fertility and reduced quality of life [5]. However, AYA cancer survivors are also known to have higher health literacy and adjustment patterns than those who did not experience cancer [5,6].

Psychosocial issues should be monitored throughout survivorship care and planning. An area that compounds psychosocial late effects for AYAs is reproductive health. While specific attention has been paid to issues of fertility, this is only one piece of the reproductive health puzzle. In oncology settings, fertility has gained momentum as an important quality-of-life issue; however it should not mire the broader context of reproductive health that also impacts on AYA patients. The WHO defines reproductive health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, reproductive health addresses the reproductive processes, functions and system at all stages of life" [103]. Reproductive health, therefore, implies that people have the autonomy to choose responsible, satisfying and safe sexual behaviors, which may or may not lead to reproduction. Individuals have the right to decide if, when and how often to perform such acts [101]. This definition was expanded and amended in 2011 by the UN Populations Fund (UNPF). The refined definition offers specific aspects of reproductive health that include the following domains: family planning; antenatal and post-natal care; prevention and treatment of infertility; treatment of reproductive

tract infections; prevention, care and treatment of sexually transmitted infections (STIs) and HIV/AIDS; provision of education on human sexuality and reproductive health; and referrals for further diagnosis and management of the above [104].

Numerous research efforts over the past two decades motivated the UNPF to expand the definition of reproductive health to capture relevant issues facing men and women. While this expansion of reproductive health in the international community is of great significance, it has yet to reach many policies on national and state levels in the USA. The National Comprehensive Cancer Network (NCCN) and the American Academy of Pediatrics (AAP) are leaders in pediatric policies and guidelines, and serve as trusted sources for AYA oncologists throughout the USA to uphold medical and ethical standards, including standards of care. The AYA definition is relatively new and patients within this population may be treated in pediatric or adult protocols or a combination. Thus, we look to the organizations that govern both age groups to establish and monitor standards of care. The research question examined was to identify whether these organizations had integrated the revised reproductive health definition from the UNPF into existing policy documents for AYA cancer patients to ensure comprehensive care.

In this article, we highlight the NCCN and AAP guidelines on issues within reproductive health, the influence of these guidelines in clinical practice and the impact of missing pieces of the reproductive health puzzle for AYAs. We chose to focus on the NCCN guidelines specifically because the NCCN Clinical Practice Guidelines are the most widely followed in 115 countries, and cover 97% of cancers [7]. Additionally, we chose to focus on the AAP guidelines due to the long-standing influence on standard-of-care practices in pediatrics throughout the USA. Analysis of other, less attended to guidelines, may have produced homogenous results and had an ineffectual impact on clinical practice patterns.

Table 1 displays the inclusion or exclusion of newly defined reproductive health issues within the NCCN and AAP guidelines specific to AYA cancer patients. Largely, these organizations have not integrated the broad definitions of reproductive health into current policies, which leaves significant gaps in legal and ethical standards of care.

Family planning

■ Contraception

The NCCN advocates contraception in its AYA clinical practice guidelines [105]. However, the recommendation is isolated to the section regarding fertility considerations, and offers oral contraceptives only as a method to suppress menses. The NCCN does not address any contraindications of some contraceptives, nor strategies in the event that emergency contraceptives are desired.

The AAP provides professional guidelines detailing the responsibility of health professionals to discuss contraception with AYAs in the general population. There are details regarding the protection against some cancers with oral contraceptives, however, this is the only reference to cancer in AAP's policy statement on contraception [8]. There is also no reference to contraception for oncology patients in AAP's long-term follow-up guidelines [9]. The AAP does have a policy statement that addresses sexuality, contraception and the media, which explicitly recommends against abstinence-only education [10].

AYAs with cancer have unique contraception needs that require personalized discussions with the healthcare team. Misconceptions regarding the sexuality of AYA cancer patients may inhibit discussions of contraceptive use for this population, but research indicates that adolescents with cancer are at least as sexually active as their healthy counterparts [11]. Personalized discussions regarding contraception are warranted, as some types can have interactions with cancer treatments. Many pharmaceutical companies have disclaimers on the websites of specific chemotherapy drugs that may produce concomitant issues with a chosen contraceptive. For example, certain chemotherapies have been shown to decrease bone density due to antimetabolites, such as methotrexate, in conjunction with corticosteroids [12]; therefore, female injectable contraceptives, which may also decrease bone density [13], should be discouraged. There are also potentially harmful interactions between hormonal contraceptive interventions and estrogen receptive tumors. For example, the prognosis of women with current or recent breast cancer may worsen with combined (containing estrogen and progestin) contraceptive use as breast cancer can be a hormonally sensitive tumor [103,106]. In addition, the Society of Family Planning has recommended that women of childbearing age undergoing cancer treatment, such as chemotherapy and tamoxifen,

Table 1. Guidelines for adolescent and young adult oncology.

Subject		AAP[†]	NCCN[‡]
Family planning	Contraception	–	▪ “AYA patients should be managed by a multidisciplinary team of providers with expertise in cancer treatment and management of … family planning, pregnancy...” (page MS-4) ▪ “Menstrual suppression (for fertility preservation): oral contraceptives may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia...” (page AYAO-6)
	Pregnancy	–	▪ “AYA women diagnosed with cancer during pregnancy require individualized treatment from a multidisciplinary team including medical, surgical and radiation oncologists, obstetrician, pathologist and radiologist. Potential benefits and risks of chemotherapy and RT for both the mother and the fetus must be carefully evaluated before the start of treatment.” (page MS-8) ▪ “Referral to a gynecologic oncologist and perinatologist with expertise and knowledge of the physiological changes that occur during pregnancy is strongly recommended.” (page MS-8)
Prevention and appropriate treatment of infertility		▪ "Ideally, the decision about candidacy for fertility preservation will be guided by an institutional policy and shaped by a medical team, including a pediatric oncologist, fertility specialist, ethicist, and mental health professional.” (page e1466 and throughout) [27]	▪ “Screening Recommendations for AYA Survivors...” (page AYAO-B) ▪ “Fertility preservation should be an essential part in the management of AYAs with cancer. Discuss the risk of infertility due to cancer therapy with all patients at the time of diagnosis...” (page AYAO-6)
Prevention, care and treatment of STIs: HPV vaccine		▪ None for STIs ▪ “HPV vaccine can be administered in these special circumstances: a. when a patient is immunocompromised because of disease or medication...” (page 602) [29]	▪ “Provide health education about STIs, diet, and exercise.” (page AYAO-7) ▪ “Since the incidence of STIs peaks among AYAs 15–24 years of age, provide preventative health education about sexually transmitted diseases.” (page MS-10) ▪ “Recommend HPV immunization (if not previously administered) for the prevention of secondary cancers since the vaccine has been shown to prevent cervical carcinoma and anal epithelial neoplasia, the precursor to carcinoma.” (page MS-10)
Information, education and counseling on human sexuality and reproductive health		▪ “The adolescent or young adult cancer survivor may be grappling with unique treatment-related health issues, such as infertility, at a time when their sexual maturity and personal relationships are developing.” (page 66)	▪ “The impact of diagnosis and treatment of cancer on their physical appearance, sexual development, and sexual function can lead to shame, social isolation, and regressive behaviors if not addressed promptly.” (page MS-9)
Appropriate referrals for further diagnosis and management		▪ “For survivors who are identified as having chronic health problems as a result of their previous cancer therapy, the pediatrician can also work with the primary oncology center to obtain assistance with referrals to subspecialists knowledgeable in issues related to childhood cancer survivorship.” (page 913) [9]	▪ “Strongly consider a referral for treatment at a cancer center with expertise in treatment of AYAs with cancer, and have access to clinical trials for AYAs.” (page AYAO 2) ▪ “Initiate referral for fertility preservation clinics within 24 h for interested patients.” (page AYAO-6) ▪ “Referral to a gynecologic oncologist and perinatologist with expertise and knowledge of the physiological changes that occur during pregnancy (and impact cancer treatment) is strongly recommended.” (page MS-8)

[†]Data taken from [9].
[‡]Data taken from [105].
AAP: American Academy of Pediatrics; AYA: Adolescent and young adult; HPV: Human papillomavirus; NCCN: National Comprehensive Cancer Network; RT: Radiotherapy; STI: Sexually transmitted infection.

should avoid combined contraceptive methods when possible due to increased risk of venous thromboembolism [14]. Even when a chemotherapeutic agent carries a high risk of ovarian failure (females) or azoospermia (males), normal reproductive function may recover post-treatment [15,16]. Thus, the need for contraceptive planning and discussions may change throughout the life span of the AYA patient. Current evidence suggests that the NCCN and AAP should consider whether existing guidelines should be modified to tailor contraceptive education and choices to AYA oncology populations, which includes information about the risks and contraindications as well as possible benefits.

Pregnancy

The NCCN provides guidelines on pregnancy during treatment among AYA cancer patients. The guidelines call for an individualized, multidisciplinary approach to manage the care of a pregnant patient on a case-by-case basis. Due to the limited data available regarding the continuation of cancer treatment as well as care for the fetus, the NCCN recommends crosscare management with a gynecologic oncologist.

The AAP does not address pregnancy during cancer treatment. This places many physicians who rely on the AAP to guide clinical practice at a significant disadvantage. The AAP does, however, address adolescent pregnancy in the general population.

Cancer treatments and radiation have known teratogenic risks to a developing fetus, ranging from spontaneous abortion to congenital malformations [17,107]. Therefore, females who become pregnant while on treatment may have their plan of care significantly altered, or pregnancy termination may be suggested [18,19]. Guidelines for discussions about the risks of becoming pregnant while on treatment, as well as clinical practice guidelines for the treatment of pregnant AYAs, should be available to physicians. The similarities between side effects of chemotherapy and pregnancy such as fatigue, nausea and disruption in menses can cause a pregnancy to be overlooked. This places the patient and developing fetus at a significant health risk.

Infertility

It is well established that some cancer treatments, such as alkylating agents in chemotherapy, total-body radiation or external-beam radiation in a field that includes the ovaries or testes, may cause prolonged or permanent infertility in both males and females. For postpubertal males, sperm cryopreservation is the only nonexperimental option and has the highest likelihood of success [20]. Frozen sperm may then be thawed and injected into a female partner or surrogate using intracytoplasmic sperm injection or other types of assisted reproductive technology. For postpubertal females, embryo cryopreservation, which involves fertilizing oocytes with sperm (donor or partner) is the only nonexperimental fertility preservation option [20,21]. The successful live birth rate from this method is approximately 50% [22]. An additional option for females is oophoropexy, where the ovaries are laparoscopically moved to a position outside of the intended radiation field, but the success rate of this procedure has not been clinically established [23–25]. There are additional experimental fertility preservation options for males and females. Testicular tissue cryopreservation is available for pre- and post-pubertal males, although at present there are no reported live births using this technique. Oocyte cryopreservation (freezing of eggs) for postpubertal females is presently considered an experimental option, however, in 2012, the American Society for Reproductive Medicine issued a statement recommending that the procedure be reclassified as nonexperimental due to the improved success rates [108]. Ovarian tissue cryopreservation is another experimental option for pre- and post-pubertal females. Currently, there are 13 known live births that have resulted from the reimplantation of cryopreserved ovarian tissue in adult women [26]. While there are both established and experimental fertility preservation options for the AYA population, there are financial and ethical issues with each option, to be considered by patients, family and other stakeholders.

The NCCN explicitly outlines the necessity of physicians to discuss risks to fertility and fertility preservation options with AYAs [105]. A flow chart is provided that guides physicians on how and when to systematically approach this discussion, including the duty of physicians to submit a referral to a reproductive professional within 24 h of the patient's interest.

The AAP released a technical report in 2008 for AYA oncology physicians providing a comprehensive overview of risks to fertility, types,

cost and ethical issues of fertility preservation [27]. This report additionally explains the role of the physician to facilitate the discussion, and offers guidance to ways this may be achieved. However, the AAP does not include details regarding compromised reproductive potential in the long-term follow-up guidelines. This is notable as infertility is considered a late effect, however is not included in the AAP's guidelines to manage late-onset complications. Even so, the NCCN and AAP have both provided guidelines to support the UNPF's mission of infertility prevention.

A first step in the field of fertility and oncology was the development of guidelines for adult cancer patients by the Ethics Committee of the American Society for Reproductive Medicine in 2005 [28], and the American Society of Clinical Oncology in 2006 [20], which detail the duty of oncologists to discuss risks to fertility from cancer or treatment, and also outline established versus experimental options for fertility preservation. Because fertility preservation options are most efficacious when used prior to the initiation of therapy, the expansion of appropriate guidelines into the AYA population is critical due to the frequent rush to start treatment. Fertility preservation options vary by pubertal status, diagnosis, age, location of the disease, dosage of treatment and pretreatment fertility of the patient, among other factors. When considering fertility preservation, a personalized approach to treatment is paramount to educated decision-making.

Prevention, care & treatment of STIs

The NCCN provides recommendations for administration of the human papillomavirus (HPV) vaccine for AYA cancer patients in the supportive care guidelines. The NCCN specifically notes the benefit of protecting against future HPV-associated cancers, and implies that despite the current diagnosis, patients are at risk of developing other cancers. In this sense, the NCCN supports HPV immunization based on the recommendations from the Advisory Committee on Immunization Practices for patients 9–26 years old [107].

Similarly, the AAP has also integrated the Advisory Committee on Immunization Practices' HPV recommendations into the AAP HPV policy statement [29]. The AAP's guidelines indicate that the vaccine may be given to patients who are immunocompromised due to disease, as it is not a live vaccine. This would include AYA cancer patients.

As the HPV recommendations fall into the age range that characterizes AYAs, it is important to discuss the justification for HPV immunization among AYA cancer patients and survivors. It is somewhat expected for a patient to be lymphopenic at multiple time points throughout cancer care and thus be particularly susceptible to infection. AYAs may be asymptomatic during this time as well. For survivors, the threat of contracting HPV is ever-present. Some studies suggest that patients who have undergone allogeneic bone marrow transplants as part of their cancer treatment [19,30], have been treated for Hodgkin's lymphoma [31] and treated with pelvic radiation [32,33] have an increased risk for contracting HPV and experiencing viral reactivation as a result of immunosuppression or therapy-related cervical tissue damage. Discussions of the HPV vaccination should be a part of NCCN and AAP guidelines for quality preventative care.

The NCCN addresses the issue of STIs among AYA cancer patients and survivors in the available guidelines. The NCCN utilizes available data to imply that because the risk for STIs is greater among general AYAs than in other age groups, it should be recognized that AYAs with a history of cancer engage in risky sexual behavior at rates similar to their peers and siblings without cancer [11].

The AAP addresses STIs in multiple publications: clinical reports specific to males, guidelines specific to sexual education and guidelines for overall health supervision [34–36]. The overarching notion is the necessity for consistent screening practices. The AAP does not address STIs in an oncology setting.

Including STIs in standard reproductive health discussions with AYA patients and survivors is critical. AYA survivors and those undergoing cancer treatment may be more physiologically susceptible to contracting STIs due to a multitude of risk factors stemming from compromised immune systems and myelosuppression. The impact of chemotherapy coupled with the long-term effects of STIs impairs the ability of the immune system to operate in the usual way, increasing the risk of infection [37]. Furthermore, STIs can cause damage to the reproductive system; chlamydia has been shown to produce blockage in the fallopian tube and

cause ectopic pregnancies as well as infertility [38]. AYAs have an increased health vulnerability evidenced by the high incidence rate of over 9 million new cases of STIs reported each year occurring among 15–24 year olds [39]. The AAP should incorporate the UNFP's guidelines to ensure this information is not missed for AYA oncology patients.

Information, education & counseling on human sexuality & reproductive health

The NCCN briefly describes the role of human sexuality for AYA oncology patients throughout its guidelines. Table 1 highlights multiple areas of text where sexual identity and development are mentioned. Largely, this information is provided as part of the psychosocial impact of cancer, during and after treatment, and the recommendation is for treatment teams to be aware and prepared to manage such experiences. The NCCN outlines the role of human sexuality and how these milestones are often disrupted for AYA cancer patients. However, this brief outline lacks detail. The NCCN further explains the necessity to monitor these issues throughout survivorship, and counsel when appropriate.

The AAP has produced numerous policies and recommendations detailing the importance of attending to issues of human sexuality including sexual identity [40] and reproductive health specific to males [34]. However, human sexuality and personal relationships are only briefly addressed in the long-term follow-up guidelines for pediatric cancer survivors. Counseling about issues related to human sexuality is recognized by the UNPF and should be recognized by the policies within professional AYA oncology organizations. A variety of psychosocial issues are encompassed within human sexuality, including body image, sexual orientation, self-esteem and negotiations within romantic relationships, among others [41,42]. Disruptions in these psychosexual milestones, such as with a cancer diagnosis which often requires at least 3 years of continuous treatment, are likely to reverberate throughout the lifespan and impact quality of life [43].

Reproductive health issues beyond fertility for AYA cancer patients should not be neglected nor assumed to be addressed within guidelines for the general AYA population. Counseling efforts and social interventions should be specifically tailored for the developmental stage of the patient, when cancer is diagnosed, to meet the needs and issues that the general AYA population does not experience.

Appropriate referrals for further diagnosis & management

The NCCN does a thorough job of indicating that referrals need to be made when appropriate. Ranging from palliation, to transportation, to disease specialists, there is consistent language throughout the NCCN's AYA guidelines that referrals are necessary for comprehensive cancer care. The NCCN highlights the benefits of the multidisciplinary team approach to AYA reproductive health management, specifically as it relates to fertility, pregnancy and other areas of reproductive health.

AAP guidelines are less forthcoming regarding appropriate referrals for reproductive health management. AAP offers guidelines for pediatric cancer centers in which referrals should be made to subspecialists when appropriate [44]. Long-term follow-up guidelines provide a similar blanket statement. The AAP does not specify which psychosocial issues would potentially need referral, however. The AAP does recommend appropriate referrals to fertility specialists for those of reproductive age in a separate policy statement focused solely on fertility preservation.

There is a distinct need to refer AYA cancer patients for management of reproductive health. This includes in-house referrals to social workers, psychologists, gynecologists or reproductive endocrinologists if available. Referrals bridge the gap to reproductive health services that are traditionally not included in oncology care. Sufficient education for AYA oncology families also helps to improve rates of referrals by stimulating a dialog about issues that patients may not otherwise be aware of [45]. Regarding fertility preservation, rates of referral to fertility specialists for AYA cancer patients are consistently low, citing the physician's lack of own knowledge and information [46,47]. A recent study suggests that the rate of referral for fertility preservation and counseling in young women diagnosed with cancer may be lower among those with less education or over the age of 35 years [48]. The authors report disparities in access to fertility preservation services based on ethnicity and sexual orientation as well. This is unfortunate because additional research suggests that receiving counseling about fertility prior to the initiation of cancer treatment

has a significant improvement in quality of life after cancer. Letourneau *et al.* assessed quality of life among women who had received fertility counseling from a specialist and/or from their oncology team. Those who were counseled by a specialist and attempted to preserve their fertility reported lower regret than those who had been counseled by their oncologists alone [43].

The AYA cancer patient is not a majority population in pediatric or adult hospitals. Therefore, it is critical for professional guidelines to recommend shared management of care to ensure specific quality-of-life indicators, such as reproductive health, are addressed.

The division between what the NCCN and what the AAP guidelines offer is important to uncover as, for example, a pediatric oncologist treating a 15 year old is likely to gravitate towards AAP guidelines, while an oncologist treating a 39 year old at a comprehensive cancer center is likely to utilize the NCCN's guidelines; however, it is unclear if the oncologist gravitates towards either guidelines when treating a 25 year old. We acknowledge that a limitation of our assessment is that we did not consider the guidelines of other organizations such the American Society of Clinical Oncology and the Children's Oncology Group to compare and contrast the mention of reproductive health issues beyond fertility from different clinical perspectives. Primary care physicians who are information-seeking have been shown to initially rely on a colleague's expertise, then will seek to answer a question using established guidelines [49]. However, the main complaint from physicians is the time that must be spent on searching for an answer [50].

Conclusion & future perspective

In summary, the NCCN AYA oncology guidelines offer a more comprehensive approach to care and integrate the UNPF's refined reproductive health definition more successfully than the AAP guidelines. A multidisciplinary approach is necessary to bridge the gaps among physician practice guidelines. While many experts and consortium groups assist in developing such guidelines, resources for comprehensive care, particularly among the AYA cancer population require unique coordination. Initial interventions such as clinical opinion pieces, systematic reviews and further research into AYA reproductive health should be undertaken to motivate the revision of current AAP AYA oncology guidelines that broaden the scope set forth by the UNPF.

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