ABSTRACT

Individuals diagnosed with cancer as adolescents and young adults (AYAs; ages 15–39 years) face unique vulnerabilities. Compared with individuals diagnosed when younger (≤14 years) or older (>40 years), AYAs have not seen the same improvement in survival. Furthermore, they sit at a complex moment of social, emotional, and cognitive development, and have a unique interface with the healthcare system. With these observations, NCI prioritized addressing the unique vulnerabilities among AYAs with cancer, and NCCN developed guidelines regarding optimal AYA cancer care. Improvements in certain locales have been seen in the wake of this focus on AYAs, suggesting that continuing to consider AYA outcomes in the context of their specific needs is critical as we strive toward additional improvements. However, it is key to consider the drivers of these outcomes to continue this trajectory. This review presents a holistic conceptual model that includes factors that influence outcomes among AYAs with cancer, including domains in these levels that influence both clinical outcomes (such as relapse and survival) and health-related quality of life (HRQoL). These include domains at the patient level, such as social constructs (race/ethnicity, socioeconomic status), behavior (adherence, risk-taking), biologic characteristics (cancer biology, host genetics), medical treatment (treatment regimen, risk-based survivorship care), and treatment-related toxicities. The model also includes domains at the system level, which include treatment location (NCI designation, facility model, AYA program presence), clinical trial enrollment, transdisciplinary communication, fertility preservation, and psychosocial support. Recognizing these multiple factors at the level of the individual and the healthcare system influence AYA outcomes (from HRQoL to survival), it is key not only to consider patient-level interventions and development of novel cancer agents but also to develop systems-level interventions that can be executed in parallel. In this way, the impact can be expanded to a vast number of AYAs.

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Adolescents and young adults (AYAs; ages 15–39 years) face unique vulnerabilities when diagnosed with cancer. For several decades, AYAs with cancer have not seen the same improvements in survival as younger (≤14 years) and older (>40 years) patients. Among some diagnoses, AYAs face worse survival rates than younger children or adults aged ≥40 years. Additionally, AYAs are at a complicated time of social, emotional, and cognitive development. Acknowledging these factors (with nearly 86,000 AYAs diagnosed annually in the United States), NCI prioritized addressing the unique vulnerability observed among AYAs and NCCN developed guidelines regarding optimal cancer care for AYAs. With this increased focus on the AYA cancer population, some regions have seen improvements despite persistence of disparities as a whole; this suggests that as we strive toward additional improvements, it is critical to continue to consider AYA outcomes in the context of their specific needs. When putting AYA outcomes into this context, it is important to consider both patient-level and healthcare-level factors. Several domains in these levels that influence both clinical outcomes (such as relapse and survival) and health-related quality of life (HRQoL) are outlined in this article. Considering these domains, however, it is key to keep in mind the heterogeneity of the AYA population spanning the 15- to 39-year age range, because the biologic and psychosocial landscapes differ between younger and older AYAs and along the age trajectory. To take a holistic approach to reviewing the literature surrounding AYA outcomes, we describe each domain in brief, with citations provided for additional depth, and propose a conceptual model in based on the literature cited.

Patient-Level Factors

Social Constructs

The domains of race/ethnicity, socioeconomic deprivation, and education have well-documented associations with outcomes in AYAs across cancer types, including acute
lymphocytic leukemia (ALL), Hodgkin and non-Hodgkin lymphoma, acute myeloid leukemia, central nervous system (CNS) tumors, and colorectal cancer.11–15 There is a complex (and not yet fully understood) interplay between race/ethnicity, socioeconomic deprivation, and health insurance,16 which together influence access to healthcare; the relationships among these domains and drivers of access may differ across cancer diagnosis. To better understand the mechanisms through which these constructs impact outcomes, NCI clinical trials groups have made efforts to integrate patient-reported outcomes, social determinants of health, and financial toxicity measurements into clinical trials. Although laudable and important, these assessments are fundamentally limited, because it has been observed that older AYAs (ages 22–39 years) with lower socioeconomic status, from nonwhite racial or ethnic groups, and with public or no insurance are less often treated at NCI-designated Comprehensive Cancer Centers (CCC)17–20 and are less likely enrolled on clinical trials.21 Given that clinical trial enrollment is strongly associated with superior outcomes for AYAs,22 this in and of itself is an additional mechanism through which social constructs impact outcomes.

Although there are limited data surrounding sexual or gender minority AYAs with cancer, LGBTQI (lesbian, gay, bisexual, transgender, queer, and/or intersex)23 patients report lower HRQoL and more distress,24 with psychological distress and financial burdens exacerbated by the combination of cancer and LGBTQI stigma.25 AYAs have a unique interface with the US healthcare system as the most uninsured and underinsured (ie, insured, but face cost-sharing or coverage limits that affect ability to afford care) age group.26 Despite variable findings regarding lag time to diagnosis,27 lag time to treatment has been associated with survival in some diagnoses,28 and insurance status is associated with lag times. Although the mechanism depending on the diagnosis likely varies, survival across a number of malignancies is associated with insurance status.29 These and other challenges prompt unique needs for legal consultation.

**Individual Behaviors**

**Adherence**

As cancer-directed therapy is an important driver of outcomes, adherence to a prescribed treatment plan is important as well. This can be in the form of maintaining the planned schedule for treatment-related visits, such as infusion-based interval compression therapy in Ewing sarcoma. This can also be in the form of taking prolonged daily oral medications, such as hormonal therapy in breast cancer, tyrosine kinase inhibitors in chronic myeloid leukemia (CML), or 6-mercaptopurine (6MP) in maintenance-phase ALL.

Across 94 Children’s Oncology Group (COG) sites, children and adolescents with ALL had a 2.7-fold higher hazard ratio of relapse if they were nonadherent (took <95% of prescribed 6MP) compared with those who were adherent (rates ≥95%); patients aged 12 to 21 years had lower mean adherence rates (86%) than those aged <12 years (93%).30 A subsequent intervention study among COG patients revealed that use of education, text-message reminders, and directly supervised therapy (by parents) increased adherence among young AYAs (patients aged >12 years; IQR, 14–18 years) who had a baseline adherence of <90%.31 Similarly, among younger and older adults with CML (median, 60.5 years), a multilevel intervention study was able to increase adherence, but only by 1.5% overall.32 These interventions are likely applicable to a subset of AYAs at pediatric or adult sites. However, it is conceivable that many of the factors in Figure 1 (both patient-level and system-level) also influence adherence (including trial enrollment),33 along with AYA-specific domains (invincibility and risk-taking behaviors, etc.); work is ongoing to understand barriers and facilitators across models of care, as well as those specific to AYAs, to design an AYA-focused intervention across AYA phenotypes.

**Biologic Characteristics**

**Cancer Biology**

Cancer biology differs across age groups. Thus, AYAs may exhibit different clinical presentations and treatment responses even when they share a common diagnosis with either children or adults aged ≥40 years.34 Although some biologic differences are established, more basic and translational research is needed to understand these differences and their implications for treatments.

Although ALL and sarcomas are common to children and AYAs, AYAs face inferior survival and have not seen the same survival improvement.35 In ALL, favorable genomic rearrangements (ETV6-RUNXI, hyperdiploidy) are more common in younger children than in AYAs, whereas unfavorable genetic abnormalities (BCR-ABL, KMT2A [MLL], Ph-like) increase among AYAs.36 Common among AYA patients are the heterogeneous group of fusion-positive Ewing and synovial sarcomas; further research is needed to identify fusion oncogene–targeted therapies. The spindle cell/sclerosing subtype of rhabdomyosarcoma (with MYODI mutation) is most common among AYAs and associated with poorer chemotherapy response and outcome.37

AYAs with breast and colorectal cancers present with more aggressive phenotypes and poorer prognosis than adults aged ≥40 years with these cancers.3 In breast cancer, tumors in AYAs are frequently higher stage and grade. An aggressive phenotype of breast (triple-negative, basal-like, HER2-enriched) and colorectal cancer (mucinous...
histology, signet ring cells) is more common in AYAs than in adults aged ≥40 years. Although AYAs and adults with melanoma have similar prognosis, AYAs frequently present with different histology (spitzoid features, Kamino bodies, epidermal hyperplasia), deeper lesions, and sentinel lymph node metastasis than expected among older adults with the same disease stage.

CNS malignancies are seen across the age spectrum; gliomas represent the most common diagnosis among AYAs. The WHO classification recently incorporated molecular biomarkers, subdividing gliomas into adult-type and pediatric-type. AYA brain tumors are classified within the gamut of glial diagnoses, with outcomes inferior to children but superior to older adults.

Host Genetic Factors
Differences in underlying genomics also likely contribute to outcomes among AYAs. Cancer predisposition syndromes such as Li-Fraumeni, hereditary nonpolyposis colorectal cancer (HNPPC), neurofibromatosis 1 (NF-1), and familial adenomatous polyposis (FAP) commonly lead to the development of first cancers in the AYA age group. For example, roughly half of AYAs with breast cancer aged <30 years have germline BRCA1, BRCA2, or TP53 mutations, and AYAs with melanoma are more likely to have predisposing conditions (giant congenital melanocytic nevi, xeroderma pigmentosum, dysplastic nevus syndrome). With this in mind, AYAs often meet national and international criteria for genetic testing, which can guide screening and/or testing of family members; decision-making regarding such testing is influenced by a number of factors, including access to testing and counseling.

Medical Treatment

Treatment Regimen
Pediatric and adult oncology approaches to therapy vary (either significantly or subtly) in many malignancies that also occur in AYAs. For example, pediatric and adult treatment regimens for ALL and Ewing sarcoma differ significantly, with pediatric regimens providing superior survival for AYAs. In Hodgkin lymphoma, AYAs have worse survival than children across pediatric trials. However, younger AYAs still fare better on pediatric rather than adult trials. Although the differences in treatment have historically provided challenges to joint trials between the adult and pediatric National Clinical Trials Network (NCTN) cooperative groups, they have also allowed for comparison of these different approaches among AYA, ultimately setting the stage for incorporation of best practices. Specifically, a recent clinical trial (C10403) demonstrated the effective implementation of a pediatric ALL regimen among adult oncologists treating AYAs. Furthermore, with this experience as the backdrop, collaborative prospective randomized clinical trials have now been developed jointly by the pediatric/adult cooperative...
groups in Hodgkin (S1826, E4412; ClinicalTrials.gov identifiers: NCT03907488, NCT01896999) and non-Hodgkin lymphoma (ANHL1931; NCT04759856), germ cell tumors (AGCT1531, AGCT1532; NCT03067181, NCT02582697), rhabdomyosarcoma (ARST2031; NCT04994132), and osteosarcoma (AOST2031, AOST2032; NCT05235165, NCT05691478).

Treatment-Related Toxicities
Just as AYA biology accounts for unique presentations and treatment response compared with younger and older counterparts, AYAs exhibit different toxicity profiles. In part, the biology driving inferior AYA outcomes leads to more intensified treatment regimens, and thus more adverse toxicity profiles. This has also been seen with newer immunotherapy agents used in melanoma, where increased toxicity in AYA compared with older adults was ultimately attributed to the intensity of the therapy.51 Examples of toxicities more prevalent among AYAs include avascular necrosis (prolonged steroid exposure), peripheral neuropathy (vincristine), and hepatotoxicity (asparaginase).52 This phenomenon may be related to differential metabolism of certain agents, developmental stage (when treatment is delivered) and associated hormonal differences impacting metabolism, or a different risk profile; this phenomenon may also explain the increased infection-related mortality seen in AYAs with ALL, with acute myeloid leukemia (AML), and undergoing blood or marrow transplant (BMT). Inferior outcomes can occur if toxicity is significant enough to de-escalate therapy.53 Paradoxically, examples of less toxicity, such as the better hematologic profiles seen in AYA receiving alkylators compared with younger patients, may represent quicker metabolism and therefore less exposure to these critical chemotherapy agents. Opportunities to alleviate these toxicities include joint development of both therapeutic trials and those aimed at toxicities and supportive care; the first is in development (ClinicalTrials.gov identifier: NCT05602194).

Risk-Based Survivorship Care
Late effects of cancer therapy, particularly second malignancies and cardiac/pulmonary toxicities, can result in longer-term morbidity and mortality.54 Although robust survivorship care exists for childhood cancer survivors and older patients with distinct diseases (breast cancer), models of care differ and programs including patients diagnosed as AYAs are rare. Long-term follow-up of childhood cancer survivors follows an algorithmic risk-based model in which treatment exposures determine the type and frequency of surveillance necessary to identify a particular late effect.54 These recommendations are based on long-standing guidelines that are rigorously maintained based on ongoing literature review. Although disease-specific guidelines exist for patients with breast cancer, they trend toward a focus on quality-of-life outcomes.55 Given the unique profiles in cancer biology and psychosocial needs among AYAs, it is likely that survivors of AYA cancers also have unique late-effects profiles (medical and psychosocial). Thus, comprehensive survivorship care for AYA cancer survivors will need to incorporate both domains, especially as they integrate their cancer experience with navigating personal independence, relationships, and education/employment among other developmental tasks.56,57

System-Level Factors
Domains Associated With Survival as a Primary Outcome
Location of Care
NCI Designation
Across diagnoses common to both AYAs/children and AYAs/adults, AYAs have superior outcomes when they are treated at NCI-designated Comprehensive Cancer Centers (CCC) compared with elsewhere.17–20 Hypotheses include that this outcome benefit is due to the comprehensiveness of care provided at these sites (including enhanced supportive care and psychosocial support), and enhanced access to clinical trials and/or clinicians practicing adjacent to those trials.

Model of Care
For some diagnoses, superior outcomes are associated with treatment within a pediatric model of care (vs an adult/internal medicine model).28,29 Similar hypotheses would suggest that this benefit is due to the delivery of pediatric-style therapy (where those outcome benefits are seen), along with enhanced psychosocial support and supportive care; the paternalistic pediatric model of care facilitates adherence to prescribed visit schedules, in contrast to the individualistic adult/internal medicine model.

Presence of an AYA Program
Rooted in the breadth of evidence discussed herein, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AYA Oncology have long recommended that AYAs be treated by a facility/oncologist knowledgeable in AYAs. HRQoL benefits related to being treated at a site with a formal AYA program have been seen in single-institution studies, and more specific evidence is actively evolving.60,61 AYA programs have many forms (psychosocial support or medical and psychosocial support, only one or many disease groups). Although each likely provides benefit, there is no means of differentiating these AYA programs from each other. There is no set of minimal services, standards, or metrics by which institutions consider their approach to be an AYA program.
**Clinical Trial Enrollment**

AYAs with cancer enroll less often on clinical trials than younger children and older adults (estimated AYA enrollment, 3%–18%).62,63 This low clinical trial enrollment correlates highly with a slower rate of survival improvement in AYAs.62 Barriers to trial enrollment among AYAs are multidimensional and inadequately understood.

At the patient level, low trial enrollment has been associated with older age, lack of insurance, not being treated by a pediatric oncologist,64 limited awareness of trials, concerns regarding research, and the unique psychosocial needs of AYAs.62 At the facility level, low trial enrollment has been associated with a lack of trial availability, enrollment patterns at treating institutions, and regulatory barriers due to facility structure, among other factors.65 Upper age limits of either pediatric trials or children’s hospitals have served as barriers to enrollment for AYAs with relevant diagnoses.66

The NCI, NCI Community Oncology Research Program (NCORP), and NCTN have led efforts to overcome system-level barriers,67–68 with favorable early signs among AYA subgroups.63 This includes cross-network studies developed jointly by pediatric/adult principal investigators (see earlier section on “Treatment Regimen”); AYA trials are activated via the Cancer Trials Support Unit (CTSU) by pediatric/adult cooperative groups, with each enrolling institution receiving credit for their chosen pediatric/adult group.

Clinical trials are the chief mechanism for determining the most effective therapies for improving cancer survival, and they facilitate the biospecimen repositories necessary for basic and translational research into cancer biology and treatment response. Multifaceted strategies are needed to improve clinical trial enrollment and are under development.

**Transdisciplinary Communication**

Collaboration by physicians and staff across medical/pediatric oncology can drive the use of novel (pediatric vs adult) therapy and facilitate clinical trial enrollment,69 supporting the notion of a comprehensive team evaluation rooted in transdisciplinary physician/staff collaboration.

**Domains Associated With HRQoL as a Primary Outcome**

A large multisite study revealed71 that unmet needs among AYAs (fertility preservation, mental health, support group and financial counseling) contribute to lower HRQoL among AYAs. Distress in patients with cancer and survivors has been associated with increased mortality and poor performance status, treatment adherence, and quality of life.72–73 Among AYAs, distress is associated with an increased risk for obesity and poor health behavior, which, in turn, increases the risk for other adverse health outcomes, such as second primary cancers and chronic health comorbidities.74

**Psychosocial Support**

AYAs are at risk for clinically significant psychological distress and adverse mental health outcomes that can continue into posttreatment survivorship.75–77 Unmet needs among AYAs are significant predictors of distress over time;76 this includes informational, counseling, practical support, legal,79 family/childcare,80 and educational/vocational needs.81 Additionally, cancer has a negative impact on the sexual function of AYAs,82,83 which, in turn, has a bidirectional effect with HRQoL.84 However, much of the work on sexual dysfunction among AYAs has focused on AYA survivors85,86 or AYAs with adult-type malignancies such colorectal cancer.87

The importance of quality psychosocial care to address the breadth and intensity of AYAs’ diverse needs has been routinely emphasized by national organizations and AYA-focused collaborators.1,6,88-89 Despite this, comprehensive psychosocial support is not always part of standard care and may not be delivered in a timely fashion.66 To address this gap, emerging research has highlighted the value of collaborative engagement among multidisciplinary teams and key stakeholders, developmentally appropriate care, and broad-based needs assessments with workflow integration to ensure connections between AYAs and appropriate psychosocial services.61,90-92 Future work needs to build from these promising studies to guide additional implementation efforts and inform real-world effectiveness trials to improve outcomes.

**Fertility Preservation**

AYA survivors identify preserving the capacity to have biological children as important to their HRQoL. Given the very different reproductive biology between males and females, gender-specific recommendations are necessary to meet this goal. To this end, there is a strong rationale that sperm banking should be offered to all male AYA patients.93 Although the greatest risk of permanent infertility for males is among those who receive 4 g/m² CED (cyclophosphamide-equivalent dose) of alkylating agents, ≥4 Gy of testicular radiation, ≥40 Gy of hypothalamic radiation, or myeloablative/reduced-intensity hematopoietic stem cell transplant, many more AYA males will develop temporary azoospermia secondary to other cancer-related treatment. Therefore, males who might not be at risk from up-front treatment may lose the window to sperm bank in the setting of relapse or intensified therapy following response-based risk stratification.94 Ovarian germ cells are generally less sensitive to destruction by alkylating agents or radiation. However, because of the naturally declining ovarian reserve over time, the likelihood of females developing infertility from these exposures increases dramatically with older age at diagnosis. Embryo, oocyte, and ovarian tissue cryopreservation
offer the possibility of preserving fertility. Despite the designation of these procedures as standard of care by the American Society for Reproductive Medicine, access to them remains difficult and far from universal. Financial toxicity is a major barrier for both males and females, because the costs for these interventions are often not covered by insurance.25

Conclusions
Several factors influence outcomes among AYAs with cancer, from HRQoL to survival. When considering how to improve AYA outcomes, we recognize that they sit at the plane of the individual and the healthcare system, keeping in mind the interrelated domains presented (Figure 1). It is key not only to consider patient-level interventions and development of novel cancer agents but also to develop systems-level interventions that can reach the true diversity of AYAs (age range, race/ethnicity, socioeconomics, and gender identity) and be executed in parallel, thus expanding the impact to a vast number of AYAs.

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Understanding Inferior Outcomes in AYAs


