

# Influencing Referral of Adolescents and Young Adults With Cancer to Sites With Higher Rates of Trial Enrollment

## abstract

Adolescents and young adults (AYAs) have lower rates of clinical trial enrollment than younger or older patients with cancer. Multiple approaches to change policy and practice need to be used to improve this statistic. This article examines the option of increasing referral to 3 types of centers that are known to have relatively higher rates of enrollment of AYAs: pediatric cancer centers, AYA oncology programs, and National Cancer Institute–designated cancer centers. There are reasonable challenges to changing referral patterns, and more research, as well as education of those diagnosing AYAs, is required.

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### KEY WORDS

adolescent, young adult, neoplasms, referral and consultation, clinical trial, health services accessibility, access to health care

### ABBREVIATIONS

AYA—adolescent and young adult

CT—clinical trial

NCI—National Cancer Institute

NCI-CC—National Cancer Institute-designated Cancer Center

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Altogether, the articles in this supplement issue of *Pediatrics*, consider the multitude of reasons contributing to the low clinical trial (CT) accrual rates for adolescents and young adults (AYAs) with cancer. Given the barriers to opening CTs at more treatment sites, 1 possible solution is to increase referral of AYAs to sites that already have more trials open and have higher rates of accrual. AYAs may be seen at a variety of clinical settings, all of which have different rates of CT utilization. If one accepts that increasing enrollment of AYAs in CTs is critical to improving outcomes,<sup>1</sup> one could argue that centralization of services to centers with high accrual may improve AYA outcomes. This article examines the option of increasing referral to 3 types of centers: pediatric cancer centers, AYA oncology programs, and National Cancer Institute–designated cancer centers (NCI-CCs). We acknowledge that some sites fall into 2 or even 3 of these categories, but for clarity we will consider the characteristics of each type of center separately. The emphasis, as for all articles in this series, is on the 15- to 19-year-old age group, but some of the issues and solutions would apply to patients in their 20s as well, especially those with “pediatric type” cancers.

### WHERE ARE CTs OPEN FOR AYAs?

There are large variations in the rates of enrollment of AYAs by clinical site, with a downward trend from pediatric cancer centers to AYA centers to NCI-CCs to community centers. This variation is likely due to a variation in the number of open CTs at those sites.

For pediatric oncologists, CTs are considered the “standard of care,”<sup>2</sup> and rates of CT enrollments have always been highest for children <15 years treated at pediatric centers.<sup>3</sup> In part because only one-third of 15- to 19-year-olds are seen at pediatric

centers,<sup>4</sup> the CT participation for that age group has usually been approximately one-quarter to one-half the rate of that in younger children.<sup>1,4,5</sup> At pediatric oncology centers, the rate of CT enrollment of AYAs is lower than for younger patients, but it is still higher than the percentage enrolled in trials when treated at nonpediatric cancer centers.<sup>5</sup> In a study at the University of Pittsburgh, 38% of the 10- to 15-year-olds and 27% of the 15- to 22-year-olds treated at Children’s Hospital Pittsburgh, but only 4% of the 15- to 22-year-olds treated at the University of Pittsburgh medical oncology center were enrolled in CTs.<sup>6</sup> In a Surveillance, Epidemiology, and End Results (SEER) cancer registry study in 15- to 39-year-old AYAs with selected diagnoses, those seeing a pediatric oncologist were 7 times as likely to be enrolled compared with those treated by medical oncologists, controlled for age, insurance status, cancer type, and cancer stage.<sup>7</sup>

When pediatric centers are part of a university program such that a single institutional review board can approve protocols and patients can be enrolled from either the pediatric or adult programs, rates of enrollment can increase. Dedicated AYA programs have been established at many cancer centers across the country, and they have the potential to increase enrollment rates by focusing efforts on targeting AYA patients and promoting available CTs. At the University of Pittsburgh, after an effort of their AYA program oncologist to encourage medical oncologists to enroll AYA patients in CTs, the rate of enrollment increased from 4% to 33%.<sup>8</sup> An AYA program can provide the focus, desire, and effort to ensure that trials are open. Shared multidisciplinary tumor boards can make all staff aware of CTs. A pilot project at the Oregon Health and Science University AYA program includes a clinical research assistant who bridges the pediatric and adult

divisions to assist in facilitating awareness of and enrollment of AYAs in CTs.<sup>9</sup> In addition, the AYA program providers’ experience working with the population is likely to help overcome patient barriers to enrollment (eg, developmental immaturity, parental involvement, literacy, concerns over school/work conflicts).

The rate of enrollment in CTs is much greater at NCI-CCs than at all other sites of care. In 2011, 17% of registrants at NCI-CCs were enrolled in a therapeutic CT,<sup>10</sup> clearly more than the national average of ~3% to 5%<sup>3</sup> (ie, enrollment at non-NCI-CCs is even lower). A further advantage AYAs may have at NCI-CCs is that such centers frequently are academic centers that have both pediatric and adult programs, and may have a common institutional review board, logistics that facilitate availability of pediatric CTs to AYAs, even without a formal AYA oncology program in place.

### WHERE ARE AYAs WITH CANCER CURRENTLY BEING SEEN?

Because of overlapping and non-regulated age cutoffs of hospitals in the United States, AYAs between the age of 15 and 19 years may be seen in a pediatric or an adult setting. Studies have estimated that approximately two-thirds of 15- to 19-year-olds are never seen at pediatric centers.<sup>4,11,12</sup> In a population-based cancer registry study, Albritton et al<sup>4</sup> found that, whereas nearly all children under age 10 were seen at pediatric centers, the rate dropped to 34% between 15 and 19 years of age. Furthermore, only 40% of these AYAs were seen at academic sites; 47% were seen at community American College of Surgeons–accredited cancer centers, and 13% were never seen at American College of Surgeons centers. This rate is slightly better than for adults in general, of whom it is estimated 75% to 80% are

seen at nonacademic centers.<sup>13–15</sup> The rate of care at a pediatric center appears to vary by age, decreasing linearly even between 15 and 19 years of age at a rate of 14% per year. It does not appear to vary by distance from the center.<sup>4</sup>

### **INFLUENCING REFERRAL OF AYAs TO CENTERS WITH HIGH CT ACCRUALS**

Given the impact of site of care on enrollment, 1 solution to increasing CT accrual is to influence referral of the 60% of AYAs currently seen at community, nonacademic centers to sites that have higher rates of enrollment, that is, to pediatric centers, AYA programs, or NCI-CCs. There are several audiences that could affect referral patterns: primary care providers, intermediary specialists, oncologists, and patients themselves.

The providers AYAs see with their first symptoms of cancer are the gatekeepers who determine the referral to a pediatric or medical oncologist and who could potentially be engaged to influence the CT process.<sup>16,17</sup> There are no data on which specialists these are. The population-level data on medical care utilization by adolescents reflect acute illness, accidents, and preventive care,<sup>18</sup> not necessarily the spectrum of providers an adolescent would see for cancer symptoms. It would likely include providers in pediatrics, family practice, internal medicine, emergency medicine, general surgery, orthopedics, neurology, and other specialties. Gordon et al<sup>19</sup> surveyed primary care providers with hypothetical vignettes of AYA (ages 13–22 years) cancer presentations. Primary care physician specialty, patient age, type of cancer, and insurance status were significant drivers of referral patterns for AYA patients with cancer. Referral to a pediatric oncologist was made in 60% of vignettes by pediatric primary care

providers and in 36.5% of vignettes by nonpediatrician primary care providers. Regardless of primary care provider specialty, referral patterns shifted with patient age: 74% of 16-year-olds versus 25% of 19-year-olds were referred to pediatric oncologists. This finding suggests that nonpediatricians could be targeted with educational messaging, encouraging them to either mention CTs or to allow the availability of a CT influence their choice of referral site.<sup>20</sup> This engagement of primary care providers in CT marketing appears to be underused; an NCI survey of primary care providers revealed that 98% did not discuss CTs with their patients and 37% were unaware that CTs might be an option.<sup>21,22</sup> Unpublished data from the Gordon et al study asked the primary care provider respondents about their awareness of and comfort with CTs. Seventy-eight percent thought the upper age limit for inclusion in NCI-sponsored pediatric oncology trials was  $\leq 21$  years; only 14% felt more than moderately confident introducing CTs, and 65% felt it was not within their job scope (L.M. Gordon, MPH, R.H. Johnson, MD, M.A. Au, and K.H. Albritton, MD, personal communication, 2013).

Other providers involved in the care of an AYA with cancer before ultimate medical treatment begins, such as surgeons and pathologists, could also be educated to encourage choice of treatment centers that have CTs available. Once the AYA is seen by an oncologist, it is less likely, but not unfathomable, that the patient would be transferred to another center to participate in a CT. A survey of community medical oncologists on their patterns of care of patients  $< 21$  years of age revealed the perception that they considered 16- to 21-year-olds as adults and did not make a distinction between their treatment of these patients and those older than 21 years.<sup>23</sup> However,

education of oncologists on the possible benefit of treatment at another center and/or in a CT could likely influence referral patterns. In addition to education, efforts should be made to facilitate access to information on CT availability. Cancer CT networks could improve the provision of information to both pediatric and adult oncologists about currently available CTs that would facilitate referral decision-making.

In addition to influencing providers, efforts could be made to increase AYA patients' and public awareness of the benefits of treatment at specialized centers and in CTs. The AYA Health Outcomes and Patient Experience study surveyed  $> 500$  AYAs aged 15 to 39 years, 13% of whom were aged 15 to 19 years, and found that 62% of AYAs did not know if there were CTs available for their cancer; an additional 19% reported that there was no CT available (S.M. Schwartz, MD and A. Wilder-Smith, PhD, MPH personal communication, 2013). Although willingness to participate in CTs has been correlated with awareness of CTs,<sup>24</sup> it is unclear how much a campaign to increase awareness will increase willingness and enrollment,<sup>25</sup> because it is unknown how influential the lack of awareness is on preventing enrollment of AYAs. Studies in other underrepresented populations (minorities, the elderly) have found cultural barriers to participation even after individuals are made aware of the option of CTs. It is likely that targeted messaging and placement will be required that especially appeals to the informational and situational needs of AYAs and their caregivers.

### **CHALLENGES TO CHANGING REFERRAL PATTERNS**

There are potential challenges to applying any of these efforts. Although AYAs are more likely to be enrolled in CTs at pediatric hospitals, some pediatric

hospitals still have upper age restrictions that would exclude those who are  $\geq 18$  years. One could argue to have those limits lifted, but they often reflect a real limit on the skills and resources, and even mission, of a pediatric hospital to care for older patients. Pediatric staff and providers may be uncomfortable or untrained to attend to the medical and psychological needs of young adults. Even if the oncology team has the ability, one must consider the need for the support services of the other specialties and staff in the entire hospital, especially the ICU and surgical services. Given the incidence of cancer in AYAs, if pediatric hospitals were universally tasked with taking on the care of all 15- to 19-year-olds, their volume of patients with cancer would increase by  $\sim 27\%$ .<sup>26</sup> Although their medical needs may be met, the AYAs themselves may feel that the physical environment and culture of the pediatric hospital do not seem age-appropriate. Furthermore, even if the age limit was raised, care for a patient with cancer can span years, either because of a prolonged acute phase, chronic therapy (eg, chronic myelogenous leukemia), or because of relapses (not to mention survivorship care). Therefore, for AYAs welcomed to a pediatric hospital, transfers to an adult medical system have to occur at some point. Therefore, efforts at partnership and planned transition programs between pediatric and adult systems should be pursued.

AYA programs are being created in part to remedy these problems, but building one is easier said than done.<sup>27</sup> The

British Teenage Cancer Trust units have been very successful, but these were funded through a very large philanthropy and aided by a national health system that provided a common financial structure, institutional review board, and other centralized operations to both the pediatric and adult side.<sup>28,29</sup> It is proving to be more of a challenge in the United States, and will likely be even more complex in the community in which pediatric and adult hospitals have less ties and structure binding them. There clearly is a financial cost to the added services, and there are no data yet to show that outcomes, either survival or even patient-related outcomes or health-related quality of life, are improved.<sup>30</sup>

Earlier this year, the National Comprehensive Cancer Network published guidelines for AYA patients with cancer.<sup>31</sup> These guidelines recommend that AYAs with newly diagnosed cancer be referred to NCI-CCs in hopes of providing appropriate services to AYAs and offering available CTs to them. However, although NCI-CCs are most likely to offer CTs, they may not necessarily have an open trial available or provide an AYA program.

In all of these cases, we assume AYAs would be amenable to the referral, despite the potential costs of additional travel and distance from school, work, and support systems. Data suggest that pediatric patients travel for care, but

that is often because of limited other choices. Early data from England suggest that patients who travel to Teenage Cancer Trust units feel it is “worth it.”<sup>32,33</sup> The other audience clearly affected by the suggested change in referral is the community providers, who would lose revenue. The impact is a greater loss to these providers, who rely on fee-for-service, than it is a potential gain to salaried academic oncologists, who are more removed from the financial impact of referral patterns. Health care reform that supports payment for performance outcomes may influence the attractiveness and feasibility of such change.

## CONCLUSIONS

It is hoped that other efforts to remove barriers to AYA CT entry are successful and that there are increases in the number of appropriate trials, in the variety of sites opening the trials, and in accrual where the trials are open. But, bearing in mind the challenges in those efforts, it is reasonable to try, at least concurrently, to increase accruals of AYAs to those sites that currently have higher rates of AYA CT entry, namely pediatric centers, AYA programs, and NCI-CCs. As efforts are made to influence referral patterns, attention should be made to collect and analyze the impact on outcomes, both of CT enrollment and on survival and other health-related quality of life and patient-related outcomes.

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