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Cancer Clinical Trials Accrual: Missed Opportunities to Address Disparities and Missed Opportunities to Improve Outcomes for All

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Stewart et al.[1] have implemented a clever strategy for documenting the underrepresentation of racial/ethnic minorities and older patients in surgical oncology clinical trials. Their approach involved calculation of an "enrollment fraction" (EF) for various subsets of the American cancer patient population. Individual EFs were computed as the ratio of National Cancer Institute (NCI)-generated data on cooperative group clinical trial accrual compared with Surveillance, Epidemiology, and End Results Program-derived cancer incidence data. The disappointing (but not necessarily surprising) results from these analyses demonstrated that EFs were substantially lower for African American, Hispanic/Latino American, and Asian/Pacific Islander cancer patients (0.48%, 0.54%, and 0.59%, respectively) when compared with white Americans (0.72%). Cancer patients age 75 years and older had an EF of 0.14%, in contrast to an EF of 1.8% for patients aged 21 to 54, and 0.91% for those aged 55 and 64.

Race/ethnicity- and age-related disparities in surgical oncology clinical trial accrual are potent examples of inequities the current American health care system. The clinical trial mechanism represents the most powerful weapon that the oncology community possesses in the effort to improve the standard of care as well as survivorship for cancer patients. Diet, comorbidities, lifestyle/culture, and socioeconomic resources are all features that vary between and within racial/ethnic communities, as well as by age category. All of these factors can affect cancer risk, treatment, and survival. Our failure to account for these variations by ensuring appropriate diversity in the clinical trial patient population is truly a tragedy because it represents a missed opportunity to understand and eliminate cancer disparities.

As an extreme example, lack of diversity is analogous to conducting a clinical trial of neoadjuvant chemoradiation for rectal cancer where all of the participants are college-educated, 45 year old Swedish men who own a car and two homes, follow a strict vegetarian diet, exercise daily, and have a perfect body mass index. A trial of this design would obviously tell us very little about the efficacy of neoadjuvant chemoradiation in a population of obese diabetic nursing home residents that happen to be predominantly elderly immigrant women. Less dramatic differences between clinical trial participants and the general cancer population will also put us at risk for misunderstanding the safety profiles of innovative cancer therapies.

The underrepresentation of minority racial/ethnic groups in cancer clinical trials is magnified when we take a critical look at the accrual targets used by most investigators. Most clinical trials aim for racial/ethnic composition that reflects the demographics of the general American population. This goal ignores the fact that most clinical trials are designed for specific cancer stages, and trials studying advanced-stage disease tend to be prioritized. Minority racial-ethnic patients are actually overrepresented among most subsets of advanced-stage cancers. Therefore, we should actually be aiming for accrual of substantially

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higher proportions of these patients for clinical trials that are designed to study advanced cancer. To address this issue, the American College of Surgeons Oncology Group (ACOSOG) Special Populations Committee[2] worked with the National Cancer Data Base to develop organ- and stage-specific accrual targets for breast, prostate, lung, and colorectal cancer trials.

The missed opportunity to understand cancer disparities through clinical trials research is an undeniable flaw in oncology research. However, the more fundamental problem is our dismally low accrual of adult cancer patients from the general American population onto clinical trials. Stewart et al. reported an overall EF of only 0.68% for all adult patients onto surgical trials for breast, prostate, colorectal, and lung cancer. Work conducted by other investigators has estimated that only 4% of all adult American cancer patients participate in any type of clinical trial. These very low accrual proportions represent a frustrating barrier to advances in overall cancer treatment and survivorship.

Clearly, we must do a better job of educating the American public about the benefits and safety of clinical trial research; and we must make it easier for the oncology community to provide their patients with opportunities to enroll onto clinical trials. Unfortunately, however, these efforts frequently counteract each other. Dense regulations and multitiered review processes accompany every clinical trial, with the intent of ensuring protection of human subjects. These protections are essential, but they are also costly and labor-intensive. The resulting impediments are apparent with two important breast cancer trials that were never completed. The ACOSOG Z0011 trial was designed to answer a question that has been debated for decades regarding the necessity of a standard axillary lymph node dissection in all cases of node-positive breast cancer. The Radiation Therapeutics and Oncology Group (RTOG) conducted a trial to determine whether whole-breast radiation is necessary for all cases of ductal carcinoma-in-situ managed by breast conservation. Both of these trials were closed because of poor accrual rates, and we therefore continue to recommend these morbid and expensive locoregional therapies as the standard of care. It is certainly possible that the slow accrual rates were at least partially attributable to the complexities involved with patient education and the logistics of clinical trial registration.

There is definitely hope on the horizon in the form of several innovative collaborative endeavors that aim to correct our current clinical trial accrual deficiencies. Through the Patient Education, Patient Advocate, and Special Populations Committees, the ACOSOG has implemented a variety of aggressive outreach programs for patients and physicians regarding clinical trial participation in areas with a high population of minorities to increase their participation in clinical trials (http://www.acosog.org/). The Education Network to Advance Cancer Clinical Trials (ENACCT) explores the use of community-based participatory research methodology for clinical trials recruitment (http://www.enacct.org/). The Eliminating Disparities in Clinical Trials (EDICT) program brings together leaders to advance policy solutions to disparities in clinical trials through which change can occur at the federal government, state government, and institutional levels, as well as public, private, and/or nonprofit sectors (http://www.bcm.edu/edict/home.html). Two complementary projects, BackPack and CLAS-ACT, are developing helpful methods that should be used by physicians, researchers, and advocates to eliminate disparities in clinical trials, specifically in recruitment, retention, and return.

The work of Stewart et al. highlights deficiencies in surgical oncology clinical trial research programs. Their research methods should be replicated by others in analyzing accrual patterns to medical oncology, radiation oncology, and imaging trials. We are likely to see the same disappointing results, but we can only move ahead by better defining our starting point. To truly redress disparities, we should not be satisfied by only looking at those who are recruited onto trials. We must also recognize the importance of ensuring that we scrutinize with equal vigor the retention of those accrued.

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