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Article type : Editorial

Title: CLINICAL TRIALS AS A PATH TOWARD EQUITY

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Running Head: Racial Differences in Survival/ Response

Keywords: Racial Differences in Survival and Response , Therapy in Patients with Metastatic Colorectal Cancer , A Secondary Analysis , CALGB/SWOG 80405 , (Alliance A15193) , by Rebecca Snyder et al.

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Precis: The editorial discusses the secondary analysis of the first line metastatic colorectal cancer trial, CALGB/SWOG 80405, which demonstrates the potential that participation in a clinical trial provides a level of equity thus far elusive for the overall population of Black individuals with colon cancer. Although encouraging, what is lacking in trial design is inclusion of factors beyond standard efficacy, safety and patient reported outcomes that address social determinants of health that clearly are detriments not only to trial enrollment but can have profound consequences in outcomes including survival.

The more things change the more they remain the same. A cliché for sure; however, the specter of disparity and implications for health care delivery in the United States is on repeat. The paucity of justice, equity and equality has been no more obvious than during our ongoing COVID pandemic as observed by many.

Racial and ethnic disparities and their effects on delivery of healthcare, in particular cancer survival, have long been described. These inequities have been prevalent across the entire spectrum of cancer care including prevention, early detection (screening), treatment and survivorship care. (1). Disparities in gastrointestinal cancer risk and outcomes have been no exception. For example, California Cancer Registry data including 161,820 colorectal cancer patients diagnosed between 2000 and 2013 showed that cancer specific mortality was

significantly higher in black males and females (36% and 34%, respectively) compared to non-Hispanic white patients although adjustment for all covariables reduced the differences in women. (2) Stage at diagnosis was a significant factor explaining overall survival disparities. A National Cancer Database assessment of over 600.000 gastrointestinal patients including 62% with colon and rectal cancers reported undertreatment of Black compared to White patients represented by disproportionally low operative rates in Black patients and decreased survival. (3) African-Americans also have the highest incidence of colorectal cancer among all United States racial/ethnic groups with a significant rate of rise for young Blacks. (4)

In this issue of *Cancer* Snyder et al have assessed whether there were racial differences between Black and White patients who participated on the first line therapy metastatic colorectal NCI cooperative group trial CALGB/SWOG 80405 including OS, progression-free survival (PFS), and response to therapy as the primary aim. (5) The trial compared the benefit of adding either cetuximab or bevacizumab to FOLFOX or FOLFIRI chemotherapy. This study is one of the most modern large randomized trials for patients with metastatic colorectal cancer to date and as such represents the standard of care for patients with this disease.

As the authors mention, Black individuals with colorectal cancer have significantly higher incidence and mortality compared to White patients. Although the mortality is decreasing in both Black and White individuals, the decline is principally seen in White patients. As referenced by the authors previously published clinical trials have shown contradictory observations among trials that have analyzed differences between Black and White patients in the adjuvant setting, although overall it did appear Black individuals had inferior outcomes compared to Whites. Limited data in the advanced disease setting (NCCTG N9741) showed no racial differences in time to progression or overall survival.

CALGB/SWOG 80405 enrolled a total of 2334 patients of whom 12% self-identified as Black and 81.5% self-identified as White. The final data set in this secondary analysis included 392 matched pairs of patients. Median overall survival and progression free survival did not significantly differ by race. In addition, there was no difference in response to therapy by race. Most toxicities did not differ by race although Black patients had lower rates and lower odds of experiencing grade 3 or greater fatigue. Those who underwent curative surgical resection for metastatic disease after initial chemotherapy were also similar in numbers. Increasingly KRAS mutation status is recognized as a prognostic factor and 80405 similarly has shown that patients with KRAS mutations have a lower survival probability than those with KRAS wild-type tumors. This study also noted no racial differences when matched by KRAS status. The authors

describe several limitations to their study as a secondary analysis of a propensity matched cohort of patients. There were differences between the Black and White patients in performance status and palliative intention of treatment (versus neoadjuvant). They note the 3-month difference in median overall survivorship between Black and White patients (26 versus 29 months, respectively); however, this did not reach significance possibly because the study was underpowered to detect differences in survival by race. The KRAS analysis was also limited because 30% of the initial cohort of Black patients had missing KRAS status.

The authors conclude that because patients received standardized treatment through their participation in this phase III randomized clinical trial, the racial disparities that have been observed in many other analyses are likely secondary to access to care and treatment delivery. Reducing variability in care is a potential significant advantage of patient access to clinical trials since the construct of most cancer treatment clinical trials defines rigorous testing, treatment parameters, toxicity monitoring and ongoing assessment to optimally evaluate safety and efficacy outcomes. Adherence to cancer treatment guidelines provides yet another algorithm to reduce variability of care and ensure that individuals are offered the most appropriate testing, treatment interventions and follow-up to optimize outcomes. For patients with colon cancer in particular, analyses have demonstrated that adherence to guidelines can improve survival. (6,7)

The issue of reducing variability in oncologic care by encouraging enrollment in clinical trials and following recognized cancer treatment guidelines, is confounded by a host of factors most notably social determinants of health. For example, a recent SWOG Cancer Research Network analysis of over 41,000 cancer patients enrolled in 55 phase III and large phase II clinical trials showed that the clinical trial participants who lived in areas with the highest socioeconomic deprivation compared to participants in the most affluent areas had worse overall, progression-free and cancer-specific survival. (8). Another systematic review of published studies from 1970 through April 1,2019 evaluated colorectal cancer and effects of social determinants of health confirming that poverty, lack of education, immigration status, lack of social support and social isolation are linked to colorectal cancer stage at diagnosis and survival. (9). Increasingly race is viewed as a social construct, and a proxy for poorer social determinants of health which are more prevalent among communities of color. The American Cancer Society, in their recent Blueprint for Practice, Research, and Policy, has provided a construct to eliminate cancer-related disparities which provides recommendations to address structural inequities, institutional environments, living environments, risk factors and the spectrum of cancer comorbidities and

mortality. (1) The American Medical Association has approved a policy that replaces race with genetic ancestry or ZIP code to more fully capture the contribution of biological differences or neighborhood deprivation on health disparities traditionally attributed to race. (10,11)

The low rate of participation in cancer clinical trials has been a longstanding dilemma that has not significantly reversed over the years. A recent landscape report assessing barriers to patient enrollment in therapeutic clinical trials for cancer estimated that the current overall rate of trial participation including NCI- and industry-sponsored therapeutic trials was estimated at about 8%. This analysis also described significant demographic and socioeconomic disparities in trial enrollment. Of note were the significant racial and ethnic disparities including marked underrepresentation of Black and American Indian/Alaska native populations and those age 70 or greater particularly in FDA-submitted cancer trials. (12). Even participation in a clinical trial does not guarantee equal treatment, as a trial standardizes the prescribed trial components not the receipt of trial components, otherwise we would not need to describe protocol deviations. Further, treatment of co-morbidities or adverse events may vary among participants that can contribute to outcome heterogeneity.

This secondary analysis CALGB/SWOG 80405 demonstrates the potential that participation in a clinical trial provides a level of equity thus far elusive for the overall population of Black individuals with colon cancer. If we believe that cancer clinical trials represent a standard of care then there will need to be dramatic changes in trial designs and clinical practice engagement with patients to more consistently ask individuals if they would consider an available clinical trial at a minimum. The structure of a clinical trial (and cancer treatment guidelines) provides a mechanism for equity by integrating consistency in testing, treatment and follow-up for all enrolled. What is lacking in trial design is inclusion of factors beyond patient reported outcomes that address social determinants of health that clearly are detriments not only to trial enrollment but can have profound consequences in outcomes including survival. At a minimum, investigators need to include neighborhood-level deprivation using ZIP code to more fully account for social determinants of health. The emphasis on shared decision making should provoke a conversation integrating social determinants of health, personal concerns and beliefs that might affect delivery of care whether on a trial or according to recognized standards of care to better ensure access and equity.

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