Next steps to improve disparities in lung cancer treatment clinical trial enrollment

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Provenance: This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

Comment on: Pang HH, Wang X, Stinchcombe TE, *et al.* Enrollment Trends and Disparity Among Patients With Lung Cancer in National Clinical Trials, 1990 to 2012. J Clin Oncol 2016. [Epub ahead of print].

Submitted Dec 10, 2016. Accepted for publication Dec 20, 2016.
doi: 10.21037/atm.2017.01.25
View this article at: http://dx.doi.org/10.21037/atm.2017.01.25

Cancer treatment clinical trials provide access to cutting-edge treatments. Treatment trial results are often used to guide clinical recommendations, decision-making, policies, and further intervention development to treat cancer patients in both academic centers and the community. In the USA, adults enroll in cancer treatment trials at very low rates and participants do not represent the USA cancer population (1). Because their primary objective is to assess efficacy, oncology clinical trials have stringent enrollment criteria. Compared to the general population of adults with cancer, patients that enroll in cancer treatment trials are disproportionately younger, male, physically fit, and are less likely to be from minority racial and ethnic groups (2,3). Assuring representative population heterogeneity in clinical trials is critical to assessing treatment safety and efficacy across diverse patients and assuring subsequent effectiveness among all members of the broader population. With the current trend toward personalized medicine, emerging treatments are often tailored for specific genotypes making enrollment of racially diverse groups particularly salient (4). As lung cancer is the leading cause of USA cancer deaths, lung cancer treatment trials stand to make a huge contribution in improving population cancer mortality.

In a paper recently published in *Journal of Clinical Oncology*, Pang and colleagues evaluated enrollment trends and disparities in National Cancer Institute (NCI)-sponsored cooperative group treatment trials for lung cancer conducted between 1990 and 2012 (5). The authors assessed enrollment disparities based on age, sex, and race among patients with lung cancer (n=578,476). They used two measures of disparities: the enrollment disparity difference (EDD, the absolute different between the estimated subgroup portion among the USA lung cancer population and the subgroup proportion among trial participants) and the enrollment disparity ratio (EDR, the estimated subgroup proportion among the USA lung cancer population divided by the subgroup proportion among trial participants). For these measures, Surveillance, Epidemiology, and End Results Program (SEER) registry data were used to define the underlying USA incident lung cancer population (6).

The authors reported that under-representation in lung cancer treatment trials improved for elderly patients (i.e., age ≥70) with non-small cell lung cancer (NSCLC) and for women with any lung cancer. Specifically, the remaining EDD for older patients with NSCLC was 0.22 (95% CI, 0.19 to 0.25) and the EDR was 1.65 (95% CI, 1.51 to 1.82) (5). For all women with lung cancer, the enrollment gap was nearly null by 2012 (EDD 0.03; 95% CI, 0.00 to 0.06 and EDR 1.07; 95% CI, 1.00 to 1.16) (5). However, enrollment disparities persisted for elderly women and racial/ethnic minorities.

Reasons for disparities and suboptimal clinical trial enrollment are multifactorial. The authors attribute some improvements in enrollment disparities to specific trial characteristics and policy changes. For example, there was an increase in enrollment of older patients in the second half of the observation period which, in part, can be attributed to six trials purposefully designed to enroll elderly patients. This echoes the National Institutes of Health (NIH) Revitalization act of 1993, which was enacted during the study observation period, requiring the inclusion of women and minorities into all NIH-funded research, including the NCI cooperative group trials included in the analysis (5,7). While this appears to have contributed to gains in enrollment of women from 1990–2012, suboptimal enrollment for women and minorities in cancer treatment clinical trials persists (5). That said, the NCI's National Community Oncology Research Program (NCORP), which evolved from the Community Clinical Oncology Program (CCOP) and Minority Based CCOP (MBCCOP) programs, introduced specific structural changes to the NCI clinical research system to directly address the challenges of racial disparities in trial enrollment. Through this structural change, the NCORP minority/underserved community sites (formerly MBCCOP) now enroll a substantial proportion (approximately half) of all minorities on cooperative group trials (4,8). The story of these six trials and the NCORP program provide strong evidence that substantial improvement cannot be expected by any single initiative, but will necessitate a concerted effort by numerous stakeholders including trial sponsors, researchers, clinicians, policy-makers, patients, and community organizations.

The study by Pang *et al*. offered a high-level view of progress in enrolling under-represented populations in trials specific to lung cancer over a substantial time period (22 years). In addition to examining enrollment for several under-represented subgroups, they further evaluated enrollment disparities by subtypes of lung cancer and found that disparities improved for elderly patients with NSCLC but persist for elderly patients with small cell lung cancer (SCLC). This highlights the need to evaluate enrollment disparities further by both patient and trial characteristics within each under-represented population in order to better understand the extent and impact of disparities in trials and identify subgroups to target enrollment improvement efforts. Future analyses should evaluate whether there are differential enrollment rates among patients with different characteristics, tumor types and participation requirements that might impact patients' willingness to enroll (9). Given various trial characteristics and intensity, it is possible that limited social support and/or financial constraints might differentially impact some patient groups more than others, potentially decreasing their likelihood of enrolling in cancer treatment trials. Differences in oncology trial design might also impact enrollment (10). For example, in a study of cardiovascular disease conducted by the Veterans Affairs Cooperative Studies Program trials found that trials with a more invasive arm enrolled fewer minority patients than expected (11).

While well-designed, the study by Pang *et al*. had a few noteworthy limitations. While SEER is the largest source of cancer registry data in the USA, it still covers a relatively small proportion (14%) of the USA population (12) and does not adequately represent the USA population, particularly for tobacco-related cancers (13). The minority population included in SEER is predominately African-American and may not be reflective of other minority groups. Minority populations in SEER are functionally oversampled from Detroit and Atlanta; it is not clear whether the biological characteristics, patient environment, or treatment access characteristics are representative of the broader minority population. Also, the geographic areas represented by SEER may not be the same areas where the treatment trials included were open for accrual. Presumably because of data availability, Pang and colleagues focused on NCI-funded cooperative treatment trials (5). While these account for a large proportion of trials, they provide only a partial view of enrollment disparities. It would also be interesting to understand disparities in enrollment in industry-funded and investigator-initiated clinical trials, which might provide different incentives.

Pang *et al*. highlight several good points—it is important to enroll more adults in cancer treatment trials, and to mitigate disparities and assure heterogeneity, thus improving the breadth of treatment effectiveness. The authors are not the first to characterize the problem of under-enrollment. Improving enrollment of under-represented populations in cancer treatment trials will require changes ranging from the individual level to funding priorities and policies. The need persists for concerted efforts to identify and address common patient barriers to participation (14). Providing trial access in rural communities and building trust within under-represented groups is crucial. Increasing patient engagement in trial design and routine assessment of patient-reported measures may increase enrollment. Changes in provider practice of recommending patients

to trials could also be beneficial. Providers could benefit from tools to identify patients in a systematic manner and open trials for which they may be eligible. Investigators and sponsors should ensure that trial eligibility criteria are adequately justified and do not unnecessarily restrict enrollment.

At the policy level, trials are expensive and more funding would be required to have substantial enrollment growth. With no large increases in research funding on the horizon, the national research enterprise may consider freeing up currently allocated funds by realigning randomized controlled trial (RCT) priorities; for example, by prioritizing funds to open additional expensive prospective RCTs or accelerating their completion by opening them at more centers to examine questions that cannot be examined using other methods. This added cost may be offset by examining other research questions through less expensive approaches vis-à-vis secondary data and comparative effectiveness research rather than RCTs. Growth in secondary data resources and advances in research methodology have opened the door to using secondary data for whole categories of clinical research that previously could only be examined through RCTs (15). Such efficiencies would help address many of the unmet needs that Pang *et al.* present.

Acknowledgements

Funding: Dr. Zullig is supported by a VA Health Services Research and Development (HSR&D) Career Development Award (CDA 13-025). Dr. Carpenter is supported by the Carolina Community Network through the National Cancer Institute's Community Networks Program Centers (U54-CA153602).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Zullig LL, Carpenter WR, Williams CD. Next steps to improve disparities in lung cancer treatment clinical trial enrollment. Ann Transl Med 2017;5(5):118. doi: 10.21037/atm.2017.01.25

