Insurance Status as a Surrogate for Social Determinants of Health in Cancer Clinical Trials

Despite advances in cancer screening, detection, and treatment, disparities in cancer care and long-term cancer-specific outcomes persist among vulnerable populations. Racial/ethnic minorities and underinsured patients remain underrepresented in cancer clinical trials, and to date, randomized trials have been underpowered to evaluate the benefits of experimental treatment within these demographic cohorts.\(^1\)

In a cohort analysis of pooled data from SWOG (formerly the Southwestern Oncology Group) Cancer Research Network phase 3 randomized clinical trials, Unger and colleagues\(^2\) examined whether observed experimental treatment benefits applied equally to patients based on health insurance status. The study compiled data from 19 trials demonstrating a positive effect of treatment, including a diverse group of cancers, and spanning a prolonged period (1984-2012). The analysis included 10,804 patients, for whom 2695 (24.9%) had data on insurance status. The investigators found that an overall and a progression- or relapse-free survival benefit of experimental therapies were observed only for patients with private insurance, not among those with Medicaid or without insurance.

Although this pooled analysis included a heterogeneous patient population, the large sample size allowed for prespecified subgroup analysis to assess whether designated demographic variables of interest, specifically insurance status and race/ethnicity, were equally associated with benefits from experimental therapies. In addition, because patients were randomly assigned to either the standard or experimental treatment arm, the introduction of selection bias based on patient characteristics was minimized.

However, on closer look, the cohort of patients with Medicaid or with no insurance in this study differed markedly from the privately insured cohort in several measured respects, including minority racial/ethnic populations (53.2% vs 18.0%) and functional limitations (51.3% vs 40.1%). It would seem likely that these groups may have also differed in many other unmeasured respects, such as socioeconomic status, health literacy, access to health care, and medical comorbidities. What the data seem to indicate is that insurance status—even in a randomized trial—is an excellent surrogate marker for other social determinants of health. Unfortunately, most of these social factors affecting long-term health status are not easily or routinely captured within contemporary clinical research.

The heterogeneity of included anatomic disease sites and their associated prognoses also introduces significant variation to the analysis, for which Unger and colleagues\(^2\) attempted to control by stratifying the analysis based on disease prognosis. However, patients with early-stage breast cancer enrolled in adjuvant therapy trials, a group with excellent long-term survival, comprised nearly 40% of the overall patient population in the pooled analysis study. It is not surprising, then, that insurance status appears to overpower the small benefit of experimental therapy in a group of patients with otherwise favorable long-term cancer-specific survival. Perhaps the most provocative finding was that nearly half of the variation in overall survival, but only 12% of the variation in progression- or relapse-free survival, was attributable to the interaction between insurance status and treatment. As the authors insightfully pointed out, the association between insurance status and noncancer outcomes, therefore, was likely the strongest.

Given the nearly prohibitive costs and prolonged time frame required to perform randomized trials, real-world evidence is growing in popularity as an alternative approach to study treatment.
effectiveness in cohorts more representative of the general patient population. Real-world evidence is based on data collected outside the traditional clinical trial setting and gathered from registries, electronic medical records, administrative claims, and even patient-generated data. Investigators subsequently use a variety of statistical methods to control for underlying measured confounders, including race/ethnicity and insurance status. It is striking that in the study by Unger et al, even across multiple randomized control trials in which all other confounders should be equally distributed, a significant interaction of insurance and treatment effect was still observed. Clearly, if insurance status is a strong surrogate for other markers of poor health in randomized trials, it is even more likely to serve as such in population-based research. Therefore, the strongest caution must be exercised when performing and interpreting real-world comparative effectiveness studies focused on survival end points.

The findings presented by Unger and colleagues also raise questions about treatment compliance across insurance groups. Could the observed lack of benefit associated with experimental therapies be attributed in part to poor adherence or to higher drop-out rates among Medicaid or uninsured patients receiving experimental therapies? Although patients with private insurance or Medicare typically have coverage for routine care associated with clinical trials, there are no federal mandates for clinical trial coverage for Medicaid patients. It seems likely that patients with Medicaid or with no insurance might incur much higher costs of care for trial participation. Therefore, it would not be surprising to see a diminished benefit of therapy in an intention-to-treat analysis if more of the underinsured patients failed to complete the intended experimental therapy.

Finally, each of the 19 studies included in this analysis focused on a single treatment intervention, which was associated with a survival advantage only for patients with private insurance. Although there will always be a role for these focused therapeutic trials, the findings presented by Unger and colleagues support the implementation of multilevel interventional trials to adequately address cancer health disparities. If the underinsured patient population cannot derive an equal survival benefit from experimental therapies, perhaps we need to refocus our resources on cancer care delivery research that studies the patient’s interaction not only with a treatment regimen but also with their caregivers, communities, treatment teams, and health care systems. To eliminate cancer health disparities, studies should address the other social determinants of health that are associated with cancer and noncancer survival for these at-risk patient populations.

For example, the Delaware Cancer Consortium was established in 2002 to reduce disparities in colorectal cancer outcomes within the state. The project included colon cancer screening reimbursement for low-income patients, implementation of a nurse navigator system, cost coverage for uninsured patients who received a diagnosis of colon cancer, and targeted community interventions to address disparities in colorectal cancer screening among African Americans. In the span of 8 years, the state eliminated disparities in colorectal cancer screening, equalized incidence rates, reduced the percentage of African Americans with regional or distant disease, and nearly eliminated mortality differences. Similarly, a multilevel pragmatic trial performed at 5 cancer centers effectively eliminated racial/ethnic disparities in the delivery of curative treatment of early-stage lung cancer by installing an electronic medical record warning system, providing race/ethnicity-specific feedback to treatment teams, and implementing a nurse navigator program. The design and implementation of these types of multilevel interventional studies should be prioritized if we are to make progress toward eliminating cancer disparities.

The findings presented by Unger and colleagues are timely and eye-opening for clinicians and investigators committed to providing high-quality cancer treatment and survivorship care. Even in the context of randomized clinical trials, patients with Medicaid or with no insurance may not derive the same benefits associated with experimental therapies as patients with private insurance. Improving access to clinical trials and novel therapeutics alone will not eliminate existing health disparities for underinsured populations. Clinical trials that take a more comprehensive approach and address cancer treatment interventions and social determinants of health in parallel are more likely to result in lasting, meaningful effects.
REFERENCES


