A Rare Cancer Opportunity

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ABSTRACT

In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Gallicchio and colleagues analyze recent rare-cancers research and suggest broad themes for accelerating progress in this important area. Whether the type of portfolio creation and portfolio management strategies that have worked for common cancers also work best for rare cancers warrants asking. This commentary argues for consideration of additional approaches. Incorporating principles and successes from large-scale network-based clinical trials and from advocacy-based research, and new ways to approach consortia, might accelerate the quantity and improve the quality of future rare-cancer research. Rare cancers significantly influence the overall cancer burden and cancer disparities. Creative community-based approaches to improve rare-cancers research should be considered.

See related article by Gallichio et al., p. 1305

As a reader, I say: message received. In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Gallicchio and colleagues summarize current population sciences research on rare cancers (1). They identify "gaps and opportunities that can be used to develop efficient and comprehensive strategies to accelerate rare cancer research." When the NCI's Division of Cancer Control and Population Sciences (DCCPS) writes about cancer epidemiology research strategies, it's time to strategize.

Gallicchio and colleagues note that rare cancers together account for one-quarter of incident cancers among U.S. adults each year. As a group, they create trouble (2). Compared with more common cancers, they are more often diagnosed at a regional or distant stage and have poorer 5-year relative survival. Seven in 10 cancers among children and adolescents are rare types; among older adults, just two in 10 are. Not surprisingly, rare cancers account for higher proportions of all cancers among Hispanic (24%), Asian/Pacific Islander (22%), and Black (20%) patients than among non-Hispanic White (19%) patients.

Research saves lives, but rare-cancer research is itself too rare. Gallicchio and colleagues found 123 DCCPS-funded awards on rare cancers in 2018. That's just 19% of the 648 total DCCPS grants awarded in FY2018. With 45 cancers meeting Gallicchio and colleagues' operational definition of rare cancers, that's an on-paper average of approximately 3 awards per rare-cancer site. Some sites had fewer. Those low numbers hinder consistency and efficiency and opportunities to leverage resources across sites.

Gallicchio and colleagues used a justifiably broad definition of rare cancers to review mortality, relative survival, prevalence, and male-female and Black-White disparities, plus median age at diagnosis, annual percentage changes (APC) in incidence and mortality rates, and changes in relative survival rates. Five clusters emerged, based on the relative rank (e.g., low, average, and high) of these metrics within the rare-cancers group. Two factors mattered most: high incidence, or high survival. Both increase researchers' chances of identifying incident rare-cancer events among existing prospective cohort studies or enrolling new rare-cancer survivors (i.e., before they die) in new studies. Cancer sites with low incidence and low survival—that is, clusters A, C, or D, in the data—are especially understudied, underrepresented, and underresourced.

These details and data on types and trends and clusters and resources can help researchers identify opportunities, plan research, and craft proposals. But this analysis has a bigger message: an organic, researcher-initiated, and community-driven approach to the portfolio works for common and most cancers, but rare cancers probably need something more.

Gallicchio and colleagues' conclusion captures this concept: "Research on very rare, and often more lethal, cancer types could benefit from novel approaches to recruitment to more quickly identify patients. Efforts to connect researchers working on these cancer types (consortium building) and to connect patients and patient advocacy groups to opportunities to participate in research would be helpful in studies of rare-cancers." What might those approaches and efforts look like?

Suppose rare-cancers research looked more like clinical trials than traditional observational studies. Even the largest observational studies will be too small to drive discovery for all rare cancers. Compared with observational studies, clinical trials are far better at multi-site-yet-single-protocol research. The growing role of "basket" or "umbrella" trials, "master protocols," and "platform trials" (3) reflects a network mindset that might work well for observational rare-cancers research. These approaches warrant scrutiny (4), but their premise sure sounds solid: as precision medicine replaces one-size-fits-all strategies, establish large-scale infrastructure nets that efficiently capture and funnel rare endpoints into those tailored research pipelines. Steps in this direction might also accelerate broader adoption of common data elements and Findable, Accessible, Interoperable, and Reusable (FAIR) data across all observational research.

Gallicchio and colleagues mentioned consortium building. Existing consortia have boosted ovarian and pancreatic cancer research, in particular. Numerous cancer consortia over the last 20 years—that is, the first generation of consortia—have enabled previously impossible research, generated important results, and provided efficient returns on previous investments. This first generation consists largely of consortia of existing studies. These "retrospective" consortia face challenges such as least-common-data-elements, post-hoc data harmonization, and aging data that particularly affect rare-cancers

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research. What if a second generation of cancer consortia instead started prospectively, taking a "basket" or "umbrella" approach? Agreeing to common protocols today and implementing standard protocols at a network scale tomorrow could accelerate the needed next generation of contemporary rare-cancers research and consortia.

Suppose also that patients and patient advocates played a larger role in observational research on rare-cancers than they do today. Recent rare-disease research has been invigorated by advocates' input. Organizations like the National Organization of Rare Diseases (NORD) offer a compelling idea: once in a rare-disease club, rarity trumps the specific disease. A network of patients, families, survivors, advocates, and researchers who combined forces could probably build a better research infrastructure together than if they each tried on their own. Cancer research has historically been site-centered, but some new team- and group-based approaches—whether as other rare-disease organizations do; or across cancer-site "clusters," as Gallicchio and colleagues have done here; or by genomic or other molecular signatures—make sense.

Finally, suppose Gallicchio and colleagues had been able to stratify their analyses by all of the potential disparities that contribute to the separate but unequal cancer burden in our communities. This analysis did the best it could with the available data on male versus female and Black versus White. But of course broader numbers of racial/ethnic, socioeconomic, sexual/gender identity, environmental, opportunity, and other disparities affect rare cancers. These should be urgently and directly studied. From an epidemiologist's perspective, these slice already-small sample sizes into even tinier groups. From a community-of-stakeholders' perspective, these issues drive home the importance of the types of core considerations mentioned above: diverse networks, equitable cooperation, and an inclusive mission.

Gallicchio and her DCCPS colleagues wrote an important, thoughtful, rigorous, and insightful examination of rare-cancers research today. Their data and conclusions make a strong case for new and novel approaches to understand the causes, outcomes, and burdens of rare cancers. As tomorrow's strategies take shape, greater emphasis on leveraging existing resources, whether for secondary data analysis or rare-cancers ancillary studies, could facilitate increased rare-cancers research in the interim. Steps taken to reengineer rare-cancer research might also create opportunities to improve all cancer research. The sooner that message gains traction, the better.

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