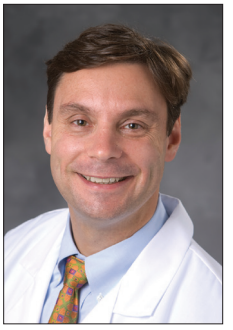
Lumpers and Splitters



I was having a dinner conversation with some of my oncology colleagues when the topic of lumpers vs splitters came up. We were talking about none other than a randomized, controlled trial with an intention-to-treat population and a prespecified subgroup analysis. (For the purposes of self-preservation, I will leave out the details of the study in question.) Maybe not the most enthralling topic for the outsider, but what I found fascinating was just how emphatic people felt about the merits of one analysis vs another.

On the one hand were the lumpers, who felt that the results from the intention-to-treat population were the most important measure of the effect of a specific treatment on a population. Any statistically significant finding in this population meant success for the study, regardless of the effect of the treatment—particularly if the clinical endpoint was important, like overall survival. On the other hand were the splitters, who scoffed at the lumpers and their bygone era of empirical medicine. They held firm that the scientific method of seeking results confirming a prospective hypothesis on the basis of biological features of well-stratified subpopulations was the purest, most robust, and most effective way to advance the field of oncology. Indeed, a particular subpopulation was likely accountable for most of the clinical benefit seen in the overall population. Without this group and its amazing benefit, the study as a whole would have failed.

Not much middle ground was being held.

Science loves the terms *lumpers* and *splitters*. A quick Internet query reveals that none other than Charles Darwin was using these terms back in 1857 as he himself struggled with the subtle differences between varieties and species, especially when the number of species reached well into the thousands (quite the splitter he was!). The terms are frequently used in medicine as well, with 77 titles in PubMed containing both these words. Here, pathology appears to be the most fraught field. As more and more biomarkers are characterized to refine our tumor diagnoses, the temptation emerges to divide our diagnoses further. When such biological features become actionable, these divisions are validated. But as we peel off one subgroup and then another from a general cancer population and develop individualized treatment pathways for each, what happens to the remaining patients? Are we creating a caste system for cancer?

The dinner left me with mixed feelings. The scientist in me felt most comfortable with the splitters, recognizing that precision medicine is a powerful and efficient way to advance our field and to promote the most cost-effective management of patients with cancer. However, the humanitarian in me felt for those patients without defined biomarkers—the others. What would be their fate? How do I tell someone that even though a study demonstrated a treatment benefit to an overall group of people with their type of cancer, we have singled out just the best responders for treatment and discarded the results for the others?

I guess it makes me both a splitter *and* a lumper to recognize that more than one path to progress exists. As for those patients in whom we have not defined a predictive biomarker—a golden ticket to treating their cancer—hope remains that we will learn of a yet-to-be-discovered biology that will lead to an unexpectedly good outcome.

Sincerely,

Daniel J. George, MD