# How Statistics and Data May Alter Care for Bladder Cancer and Lymphoma

For Fred Hutch biostatisticians at the SWOG Statistics and Data Management Center, numbers are no game.

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Two potentially practice-changing studies published in October in the New England Journal of Medicine showcase the biostatistical expertise at the SWOG Statistics and Data Management Center (SDMC) housed at Fred Hutch Cancer Center. One upends the common approach at many high-volume institutions of removing more, rather than fewer, lymph nodes during surgery for muscle-invasive bladder cancer. The other yielded promising results for the combination nivolumab (a targeted therapy drug) plus AVD chemotherapy for stage 3 or 4 classic Hodgkin lymphoma.

Lead biostatisticians on the studies were Catherine M. Tangen, DrPH, professor in the Public Health Sciences Division and deputy director of the SWOG SDMC, and Michael LeBlanc, PhD, professor in the Public Health Sciences Division and member of the Translational Data Science Integrated Research Center. LeBlanc is director of the SWOG SDMC.

This year marks the 40th anniversary of the SDMC moving to Seattle from Houston after Fred Hutch won the National Cancer Institute (NCI) grant that provides much of the center's funding. John J. Crowley, PhD, was Fred Hutch's original SDMC group statistician and director, roles he held until 2012. The NCI grant is up for renewal about every six years with the next renewal coming in 2025.

## Behind-the-scenes experts are involved from start to finish

SWOG Cancer Research Network is one of five cooperative groups in the United States that make up NCI's National Clinical Trials Network. More than 1,300 institutions and 20,000 individual members are part of SWOG. Like each group in the clinical trials network, SWOG has a statistics and data management center, co-located at Fred Hutch and Cancer Research and Biostatistics (CRAB), a nonprofit in Seattle, and a network operations center, based at Knight Cancer Institute at Oregon Health & Science University. CRAB Chief Executive Officer Antje Hoering, PhD, is a Fred Hutch affiliate professor.

All SWOG studies go through the hands of LeBlanc, Tangen and other SDMC staff at Fred Hutch and CRAB. These experts contribute to study design, review and quality assurance; collect and manage data; randomize study participants; produce reports; analyze and interpret data; provide data and safety monitoring; prepare manuscripts; and develop, maintain and support computing systems. At any given time, SWOG has about 100 studies that are in active development, are enrolling patients or have closed enrollment but are following patients.

“The SDMC has stayed here for four decades in part because Fred Hutch is Fred Hutch: It’s historically strong in both biostatistics and cancer prevention, both interests of SWOG. That’s part of the long-term success,” said LeBlanc.

## To ensure care is evidence-based, first collect the evidence

Tangen is a co-author on the phase 3 study comparing standard versus extended lymphadenectomy, the surgical removal of lymph nodes to check for cancer spread, in people with bladder cancer that has invaded the bladder’s muscle wall. Though Fred Hutch clinical investigators typically enroll patients in SWOG studies, they didn’t for this particular trial.

“At the Statistics and Data Management Center, we’re regularly interacting with researchers from around the country, but not necessarily with the people down the hallway,” who may be focused on some of the many other types of research also taking place at Fred Hutch, said Tangen. Most SDMC-associated faculty members and several SDMC staff do collaborate with other Fred Hutch faculty on research that’s non-SWOG related.

The study randomized nearly 600 patients with localized muscle-invasive bladder cancer to receive either extended or standard lymphadenectomy along with bladder removal. Three dozen experienced urologic oncology surgeons at 27 sites were rigorously credentialed to adhere to the study protocol, reducing differences in care that might have clouded the results.

Many academic medical centers and other high-volume centers have adopted more extensive lymph node removal as the standard of care, though there was only low-level evidence showing this was better for patients, according to the published report.

The research team set out to test the hypothesis that a more aggressive approach improves disease-free and overall survival. In fact, they found extensive lymphadenectomy doesn’t provide disease-free or overall survival benefit, and it’s linked with higher rates of health problems or death around the time of surgery (perioperative morbidity and mortality).

## Reliable results require careful design

“The most important part of the biostatistician’s role is to be involved at the early stages of designing a study in order to get convincing results at the end. It might not be the result the researchers wanted, but it will be a reliable answer,” said Tangen.

For example, for this study, the early steps included Tangen talking with principal investigator Seth P. Lerner, MD, of Baylor College of Medicine Medical Center, in 2009, to define his study question. Next, she got to work coming up with a sample size and power calculations — essentially determining how many patients would need to enroll to achieve the number of events (such as relapse or death) that would allow the team to answer the primary objective. The biostatistics team also designed tools for collecting surgical quality control and complication data.

“This can be an iterative process between the biostatisticians and others involved in designing the trial, to come up with a study that’s both scientifically meaningful and feasible to run,“ said Tangen. ”You need a clear road map and then have to follow it.”

## Which is better? Comparing medicine combinations

The study on classic Hodgkin lymphoma compared outcomes for adolescents and adults with newly diagnosed stage 3 or 4 disease receiving initial treatment with nivolumab plus AVD chemotherapy (N+AVD) to outcomes for patients receiving brentuximab vedotin plus AVD, a standard combination. AVD stands for the chemotherapy drugs doxorubicin/Adriamycin, vinblastine and dacarbazine.

“This study is unusual because there aren’t many phase 3 studies in which we have a significant cohort of kids along with adults — multiple ages being treated essentially the same way,” said LeBlanc. Researchers enrolled 970 patients, some as young as 12 years old, at 256 sites in the U.S. and Canada. The study chair was Alex Herrera, MD, from City of Hope.

Patients on the investigational therapy had significantly lower risk of disease progression or death compared to those on the standard regimen. Treatment with nivolumab was also better tolerated by patients. After formal interim analysis, the SWOG Data and Safety Monitoring Committee recommended releasing the trial data, which showed positive results, in 2023. Now, a follow-up analysis has confirmed the findings. LeBlanc noted that successful conduct and analyses for the trial would not have been possible without Fred Hutch staff statistical colleague, Hongli Li, MS, also an author on the paper.

Based on the results, N+AVD should be a strong candidate for primary treatment in adolescent and adult populations with stage 3 or 4 Hodgkin lymphoma, according to the published report. Spurred by the promising findings, the maker of nivolumab, Bristol-Myers Squibb, intends to request approval from the U.S. Food and Drug Administration to use nivolumab in this clinical setting.

Like Tangen, LeBlanc champions the role of biostatisticians in careful study design.

“We try to limit the data points we’re bringing in, focusing on the key things we need in order to answer the questions for that study,” he said. “We want to do studies that have impact, so our goal is to keep the data ‘lean and mean.’”

LeBlanc has been with Fred Hutch for 30 years — not as long as the SWOG SDMC has been here, but long enough to have witnessed the center's evolution.

"One of the accomplishments we're quite proud of is that we adopted standards across diseases that we've used for a long time now, such as how the team codes for disease progression. While 'progression' for each disease, such as lymphoma versus leukemia versus melanoma, may have its own definition, progression appears in our database in a standard way. Standardized reporting mechanisms and tools help to ensure that the results of studies are reproducible — that following the same procedures will lead to the same answer," he said, such as whether a particular treatment regimen is more effective in a certain type of patient and situation.

## Teamwork underpins each successful study

Together, the SWOG SDMC at Fred Hutch and CRAB have more than 100 staff members who contribute to SWOG research in a variety of ways. Along with faculty biostatisticians, there are statistical research associates, statistical unit assistants, data coordinators, administrators, applications developers, information technology specialists and more. Both LeBlanc and Tangen stress that when their names appear on published manuscripts in the New England Journal of Medicine or elsewhere, they represent a multitude of staff members who've put in hours of meticulous work on both the statistical science and data management of the trials.

"So many people are part of the team," said Tangen. "I'm a general for a huge army behind me."

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