Cancer researchers propose new ways to select patients for clinical trials

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Dr. Lajoz Pusztai demonstrated in a new study that more sophisticated models to assess patient risk for cancer can result in better clinical trials with more definitive results. Credit: Yale Cancer Center

Many clinical trials for breast cancer fail to give clear answers on the efficacy of new therapies, despite enrolling thousands of patients and painstakingly tracking their outcomes for years. Now Yale Cancer

Center (YCC) investigators have demonstrated in a new study that more sophisticated models to assess patient risk for cancer can result in better clinical trials with more definitive results.

Often the problems with clinical trials begin in patient selection methods that underestimate how many of these patients can be treated successfully with standard-of-care therapies, and won't benefit from a more effective drug under study.

Many factors contribute to a breast cancer patient's risks of recurrence or death from the disease, including tumor size, presence of cancer in lymph nodes, patient age, and their overall health. "Historically, clinical trials select patients using mostly tumor size and lymph node status," said Lajos Pusztai, M.D., DPhil, senior corresponding author of a study published in *JAMA Oncology* and chief of Breast Medical Oncology at YCC.

All too often, the result is that patients included in the control arm of a trial who receive standard-of-care treatment experience too few "events"—cancer recurrences or deaths—to allow statistically conclusive comparisons with patients receiving experimental therapy. "If there are not enough events, one can miss a truly effective drug that could help patients who remain at risk for recurrence despite current best therapies," said Pusztai.

This problem can be avoided by employing a statistical model that combines multiple variables such as tumor size, lymph-node status, and benefit from standard-of-care therapy into a single score that corresponds to the predicted risk of recurrence after receiving current best therapies.

"Several such models exist that have been extensively validated and predict fairly accurately the likelihood that an individual will experience

an event," Pusztai said. Using this risk score to select patients with predefined minimum risk of recurrence (such as 25% or greater risk of recurrence in five years) ensures that the control arm has the required number of events for statistically sound comparisons.

The YCC researchers performed simulations for randomized, two-arm breast cancer adjuvant trials that compared traditional patient selection methods based on tumor size and lymph node status with patient selection based on minimal risk of recurrence generated by a widely used risk prediction model known as AdjuvantOnline. "We showed that the range of event rates varies very broadly if you use the traditional method of selecting patients, and a particular trial may end up with substantially lower events than intended by the statistical design," Pusztai explained.

In contrast, with statistically validated multivariant risk models, "we can select patients who really require clinical trials because their outcome with current treatments is less than optimal," Pusztai said. "This approach guarantees that the statistical power of the study is adequate to demonstrate if the new treatment is really effective or not. We also can expose fewer patients to the side effects of the new treatment. That's good for the patients."

"Our residual risk-based selection method also renders trials more efficient and cost-effective for drug companies, because it allows smaller studies with more guaranteed statistically power to succeed," he added.

This approach could benefit clinical trials for other types of cancer as well for which validated multivariant risk prediction models already exist, Pusztai noted.