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Should criteria for inclusion in cancer clinical trials be expanded?

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Imagine the following: A 58-year-old surgeon recently diagnosed with Stage 4 lung cancer comes to see you for clinical trial options. He is otherwise in excellent health, and he takes no medications. He is highly motivated to receive cutting-edge treatments, has a thorough understanding of the nature of the disease and potential therapies, and states he will be strictly adherent to any recommended treatment regimen. However, he is not eligible for any clinical trial available at your institution due to a history of localized prostate cancer treated surgically three years previously.

In recent years, eligibility criteria for cancer clinical trials have come under heightened scrutiny. Critics cite increasingly restrictive eligibility criteria as a key reason for low study accrual rates.[1–4] In turn, low accrual rates prolong study duration, result in premature study termination, limit the number of patients exposed to potentially beneficial experimental therapies, and leave important clinical questions unanswered. Strict inclusion and exclusion criteria also reduce generalizability of results. Furthermore, criteria are variably applied across studies, suggesting lack of clear rationale or justification.[5]

These concerns are not limited to oncology clinical trials. A study of more than 20,000 Medicare beneficiaries from acute care hospitals with a principal diagnosis of heart failure found that only 13–25% met enrollment criteria of three landmark randomized controlled trials (RCTs) that have shaped the treatment of that disease.[6] An analysis of 283 RCTs

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(encompassing 2,709 exclusion criteria) published in high-impact medical journals found that 37% of all exclusion criteria were poorly justified, and that 84% of all trials had at least one poorly justified exclusion criterion.[7]

Why do clinical trials have eligibility criteria? Traditionally, RCTs have predominantly focused on assessing an intervention's efficacy rather than effectiveness. These studies represent a make-or-break step in the development of drugs, devices, and other interventions, so optimizing internal validity is critical. The clinic serves as the researchers' laboratory. Maximal control of experimental conditions—including patient characteristics—is sought. This approach may increase the ability to detect a modest real treatment benefit by studying a homogeneous population that differs only by study drug exposure. Although such stringent circumstances may differ substantially from real-world clinical medicine, if efficacy in a tightly controlled environment is not demonstrated, investigators may never even have an opportunity to assess the intervention's external validity in broader populations. Investigators also face regulatory, funding, and publishing biases, with tightly and thoroughly defined research populations expected by institutional review boards, industry partners, government and foundation funding agencies, and journal editors.

Trial enrollment criteria may also be driven by the desire to protect patients from potential excessive toxicity, as the case for minimum performance status, blood count, and organ function requirements. Patient safety concerns also drive the exclusion of women who are or may become pregnant, patients taking medications that potentially interact with the study agent, or individuals with baseline abnormal electrocardiogram readings.

Clinical trial eligibility criteria fall into several domains. These include demographics, disease characteristics, prior treatments, and overall illness burden and physiological reserve. They also include non-clinical logistical factors designed to streamline study accrual and conduct—such as language proficiency, distance from study site, and transportation availability—that may indirectly favor certain socioeconomic groups. Expert opinions on these and other criteria vary widely, but strong consensus indicates the need for clear justification for restricting eligibility.[7] Accomplishing this, however, may not be a straightforward undertaking. The rationale for a particular eligibility factor will vary by disease, intervention, and population of interest.

The time is right to take a more evidence-based approach to assessing the validity of many traditional exclusion criteria for cancer clinical trials. For example, inspired by real-world examples such as the case described above, we recently evaluated the longstanding and widespread practice of excluding patients with prior cancer from lung cancer clinical trials.[8,9] First, we systematically reviewed the prevalence of this practice by examining lung cancer clinical trial protocols sponsored or endorsed by the National Cancer Institute (NCI) Eastern Cooperative Oncology Group (ECOG) (N=51; total enrollment=13,072). Overall, 78% of protocols excluded patients with a prior cancer diagnosis as follows: any prior (i.e. lifetime prior cancer history) (16%), within 5 years (39%), within 2 or 3 years (7%), or "active" cancer (16%). While trials with an overall survival endpoint were more likely to have prior cancer exclusions (89%), we found that 70% of clinical trials with non-survival

endpoints (such as response rate, toxicity, and feasibility) also excluded patients with prior cancer.

Next, to understand the potential impact of prior cancer on trial accrual, we used comparative effectiveness research (CER) techniques—including multiple methods to control for potential biases inherent in observational data—in an analysis of nationally representative Surveillance Epidemiology and End Result (SEER)-Medicare linked data (N=210,509). We estimated the proportion and absolute number of potential subjects for each ECOG clinical trial who would be excluded due to a prior cancer diagnosis. Our findings were sobering. The proportion of potential subjects excluded due to prior cancer per trial ranged up to 18%, with the estimated absolute number of excluded subjects per trial ranging up to 207.

Finally, we examined the rationale for the ongoing exclusion of patients with prior cancer from lung cancer clinical trials. Presumably, this practice reflects concerns that a prior cancer diagnosis conveys worse prognosis. However, the impact of prior cancer on survival in lung cancer had not been clearly documented. To answer this question empirically, we examined patients with stage 4 (metastatic) lung cancer in the SEER-Medicare dataset (N=102,929), 15% of whom had a history of prior cancer. Over half of the prior cancers were diagnosed less than five years before the stage 4 lung cancer diagnosis (and would therefore be excluded from trials employing the common five-year exclusion window), and more than 75% of prior cancers were localized or regional stage. In the overall population and every subgroup examined (according to stage, type, and timing of prior cancer), *prior cancer did not convey an adverse effect on all-cause and lung cancer-specific survival*. In fact, these patients appeared to do slightly better statistically than those without a prior cancer in both raw and propensity score-adjusted analyses. Whether this trend represents early detection bias, higher quality of clinical care, or a physiologic survivor effect is not clear.

In sum, we found broad but highly variable application of prior cancer exclusion criteria in lung cancer clinical trials. This practice results in exclusion of a substantial proportion of patients. However, there does not appear to be a clear justification for this policy. Could prior cancer impact other relevant clinical endpoints aside from survival, such as tolerability of study treatment? Absolutely. However, it seems that such concerns could be addressed through other eligibility criteria, such as blood counts, organ function, performance status, and the type and timing of any prior cancer *treatment*. Can our findings be generalized to other lung cancer stages, or to other cancer types? No. The prevalence and prognostic impact of a prior cancer diagnosis will vary according to the individual cancer type and stage in question. Future research in those populations will be needed. For these efforts, large-scale observational studies using SEER-Medicare or similar datasets represent an attractive approach, as they permit the empiric assessment of selected factors on treatment-outcomes relationships in real-world practice. Such studies provide an alternative to randomizing or stratifying on these factors prospectively, which may not be feasible due to the patient numbers and resources required. In the meanwhile, it seems reasonable to reconsider the reflexive exclusion of patients with a prior cancer diagnosis from clinical trials for stage 4

lung cancer. Already, ECOG has revised its prior cancer exclusion policies for metastatic lung cancer clinical trials as a result of our work.

Clinical research in cancer and other fields represents a balancing act. Scientific yield, feasibility, cost, and generalizability must all be taken into consideration. A step-wise approach incorporating different types of studies may provide the needed framework to advance the evidence base for cancer therapy. As a first step, traditional RCTs assess efficacy in homogeneous populations and optimal clinical settings, thereby maximizing efficacy signals and minimizing potential toxicity. Subsequently, more inclusive or pragmatic trials increase generalizability by assessing efficacy and toxicity in real-world patients and settings. Alternatively, CER techniques using large, observational datasets can be employed to assess an intervention's risks and benefits in an unselected community setting. In turn, observational CER studies may also yield hypothesis-generating insights that drive the rationale for and design of subsequent RCTs.

With fewer than five percent of adults with cancer in the U.S. participating in clinical trials,[10–12] the oncology clinical research enterprise is facing a crisis. Reasons for low accrual include patient, provider, and system factors.[1,10,12–14] Trial eligibility criteria represent one of the few factors directly controlled by investigators and sponsors. As investigators, it is critically important that our selection of inclusion and exclusion criteria be thoughtful, deliberate, and justified. To accomplish this, we will need to use an array of methodological approaches to assess their validity and impact.

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