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Big data: Are large prospective randomized trials obsolete in the future?

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A B S T R A C T

Big data represents a new opportunity to increase our understanding of cancer care as it is practiced globally and to improve it through the refinement of clinic guidelines and the identification of knowledge gaps. Here we review the historical approach to evidence development (randomized clinical trials), some of their limitations, and the complementary role that big data analytics may play.

Introduction

Big data represents a new and evolving opportunity as we develop clinically useful guidelines. It can address some of the challenges and gaps that remain despite many well-conducted randomized clinical trials. This paper serves to review the development of randomized clinical trials some of their recognized limitations and the ways in which big data may be complementary and supportive as we continue to develop new treatment guidelines for general use.

The global challenges of breast cancer

Breast cancer remains a global challenge [1]. It is the most common cancer in women, the second most common cancer globally, and the fifth most common cause of cancer associated death per year. There are wide variations in the incidence of breast cancer as well as its mortality around the globe. On the other hand, breast cancer is frequently curable and, especially in the early stage setting, many of the patients who may be accrued to prospective randomized clinical trials never experience the event that defines the primary endpoint. This introduces expense and inefficiency since these patients must be followed for many years in anticipation of ay event that never occurs. The low event rate is, however, a paradoxical justification for prospective randomized trials. In addition, the modest therapeutic benefit of most active agents, the presence of significant toxicities, the possibility of biased observations, and the well-recognized placebo effect all justify and even require the use of prospective randomized clinical trials to resolve clinically relevant treatment questions.

Randomized clinical trials

Key features of randomized clinical trials include a comparison, under controlled conditions, of 2 or more therapeutic interventions and the use of a statistical design focused on the possibility of error [2]. To achieve these features, the components of a prospective randomized trial include assignment in unbiased fashion to control or treatment groups and, whenever possible, blinding of the part of both the study subjects and the experimentalists. Not all of these components, especially blinding, can be achieved in all studies.

As we have improved the outcomes for patients with early-stage breast cancer, additional challenges to the conduct of randomized clinical trials have emerged. These include their speed (they are slow), expense (high and increasing), efficiency (falling event rates), and the confounding effect of the selection of more or less meaningful and appropriate primary and secondary endpoints.

Randomized clinical trials have changed practice in many areas of medicine, oncology and specifically breast cancer. Recently, large studies in the area of HER2-directed therapies have quickly led to changes in standard of care for advanced and early stage disease. Another example of the success and utility of randomized trials has been through their aggregated interpretation as performed by the

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Early Breast Cancer Trialists Collaborative Group [3]. Because of small size and modest treatment effect, it was common for individual randomized adjuvant therapy trials to seem to reach conflicting conclusions or interpretation. The assembly of these many randomized trials using the meta-analysis technique enabled us to identify sometimes modest but critically important improvements in disease-free and overall survival for widely available systemic therapies in the postoperative setting and for local treatments for early stage breast cancer. Given the prevalence of breast cancer and its high incidence in many parts of the world these small differences have profound public health impact when applied consistently. Clearly then a role for prospective randomized trials is supported both at the level of the individual study and its conclusions but also through their contribution to aggregate analyses that provide greater certainty.

Levels of evidence

Placing the results of randomized clinical trials into clinical context has largely been the responsibility of guidelines groups that have been organized on a global level over the past decades. To use the results of clinical research in writing of guidelines efforts have been made to establish so-called "levels of evidence" [4]. An early example cited by the Canadian Task Force on Periodic Health Examinations separated guidelines into those based on at least one randomized clinical trial conducted properly as opposed to those based on a well-designed cohort study, a time series comparison, or evidence of dramatic results from uncontrolled studies and then finally expert opinions. A second version of that scale used 5 defined levels of evidence ranging from large randomized clinical trials with clear results to smaller ones with unclear results and ending with case series. The NCCN, which has been highly influential in establishing clinically useful guidelines at least in the United States, uses 4 categories of evidence [5]. Category 1 is a guideline based on high level evidence with uniform consensus on the part of the committee. Category 2A is based on lower level evidence but uniform consensus. Category 2B uses lower level evidence and non-uniform NCCN consensus that the intervention is appropriate. Category 3 essentially means that their recommendation is based on any level of evidence but there is major disagreement within the panel that the intervention is appropriate. Reflecting the state of the available data the NCCN notes that almost all of its recommendations are category 2A, unless otherwise noted. This tells us that for many or most of the routine treatment guidelines in use we do not have high level evidence from prospective randomized trials to guide us. Hence we are actually quite used to making decisions and issuing guidelines even when we lack prospective randomized data. This is highlighted by careful study of the actual levels of evidence in the NCCN breast cancer recommendations [6]. Seventy-three percent of the recommendations are identified as category 2A and only 19% are category 1. In addition to the limited amount of contemporaneous high level evidence, a surprising amount of breast cancer management is based on evidence and case series that predate the modern era. For example, surgery to treat breast cancer while it is clinically localized was recommended in 1757. William Halstead began performing radical mastectomies in 1882. These approaches informed standard surgery for nearly a century without randomized data. Even the Foundation of modern hormone therapy is based on 3 patients who responded to ovariectomy and were published in 1896 [7]. The point here is not that we can avoid randomized clinical trials but instead that it is also possible to complement them by making observations and issuing guidelines even when we lack level I evidence.

Electronic health records: an untapped opportunity

Observational data has frequently been decried as limited and biased. But the world is evolving and we are facing a near future in which we will have even more observational data available than ever before. And this data will be larger ("big data") and less biased in that it will encompass ever-larger subsets of our patients and population than in the past. The question for us is whether, and how, we will use it. One example from outside of breast cancer concerns the anti-inflammatory agent rofecoxib. From the time of approval until the subsequent withdrawal of the label for this drug on the basis of a twofold increase in myocardial events it took 61 months or just over 5 years. It is estimated that a large integrated health system (such as Kaiser in Northern California) could have identified this cardiac signal in about half that time with between 7 and 8 million patients under observation. If about half of the United States had been tracked as carefully (that is 150 million subjects) than this observation might have been made in 6 months. And if the entire United States had its clinical data in a useful and mineable data set this toxicity might have been recognized in 8–10 weeks [8]. Simply put, now that we have access to big data it will be tragic if we do not identify useful ways to mine this data to improve public health. This is the promise of big data.

Access to big data is being eased by the widespread adoption of electronic health records by physicians and hospitals both within the United States and around the world [9]. This improves data processing while growing storage capacity allows us to develop tools for rapid data analysis. A key step is the development of natural language processing as it would unleash substantially more data with nuance and subtlety that eludes us in laboratory reports. Just within United States as of 2012 almost two-thirds of practices were already using an advanced electronic health record or electronic medical record and indeed only a very small percentage had no electronic records at all and no plans to implement one. These records are generating unprecedented amounts of data that could be informative and useful for clinicians and investigators in the years ahead. The fundamental challenge that we face is that the data is not necessarily being developed and stored in an interoperable or transparent fashion and there are boundaries to data sharing and mining that must be overcome. Some of these boundaries are structural and others are regulatory or legal but almost all can be addressed.

CancerLinQ

To begin to capitalize on this evolving big data opportunity, the American Society of Clinical Oncology has envisioned a system called the Cancer Learning Intelligence Network for Quality (CancerLinQ™) [10]. The concept is that this system will interact with any or possibly all electronic medical records. It will allow us to obtain data from many practices and electronic health record systems, transform the data, aggregate and analyze it, and then begin to make observations of associations that can be hypothesis-generating or used to correlate and confirm the results of conventional randomized clinical trials. Trend analyses can be obtained and services can be delivered back to clinicians at the point of care. This would evolve to an ever-strengthening resource that will allow us to begin to explore the care and outcomes of the 97% of adults who are treated outside of conventional prospective randomized trials.

CancerLinQ has been built in prototype form. Beginning in June 2012 the demonstration model was planned and completed within 8 months. Planning for about 30,000 patients with breast cancer, more than 170,000 were actually included using de-identified records. Built with mostly open source software this system was functional thereby demonstrating that full CancerLinQ could be a reality.