

Surrogate end points save lives

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See also the research paper by Adie et al. on page 86.

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SUMMARY

Patient-centric markers are important, and when they can be conveniently measured they should dominate research questions. However, when the research question pertains to serious or potentially fatal illnesses and it will take years or even decades to answer with patient-centric outcomes, then a pragmatic approach based on common sense and surrogate markers should be adopted. This commentary discusses the important role that surrogate markers can play in medical research.

In this issue of *CJS*, the research paper by Adie and colleagues,¹ which was early-released in February, presents the results of a detailed analysis of the frequency of patient-important outcomes in clinical trials. They found that only 60% of outcomes were patient-important and concluded that authors, journals and trial funders should insist that patient-important outcomes rather than surrogate markers or laboratory values be the focus of study.

While I respect the authors' focus on patient-centred outcomes, I do not share their disdain for surrogate markers. Surrogate end points play an important role in research and are typically chosen in order to expedite the answer to the clinical question. For serious or potentially fatal illnesses, this is not just a matter of getting it right, but can be a question of life or death. Treatment delayed is treatment denied, and the potential harms of such delay need to be considered carefully. From a patient's perspective, dying on the waiting list for evidence is not a more noble death than dying of a well-intentioned intervention based on imperfect but available evidence. Commissions of inquiry into previous major failures of the Canadian health system share this concern and perspective.

In the 1980s at least 10 000 Canadians were harmed when experts at the Canadian Red Cross did not take appropriate action to protect the blood supply because there was "no high-quality evidence to support change." They were unwilling to accept surrogate markers (elevated transaminases) as an indicator of infected blood, as had been done in many other countries; instead they were waiting for the results of a multicentre randomized clinical trial. Justice Horace Krever, who authored the report of the commission of inquiry, was highly critical of this approach: "the need for such a study had passed before it was begun."

He was explicit in his criticism: "Where there is reasonable evidence of an impending threat to public health, it is inappropriate to require proof of causation beyond a reasonable doubt before taking steps to avert the threat." As an editorial in the *American Journal of Public Health* in May 1984 put it:

The incomplete state of our knowledge must not serve as an excuse for failure to take prudent action. Public health has never clung to the principle that complete knowledge about a potential health hazard is a prerequisite for action. Quite the contrary, the historical record shows that public health's finest hours often occurred when vigorous preventive action preceded the crossing of every scientific "t" and the dotting of every epidemiological "i."²

In 2003, an outbreak of severe acute respiratory syndrome (SARS) affected 375 Canadians and killed 44. The subsequent SARS commission, chaired by Justice Archie Campbell, into the failures of the Canadian health system came to an almost identical conclusion.

Perhaps the most important lesson of SARS is the importance of the precautionary principle. SARS demonstrated over and over the importance of the principle that we cannot wait for scientific certainty before we take reasonable steps to reduce risk. This principle should be adopted as a guiding principle throughout Ontario's health, public health and worker safety systems. If we do not learn this and other lessons of SARS, and if we do not make present governments fix the problems that remain, we will leave a bitter legacy for those who died, those who fell ill and those who suffered so much.³

A more contemporaneous example that those words fell on deaf ears is the current situation with colorectal cancer screening in Canada and the striking difference between American and Canadian approaches and outcomes. The recently resuscitated Canadian Task Force on Preventive Health once again published recommendations based on an interpretation of evidence-based medicine that treats the hierarchy of evidence as if it were an infallible dispensation from higher beings. They recently recommended that persons of average risk for colorectal cancer should *not* undergo screening colonoscopy owing to a lack of high-quality evidence.⁴ Presumably they are waiting for the results of a meta-analysis of the 4 clinical trials that are now underway and will be published in the late 2030s when the trials are completed.

Colorectal cancer is a highly preventable disease that kills more than 9000 Canadians every year. The US Preventive Services Task Force (USPSTF), clearly not constrained by any patient-centric evidentiary deficits, made the pragmatic decision to recommend average risk screening for colorectal cancer colonoscopy 14 years ago,⁵ and after recently reviewing the same body of evidence that its Canadian counterpart reviewed, came to the opposite conclusion and reiterated support for average risk screening colonoscopy.⁶ Participation rates have been high, and in some states more than 70% of the eligible population has been screened, with colonoscopy dominating. The difference in outcomes is dramatic. In Canada the number of deaths from colorectal cancer has increased by 50% in the last 20 years,^{7,8} whereas the United States, with a similar population profile, population growth and risk factors, has seen an 8% drop.^{9,10}

To clarify this comparison in a patient-centric manner, if Canada had achieved the same reduction in colorectal cancer mortality that the United States has achieved since 1996, we would have 3200 fewer deaths per year. If we had achieved the same incidence reduction that the United States has achieved, we would have 8800 fewer cases per year. These are not trivial numbers; picture a Boeing 777 crashing every month! These numbers exceed the total annual case and mortality counts of most cancers. Only breast, lung, prostate and pancreatic cancers exceed the calculated excess deaths from colorectal cancer. The estimated cumulative difference over the last 20 years is on the order of 35 000 excess deaths and 80 000 excess cases of colorectal cancer in Canada.

Accepting the non-patient centric surrogate of advanced adenoma detection rate as a valid and appropriate end point could have resulted in the adoption of screening colonoscopy years ago and would likely have saved many of those lives. A generation of Canadians has been denied the opportunity to prevent one of the leading causes of cancer death because of rigid choices about rules of evidence and appropriate end points.

Outside the field of medicine, surrogate markers seem to work very well. I suspect that most of us appreciate the fact that civil engineers use surrogate markers of material strength and durability rather than wait for a patient-centred metric, such as fatality rate due to bridge collapse, when they build our infrastructure. And I suspect that even the most hard-core patient-centred outcome aficionados readily accept rising atmospheric carbon dioxide as a surrogate for climate change rather than waiting for sea levels to intrude into homes in a very patient-important manner. The cognitive dissonance of accepting surrogate markers in nonmedical situations but rejecting them in medical research is not rational or scientific.

Patient-centred markers are important, and when they can be conveniently measured they should dominate research questions. But when the research question pertains to serious or potentially fatal illnesses and it will take years or even decades to answer with patient-centric outcomes, then a pragmatic approach based on common sense and surrogate markers should be adopted.

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