Translating Medical Evidence to the Individual Patient

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“Prediction is very hard, especially about the future.”
– Niels Bohr

The amount of clinical research available to clinicians today has never been more extensive or complex. By one estimation, almost 2100 scientific publications, 75 clinical trials, and 11 systematic reviews are generated daily. This explosion in information greatly exceeds a clinician’s cognitive ability to integrate the full body of literature when considering a specific clinical situation or patient. Accordingly, clinical decision support, defined as a system that integrates patient information with a computerized database of clinical research and guidelines, is one of the more exciting potential applications of electronic health records to clinical medicine. However, the potential of clinical decision support is not without peril.

Clinical decision support relies on the fundamental assumption that medical evidence can be precisely translated to the individual patient. This translation is not as simple as it may initially appear. Clinical trial results are reported as the average effect of a therapy among the trial population, but these aggregated results rarely correspond to an individual’s response to the therapy. Patient characteristics can significantly exaggerate or attenuate its impact. For example, a therapy that reduces myocardial infarction by 10% would have significantly greater effects in a patient whose baseline risk for myocardial infarction was 20% compared with a patient whose risk was only 1%. In addition, therapy effects often occur in a skewed distribution, where a relatively small number of patients derive a significant benefit, whereas most experience little or no effect. Thus, the mean measure of effect in the population fails to describe a typical patient’s expected response to the therapy. Patient characteristics can significantly exaggerate or attenuate its impact. For example, a therapy that reduces myocardial infarction by 10% would have significantly greater effects in a patient whose baseline risk for myocardial infarction was 20% compared with a patient whose risk was only 1%. In addition, therapy effects often occur in a skewed distribution, where a relatively small number of patients derive a significant benefit, whereas most experience little or no effect. Thus, the mean measure of effect in the population fails to describe a typical patient’s expected response to the therapy. Finally, because most therapies usually entail at least some potential for harm, variations in patient characteristics can also significantly increase the likelihood of harm relative to benefit and, in some cases, result in net harm to a subset of patients. Clinical trialists recognize this heterogeneity of effect on trial populations and often conduct multiple subgroup analyses to determine the impact of individual patient factors on treatment efficacy. Unfortunately, these subgroup analyses are less informative for predicting individual responses, which are governed by the complex interplay of multiple factors rather than any single characteristic.

Recognizing the difficulty in and need for translation of trial findings to individual patients, in this issue of Circulation Cardiovascular Quality and Outcomes, Salisbury et al attempt to bridge this gap. They conducted an analysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, which demonstrated that the antiplatelet prasugrel, as compared with the antiplatelet clopidogrel, provided better prevention of ischemic events, albeit with a higher rate of bleeding, among a population of patients with myocardial infarction undergoing percutaneous coronary intervention. The investigators used multivariable prediction models to determine the likelihood that each therapy would reduce future ischemic adverse outcomes or increase future bleeding as a function of individual patient factors. The investigators found wide variation in antiplatelet effects on both outcomes. After accounting for this variation, only 42% of the trial population had a predicted net clinical benefit of prasugrel over clopidogrel—a strikingly different conclusion from the primary results of the original trial.

Salisbury et al provide one of the best examples to date for translating the aggregate results of a clinical trial into individual effects. Their approach is vastly superior to either accepting the aggregated results as the likely outcome for the individual patient or even using the subgroup analyses to guide therapy. Accordingly, they make a strong argument that all clinical trials, both past and future, should undergo similar analysis—an argument also advanced by others.

Yet the study also reveals that any approach to determining the individual response to any particular medical intervention is fraught with uncertainty. Although it demonstrates improved precision of therapy effects on individuals, it also illustrates, perhaps ironically, that perfectly precise prediction is impossible. The individualized risk models presented in the article provide only modest discrimination and misclassify up to 32% of patients. In addition, confidence intervals around point estimates for both the individual outcomes and the expected net clinical benefit are fairly wide, which can lead to significant swings in possible outcomes. For example, the point estimates illustrated in the hypothetical case of the 65-year-old woman in Figure 4 demonstrate that use of prasugrel would result in net harm and should be avoided. However, examination of the confidence intervals around the point estimate indicates a range of possibilities where net clinical benefit is possible. Prediction precision is complicated further by the interdependence of variables, such as age and frailty, which can increase the risk..
of both ischemia and bleeding. Although the investigators included potential interactions in their analysis, many of these relationships are unknown and thus unaccountable. Importantly, these limitations are not the result of an inadequate analytic approach but rather inherent in probabilistic prediction.

So what do these findings mean for clinical decision support and its ability to provide patient-specific information to assist clinicians in determining optimal treatment for their patients? There is little question that clinical decision support algorithms should apply similar methodology to that presented by Salisbury et al.4 Doing so can provide greater insight into the expected response of the individual patient to the therapy under consideration, and thus enhance clinician recommendations and patient decisions. However, it is essential that proper communication of both the results and limitations of this analysis occurs. Understanding and communicating risk and probability are difficult to do well, and work is needed to identify and implement the optimal way to execute these critical tasks in the context of the clinician and patient discussion.

This study also illustrates the need for continuous monitoring of outcomes among patients after the decision has been made and the therapy instituted (or declined). For this to occur, electronic health records will need to comprehensively characterize ongoing care and outcomes using structured data elements, real-time provision of clinical data for immediate feedback, and quality monitoring mechanisms able to respond to adverse events in a timely fashion. Doing so can provide a safety mechanism for those patients where prediction models fail and unexpected outcomes occur. In addition, analysis of those failings can potentially identify previously unknown patient variables associated with benefit and harm, which in turn could be incorporated into improved versions of the prediction models and attendant increases in precision. This digital, capture of the care experience, to better understand and learn from delivered care is a fundamental tenet of the learning health care system and higher value health care outlined in the recent Institute of Medicine report, Better Care at Lower Cost.2

Clinical decision support is imminent. Current health reform efforts strongly encourage the use of clinical decision support. The Health Information Technology for Economic and Clinical Health Act (HITECH) requires implementation of at least five clinical decision support interventions in stage 2 of its meaningful use incentive program for electronic health record adoption.6 The Better Care at Lower Cost report identifies clinical decision support as essential to access the full spectrum of medical evidence and provide better care to patients.2 Private industry is also investing in clinical decision support. IBM is configuring its Watson supercomputer to analyze millions of pages of unstructured text in patient records and the medical literature and then use probabilistic algorithms to provide clinical decision support for cancer patients.7 The enthusiasm around clinical decision support is high, but it must be tempered with realistic expectations.

Ultimately, the Salisbury analysis makes apparent that clinical decision support cannot supplant clinicians in the medical decision-making process because all data analytic methods are, by definition, probabilistic and inherently limited. Although their use can provide additional precision to expected outcomes, these results must always be partnered with clinical intuition and experience, ongoing collection of actual outcomes, and continued investigation into the differences between prediction and reality. In addition, clinicians have an essential role in communicating potential options to patients, eliciting their preferences, and incorporating these factors into a shared decision. The promise of clinical decision support and the peril of its inherent limitations, both elegantly illustrated in this study, demonstrate that optimal care sits where the science and art of medicine intersect.

Disclosures

None.

References

Promise and Peril of Clinical Decision Support: Translating Medical Evidence to the Individual Patient
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