

Moving From Clinical Trials to Precision Medicine

The Role for Predictive Modeling

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Evidence-based care has been defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”¹ However,



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until now, most treatments have been designed with a “one-size-fits-all” approach: useful for some patients but not helpful or even harmful for others.² Analyses of clinical trials generally focus on summarizing overall average treatment effects without more deliberate investigation of which patients actually benefit. For example, if the number needed to treat using a new therapy is 50, then 50 individuals need to receive this treatment for 1 individual to benefit. But what characterizes that benefiting individual? Therapies can also both help and harm, successfully improving some outcomes while also placing patients at increased risk for other adverse events.

The Dual Antiplatelet Therapy (DAPT) trial provides an example of such complexity. The DAPT trial concluded that, among patients who had undergone a coronary artery stent procedure in which a drug-eluting stent was placed, those who continued thienopyridine therapy beyond 12 months, on average, had a reduced risk of ischemic events but at a cost of increased risk of moderate or severe bleeding.³ Such mixed results leave clinicians and patients in a quandary, struggling to know how these overall benefit and risk estimates apply to their particular situation. More sophisticated approaches to analytics and decision tools are critically needed.

Precision medicine calls for the customization of health care, with medical decisions tailored to the individual patient.³ Sometimes precision medicine can identify a single variable such as a gene or biomarker that can successfully differentiate individuals who benefit or are harmed by a given treatment. However, in many situations, the outcomes of intervention are associated with multiple variables. In these instances, statistical risk prediction models can estimate the likely implications of a therapeutic intervention and thereby assist medical decision making. Specifically, these models can simultaneously aggregate multiple patient characteristics into a simplified “risk prediction score” that can provide individualized probabilities of outcome with or without treatment.

In this issue of *JAMA*, the study by Yeh et al⁴ describes an interesting application of predictive modeling as a means of better interpreting a clinical trial, in this case the DAPT study. Their analytic goal was to identify which patients who had received drug-eluting stents and were assigned to receive extended thienopyridine treatment (relative to without receiving extended treatment) had the most (or least) favorable absolute benefit-

risk ratio. Specifically, the authors built predictive models estimating 4 distinct probabilities: the risk of ischemic events and the risk of bleeding if thienopyridine was extended, and similar ischemic and bleeding risk estimates if thienopyridine was not extended. If both ischemic and bleeding risks were reduced with extended treatment, then the obvious decision is to extend treatment with dual antiplatelet therapy. Conversely, if both risks were increased, stopping treatment would be the correct decision. However, many patients are in this category in which extending thienopyridine decreases the risk of ischemic events but also increases the risk of bleeding. Yeh and colleagues used linear regression to reduce this 4-dimensional prediction problem to a single dimension. Specifically, they developed a simplified prognostic tool that simultaneously identified 9 independent clinical factors that best maximized the absolute benefit-risk difference for each patient.

These findings are important for several reasons. First, in the spirit of precision medicine, the study by Yeh et al moved the focus from a single overall conclusion for the DAPT trial to a decision analytic approach that recognizes patient diversity in response to therapy. Second, when investigating therapeutic heterogeneity, the authors employed an analytic framework that simultaneously considered more than a single factor at a time (eg, young vs old, or diabetes vs not diabetes). Third, the DAPT risk score (–2 to 10) seems to achieve its goal of differentiating patient subpopulations in whom benefits of treatment outweigh risks and vice versa. When applied in the original sample of 11 648 patients, of whom 348 developed ischemic events and 215 developed bleeding events, patients with a DAPT score of 2 or higher ($n = 5917$) who continued thienopyridine therapy vs placebo had a lower risk of ischemic events (2.7% for continued thienopyridine vs 5.7% for placebo) and similar risk of bleeding (1.8% for continued thienopyridine vs 1.4% for placebo). Among the 5731 patients with a low score (<2), those who continued thienopyridine therapy vs placebo had a similar risk of ischemic events (1.7% for continued thienopyridine vs 2.3% for placebo) and higher risk of bleeding (3.0% for continued thienopyridine vs 1.4% for placebo). Fourth, the authors took the additional important step of evaluating the generalizability of their risk score in an external sample.

The study by Yeh et al also has several important limitations. First, any analysis is only as strong as the data on which it is derived. The DAPT score was derived from a population of patients selected to participate in a clinical trial and may differ from patients treated in routine clinical practice.

Second, since the DAPT trial was originally designed, management practices in interventional cardiology have evolved.

Specifically, the DAPT trial included mostly patients who received early-generation drug-eluting stents and bare metal stents. These patients were randomized only after they had successfully been treated for a year with thienopyridine therapy (the accepted standard at the time the trial was designed). In contemporary practice, these older stents have been largely replaced by second- and third-generation DES designs that appear to have much lower risks for stent thrombosis, even with much shorter (<6 months) courses of thienopyridine therapy. Thus, it will be important to see if the DAPT score can be applied at the time of initial stent placement or when used in clinical populations receiving newer-generation drug-eluting stents.

Third, the candidate predictive variables for the DAPT risk score were also limited to those collected in the DAPT trial. As such, potentially important clinical predictors of bleeding (such as anemia or frailty) or predictors of stent thrombosis (such as genetic polymorphisms for CYP2C19) could not have been considered by the model.

Fourth, in developing their final DAPT risk score, Yeh and colleagues also emphasized simplicity over complete information. To make the score more readily accessible to clinicians at the bedside, the authors limited a multidimensional problem to a 1-dimensional, integer-based score based on limited number of final variables. By its design, this single entity equally weights ischemic and bleeding risks, and such weighting may or may not best approximate the effects of these outcomes on a patient's long-term prognosis or personal value systems.

Fifth, while trying to limit the number and weighting of various predictor variables may seem appealing in practicality, current electronic health record systems can compute complex equations automatically. Thus, it is unclear whether simplification of prediction tools to just a few variables or weighting them based on simple integers is still required to make these tools accessible. The loss of information inherent in such simplifications may have compromised part of the predictive accuracy of the DAPT score, which was modest at best (C index 0.64 in the validation sample).⁴

Randomized clinical trials are an invaluable asset in generating new knowledge. However, in the majority of in-

stances, the rich data generated from clinical trials find relatively limited uses beyond the main study goals. Furthermore, methods used to apply the average trial effects to more individualized approaches have rarely gone beyond simple subgroup analyses. In the future, predictive models like the ones developed by Yeh and colleagues may become more commonplace, potentially forming the missing bridge between clinical trials and precision medicine. Investigators designing future clinical trials should plan for appropriate data collection that will facilitate construction of predictive models and include such approaches in their primary statistical analysis plans.

Yet to reach their full potential, the goal for prediction models should not end with their publication. Journals are already filled with articles that include prediction models, yet few of these are routinely used in clinical practice. This partially is explained because, in the past, risk calculation has not been user-friendly. However, in an era of electronic health records, clinical decision aids can be built to automatically calculate probabilistic estimates and provide those estimates to clinicians at the point of care. But accurate risk prediction alone is only a start of the process; such probabilistic estimation needs to be actionable and linked to clear decisions. Based on different combinations of estimated risks and benefits, clinicians need a clear menu of care management strategies. It is also necessary to continue to enhance educational efforts for practitioners and patients to better understand the benefits and limitations of these models.

Interpretation of probabilistic estimates can be challenging.⁵ Understanding the strengths, weaknesses, and validity of the methods used to develop and evaluate these estimates can be even more complex. However, such skills are becoming a necessary part of modern day evidence-based care. According to a saying attributed to Lao Tzu (circa 604-531 BC), "Those who have knowledge, don't predict. Those who predict, don't have knowledge."⁶ Hopefully, the day is coming when this quote will be turned on its head: "Those who have knowledge, can predict. And those who can predict based on knowledge can practice precise medicine."

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Peterson reports receiving grant funding from the American College of Cardiology, American Heart Association, and Janssen; and consulting fees from

Bayer, Boehringer Ingelheim, Merck, Valeant, Sanofi, AstraZeneca, Janssen, Regeneron, and Genentech. Dr Pencina reports receiving grants from Regeneron/Sanofi.

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