The Predictive Analytics and Comparative Effectiveness (PACE) Center focuses on better understanding heterogeneity of treatment effects (HTE) — the fact that the same treatment can yield different results in different patients. What factors have inspired you to focus your research in this area?

The main insight that informed this framework came from my experience as a clinician. I was frustrated with evidence-based medicine, which seemed to provide a profoundly impoverished view of how the risks and benefits of a given therapy might differ from one patient to the next. When I examined the methods used to make inferences about therapy more closely, it became obvious why this is the case. The methods used are designed to estimate the main (average) treatment effects, yet they remain valid and well calibrated across a variety of settings. This will require advances in informatics, permitting local data to be used to calibrate risk models for better decision making.

Your work has shown that treatment risks and benefits often vary substantially between patients in clinical trials. What do you see as the major barrier to implementing treatments that are better tailored to patient risk?

One of the major remaining challenges is technological. We need useable risk models that can be updated continually so they remain valid and well calibrated across a variety of settings. This will require advances in informatics, permitting local data to be used to calibrate risk models for better decision making.

What is paradoxical embolism and how does it affect the human body?

A paradoxical embolism is a venous embolism that usually derives from a clot in the leg veins. It gains access to the systemic arterial circulation through a right-to-left shunt in the heart, typically via a patent foramen ovale (PFO) — a very common anatomical variant in which a small hole in the septum between the atria of the heart from foetal life persists into adulthood. Thus, a blood clot from the leg can float up into the brain and cause a stroke.

Why did you create the Risk of Paradoxical Embolism (RoPE) Study?

The RoPE Study developed as a collaboration between myself and David Thaler, Director of our Stroke Center. In our discussions, it became clear that a more informed patient selection process was necessary to decide which patients with a cryptogenic stroke might benefit from having their PFO closed. From the point of view of methodology, this was a very challenging and interesting problem for me because I realised that my usual methods of predicting outcome risk (in this case recurrent stroke) would not work in terms of selecting the right patients for closure.

How do you decide which patients would benefit from having their PFO closed?

Patients with the highest outcome risk were actually the same patients that were least likely to have strokes due to their PFO. These were older patients who had multiple conventional stroke risk factors such as diabetes, hypertension and hypercholesterolemia. Closing PFOs in these patients was highly unlikely to benefit patients because the PFOs were less likely to have caused the stroke in the first place. We therefore had to be able to predict who had a high ‘attributable recurrence risk’, which required us to develop a way to estimate the PFO-attributable fraction – the proportion of strokes likely to be caused by PFO – in different patients with different characteristics. Figuring out how to do this was one of the key insights that made the project possible.
Modelling risk in medical care

Researchers at the Predictive Analytics and Comparative Effectiveness Center at Tufts Medical Center in Boston, Massachusetts, are using risk modelling to add the individual back into the patient care equation.

PERSONALISED MEDICINE HAS become much hyped, yet it seems to mean different things to different people. To some, the phrase emphasises the need for doctors to treat each individual patient with dignity and respect, and with a bedside manner tailored to their personal needs. To others, it connotes medicine guided by a detailed understanding of each patient’s unique molecular and genetic signature. The former notion could be considered a timeless description of medical professionalism, while the latter beyond reach, perhaps now and forever the future of medicine. However, one researcher is taking a different approach towards the concept of personalised medicine. David Kent, MD, at the Tufts Medical Center in Boston, Massachusetts, is confident that treatment can be better tailored to the individual even without full knowledge of his/her’s complex molecular interactions. It can also be improved through better understanding of the fundamental dimensions of risk that determine the opportunity for treatment benefit, employing readily available – but underutilised – clinical information.

For instance, two heart attack patients may both qualify for thrombolytic drugs, by virtue of the fact that they have the same disease – a clot in their coronary arteries. Yet they may have radically different probabilities of benefiting from that treatment. In this scenario, the first patient could be an older, diabetic man with a heart attack that has affected a vital area of his heart muscle, giving him a mortality risk of 25 per cent. Whereas the second could be younger with no known long-term illnesses, and a heart attack affecting only a small area of his heart muscle, causing a mortality risk of around 2 per cent. The patient with the higher mortality risk is likely to benefit from the thrombolytic treatment, regardless of the associated risks, while thrombolytic drugs are statistically less likely to have a therapeutic effect on the second patient. In fact, they could actually increase the risk of mortality if the person has high blood pressure or a history of stroke.

Clearly, no two patients are the same. However, due to the nature of randomised clinical trials – where patients with the same disease but greatly different risks are placed together in the same trial – they are often treated that way. The medicine that is most effective for the average patient is usually deemed to be the best medicine for all.

PACE

The Predictive Analytics and Comparative Effectiveness (PACE) Center is leading research into how to make decisions that are best for each patient. The Center, which is a recent addition to the internationally renowned Tufts Medical Center in Boston, Massachusetts, is headed by Kent, who serves as Director and Professor of Medicine. With his background in clinical medicine, epidemiology and statistical modelling, Kent is ideally placed to lead PACE’s team of researchers, epidemiologists and statisticians to hopefully model individualised cures. Kent’s team at PACE has launched a number of projects that aim to summarise all the different ways that patients can vary into a few fundamental dimensions of risk; and to develop targeted treatment approaches based on this understanding. With robust funding from the National Institutes of Health (NIH) and Patient-Centered Outcomes Research Institute (PCORI), the team at PACE seeks to understand and address the limitations of using group-derived evidence as the basis for decision-making in specific cases. By combining predictive modelling with comparative effectiveness research methods, PACE is able to integrate clinical and statistical reasoning in order to provide clinicians and patients with the evidence they need for better tailored care.

RISK FACTORS IN CRYPTOGENIC STROKE PATIENTS

A key area of investigation for the team is cardiovascular and cerebrovascular disease, and one major project is the Risk of Paradoxical Embolism (RoPE) Study. Sponsored by the US National Institute of Neurological Disorders and Stroke (NINDS), RoPE seeks to understand which cryptogenic stroke patients might benefit most from the closure of a patent foramen ovale (PFO). This is a common condition in which a hole in the septum separating the left and right atria – important in foetal circulation

Dates for your diary

European Stroke Conference
6-9 May 2014, Nice, France

Society for Clinical Trials
35th Annual Meeting
18-21 May 2014, Philadelphia, USA

International Society for Pharmacoeconomics and Outcomes Research, 19th Annual International Meeting
31 May-4 June 2014, Montreal, Canada
INTELLIGENCE

THE PREDICTIVE ANALYTICS AND COMPARATIVE EFFECTIVENESS CENTER

OBJECTIVES of selected projects

• To create a framework that improves our understanding of how treatment effects vary across individuals in clinical trials by prioritising the analysis and reporting of multivariate risk-based heterogeneity of treatment effects (HTE) over conventional one-variable-at-a-time subgroup analysis

• To develop and test a set of predictive models that can identify patients most likely to benefit from preventive treatments for patent foramen ovale (PFO) related stroke recurrence, such as PFO closure

KEY COLLABORATORS

William Crowne, PhD, Optum Labs, Cambridge, Massachusetts, USA
Rod Hayward, University of Michigan, USA
Peter Neumann, Center for the Evaluation of Value and Risk, Tufts Medical Center, USA
David Thaler, Department of Neurology at Tufts Medical Center, USA

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DAVID M KENT, MD, MSc is a clinician-methodologist focused on tackling the problems of making inferences to individual patients based on effects measured in groups. He has a broad background in clinical epidemiology with a focus on predictive modelling in cardiovascular and cerebrovascular disease, as well as experience in meta-analytic approaches, particularly individual patient data meta-analysis as the basis for risk modelling.

Kent is a principal investigator of five active federally-funded research grants related to risk modelling and HTE, as well as other funded research awards from industry and foundations. His research efforts have recently been organised in the Tufts Predictive Analytics and Comparative Effectiveness (PACE) Center, which he directs.

– remains open into adult life. This opening is big enough for blood clots to travel through and make their way to the brain. While some centres routinely close PFO in cryptogenic stroke victims, statistical analysis and risk modelling by Kent and his team suggests that this may not be appropriate for everyone. A major issue is that PFO can often be an innocuous, incidental finding in patients whose stroke was caused through some other occult mechanism. Closing such incidental PFOs would be of little potential benefit and expose patients to procedural- and device-related harms.

Working closely with an international team of cardiologists and stroke neurologists, PACE researchers have constructed the largest database of patients with cryptogenic stroke and PFO. Using this data, they have identified patient characteristics associated with the presence or absence of a PFO and, in patients with both a cryptogenic stroke and PFO, their mathematical models can provide an estimate of the probability that the stroke was caused by the PFO. Simultaneously, Kent’s team has developed a predictive model using clinical, radiographic and echocardiographic characteristics to estimate stroke recurrence risk, thus permitting targeting to patients at the highest attributable recurrence risk.

Now, applying these predictive models to clinical trials testing endovascular PFO closure against medical therapy, the PACE researchers are hoping to confirm the expected differential benefit across patients with different attributable recurrence risks. This could provide practitioners with the predictive models necessary to inform treatment decisions in cryptogenic stroke cases, leading to the best outcome for each healthcare recipient. A related project is currently underway to examine the use of anticoagulant versus antiplatelet therapies in the same group of cryptogenic stroke victims.

SEEING THE INDIVIDUAL IN CLINICAL TRIALS

With recent research suggesting that clinical trials often obscure the potential risks of a medical decision to certain subgroups in favour of an average benefit or average effect, the group has launched a PCORI-sponsored project to investigate heterogeneity in treatment effects (HTE) across a broad range of cardiovascular and cerebrovascular conditions, collaborating with researchers at the University of Michigan, USA, and Oxford University, UK.

Since conventional subgroup analysis of clinical trials so rarely reliably detects large variations in the potential benefit or harm to patients, PACE has developed a framework that prioritises the analysis and reporting of multivariate risk-based HTE that can provide better evidence for tailoring care. Evaluating this framework across more than 30 large, randomised clinical trials, Kent’s team has explored how this new approach to the conduct of subgroup analysis can enable a more transparent reporting of individual patient risks and benefits, in contrast to the conventional ‘one-variable-at-a-time’ approach to subgroup analysis. This research could substantially improve the utility and interpretability of clinical trials to support therapeutic decision making better tailored to each subgroup.

The team at PACE

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COST EFFECTIVE TREATMENT

Complementing the group’s PCORI-sponsored HTE project, Kent is also heading up an NIH Common Fund supported project to develop a framework to assess the value of providing personalised risk information. Partnering with health economists from the Center for the Evaluation of Value and Risk (CEVR) at Tufts Medical Center, PACE is examining the potential economic consequences of better targeting therapies with clinical prediction models. Kent and his team aim to assess the economic value and policy implications of a risk-based approach to individualised care, to better understand how it can improve outcomes – and where it might go wrong.

These studies, together with several other applied and methodologic projects, provide a comprehensive programme that promises to greatly improve our understanding about how best to apply the group-derived data of clinical trials to individual patients. In addition to making fundamental methodologic contributions, this work can have an important practical impact on how healthcare is administered. By modelling individual health risks and benefits of various treatments, Kent and his team could lay a foundation that helps change the way practitioners make decisions and considerably improves the health and wellbeing of patients.