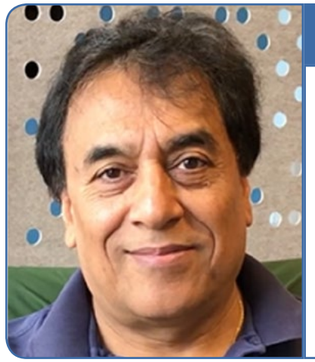
# PRECISION MEDICINE AND BIOMARKERS



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Dr. Khatry is a biometrician with 20 years of statistical experience in integrating measurement theory, statistical methodology, study designs, and state-of-the-art knowledge from regulatory guidelines and the statistical and biomedical literature. He received his PhD at the University of Michigan. His primary interest is in using quantitative methodology and tools to discover, develop, and validate biomarkers and diagnostics and, subsequently, to incorporate these into optimal clinical trial designs for precision medicine development. Dr. Khatry is currently with MedImmune/AstraZeneca and worked previously at the Harvard Clinical Research Institute, Dana Farber Cancer Institute, and Sugen. He has worked in multiple therapeutic areas including Respiratory, Inflammation, Oncology, Vaccines, Neuropsychiatry, Renal and Cardiovascular.

**How can biomarker-enriched clinical trials improve precision medicine?**

Ultimately, to improve precision medicine practice, we have to present evidence that the biomarkers used in clinical trials help us to select the right patients. Then we have to be able to demonstrate this in clinical trials of new therapies. Ultimately, we must provide clinical evidence that the new therapy performs best when the patients are selected using the biomarker or diagnostics. Thus, two types of evidence must be presented: that the biomarker selects patients accurately and that the selected patients obtain at least the pre-specified minimum clinical benefit from the new therapy.

**Is the pharma industry in general pushing towards precision medicine?**

It is. I cited some numbers in my talk that show it is pushing towards that. Ten years ago, of all the drugs approved yearly by the FDA, less than 10% had a personalised medicine component. Last year, in 2018, there were 52 new drugs approved. Twenty two of these (42%) had a personalised medicine component, such as a biomarker or something they could put on the label to select the right patients. So over the last two years, 2018 and 2017, this number has gone well above 30%. Before that it was less than 10% and over the years it has gone up, so I think that trend is going to continue.

**What are the challenges with bringing out medicine with a biomarker component?**

There are challenges all the way through. You need good biomarkers and good early studies and evidence to show that they work. This is an internal need of sponsors because if they are not good, then the clinical trials will not succeed. So that is internal to the companies. Sponsors have a stake in getting those things right, right from the beginning. Then you bring it to people to conduct the first few trials in humans and that is external – that is the evidence you have to present to get your drug approved. After that, your drug gets marketed for approval with whatever label that can be justifiably attributed to your biomarker. However, if that evidence is not accepted by clinicians and the scientific community and the prescribers do not buy into it, then your drug will not get prescribed. Even if your drug is approved, prescribers and payers might go for a competitor's product. You need to provide evidence to them so that they buy into it. For instance, in biologics, the annual cost for a drug could be around $30,000 – which is very expensive. If you do not show that the drug works in the majority of patients that it is prescribed to, then the payers will not want to pay for that – unless there is no alternative. It is to your advantage to show that evidence, so that the payers, prescribers and, ultimately, the patient benefits from it. If you take a drug then you expect that drug to work for you. If someone tells you a drug only works in 30% of the patients, you would rather a drug that works at 80-90%.

**It is very important for pharma companies to show that there is evidence of biomarker efficacy. What sort of data is generated and what evidence is required?**

Ultimately, biomarker data can come from different platforms and different types of data. Some can be images which get quantified and can be used as a diagnostics. But when you bring it into a clinical trial setting, you almost always make it binary – a biomarker positive or negative, depending on the threshold chosen. Then you can use that to stratify your patient population in trial design. Going into the clinical trial design, you can have different types of data endpoints, with continuous measures of something like people's response rate, or in terms of cancer such as tumour shrinkage, or with asthma and Chronic Obstructive Pulmonary Disease (COPD) you would be looking at lung function or symptom score. With asthma and COPD, you can also look at people's annual exacerbation rate. For a clinical trial in those, we enrol patients who have a history of at least two exacerbations in the previous twelve months, but it could be 3, 4, 5, 6, or even 9 or 10 per year. That is a different type of data – it is count data. You can take an average of that, as in continuous measures. You need different types of statistical techniques and tools to analyse such data. Ultimately, to show efficacy you need to come up with MCID, the Minimum Clinically Important Difference. If we started out with patients that had two or more exacerbations of asthma or COPD, in the previous twelve months, if that drug is good, it should reduce to less than two anually. It should be one or zero going forward in the next twelve months. Let us say you are under strict criterion for the Minimum Clinically Important Difference and say if you take our drug, within twelve months most people will have zero exacerbations.

When you use that as a cut off, then your minimally important clinical endpoint is also binary. Your diagnostic biomarker is binary positive or negative and your clinical endpoint also becomes positive or negative. When you show the clinical evidence of that, you get a significant p-value that shows the drug works, but the binary value allows you to show the probability that one individual patient will be likely to benefit from the drug. That is the evidence that clinicians want so they can look at the patient in front of them and know if the drug has a high probability of benefitting the individual patient or not. That is what the payers want to see: if the drug works for the majority of the patients, we will pay for this expensive drug, if not, we will not. It all comes down to binary choices, so that one can compare the benefits, costs and different options for drugs, and they become easily understandable, objective measures that patients, clinicians and payers can understand.

I just published two papers related to this topic that I presented in my talk at the Biomarkers Congress. One is published in the Journal of Comparative Effectiveness Research, where you use that kind of concept in designing your clinical trials, you do simulations, and then design the clinical trials. This was published a couple of months ago. Also, in another journal called Personalised Medicine, I published a paper three or four months ago, which speaks to this issue.

But I think that is the future of personalised medicine, where clinicians have probabilistic evidence to prescribe drugs to a certain patient and the payers would agree to pay for the drug. Within this broader topic, there can be a lot of variations in data types and workshop types, but oftentimes those are done among statisticians. Together with the FDA, over the last ten years, every year we convene an annual workshop in Washington, D.C., where about 800 people from the FDA, industry and from academia come together for a three-day conference. There is a lot of statistical depth covered, but oftentimes presented newly developed methods may only show marginal statistical improvements. What is really needed is to generate valid binary biomarker/diagnostics performance and minimum clinically meaningful efficacy results data that together can be used to generate practical, decision-aiding evidence that can be used by all stakeholders including patients, prescribers, payers, regulators, and the drug developers.