Image: © Les Cunliffe – Fotolia.com

For Good Measure

Biomarker-based tests are becoming a necessity for much therapeutic research, but they add unwelcome time and cost. In the drive for efficiency, drug developers should focus on appropriate biomarker selection and using biobanks for pre-trial validation work

Simon Goldman and Mike Fisher at Abcodia Ltd

There has been quite some controversy in recent months surrounding the estimate from Tufts Center for the Study of Drug Development that the cost of bringing a new drug to market is now in the order of $2.5 billion – up from around $1 billion a decade ago. A number of factors have contributed to this increase, from a heavier regulatory burden to more complex drugs and targets being developed. The rising cost of generating new drugs to meet patients' needs is simply unsustainable.

One issue from the last decade has been the greater adoption – and recognition from regulatory authorities worldwide – of biomarker-guided strategies for drug development. These are implemented for all the right reasons: they lower the risk for patients, enable selection of patients that have a higher propensity to respond, and increase the likelihood of regulatory approval. There is an economic benefit too, in that payors tend to accept higher costs when they know they are not wasting money treating people who might not respond.

However, this does mean more costs for the drug developer; in addition to the traditional hurdles, companies now have to develop diagnostic tests in parallel that will stratify their patient populations, or demonstrate a clinical end-point for the trial. This not only adds direct costs to commercialisation activities, it also adds time, which accounts for nearly 50% of the drug development costs estimated by the Tufts research group.

The big question, therefore, is how to develop these biomarker-based tests as efficiently as possible, without additional clinical trials (to prove the diagnostic) that add to development cost and time?

Biomarker Objective

The first step is to work out for what purpose a given biomarker (or panel thereof) is being used – how is the strategy intended to either improve clinical outcome, or reduce time/cost/risk? This should be established before the trial starts to ensure the relevant samples are systematically accessed. It is possible to recall any number of trials that have failed to reach their primary end-points, to then see management scrambling to identify and test biomarkers that might indicate some positive secondary outcome.

Many drug developers will seek to set surrogate markers as clinical trial end-points. This is a reasonable approach, since most trials will not continue long enough to fully demonstrate treatment outcomes, such as mortality. They are also important from the perspective of facilitating early 'go, no-go' decision-making, whether from a safety or an efficacy point of view – killing a trial early can be critical. As noted, regulatory authorities in both North America and Europe are increasingly recommending biomarker qualification submissions, feeding into the clinical trial process.

Key Characteristics

Next, for effective implementation in a trial setting, a biomarker or panel needs to show several important features. It should, of course, be easily measurable. This means that relevant samples from patients can be accessed without difficulty – for example, a swab or blood-draw would be preferred to tapping cerebro-spinal fluid.

In addition, it is preferable if the technology being used to measure the biomarker(s) is not only cheap and fast to use, but also robust under various user conditions – a single-centre Phase 1 trial versus a large multi-centre Phase 3, for instance. Clearly, the biomarker or panel should provide information that is not apparent in any other way.

Most importantly, however, its measurement should result in some sort of change in patient management within the clinical trial – for example, by enabling patient stratification. This is achieved first by establishing what the baseline level and normal variation of the biomarker(s) in healthy individuals look like, preferably over a period of time for non-genomic markers. An effective biomarker or panel would then presumably indicate some form of altered profile for individuals either showing, or at risk of, a pathogenic phenotype.

Demonstrating this variation from baseline is the key challenge for selecting appropriate biomarkers. Mechanistic involvement of a biomarker in a disease process might then be corroborated in the clinical trial if levels return to normal with treatment – a powerful supporting factor for regulatory approval and label claims, and therefore improved uptake in the market.

When It Goes Wrong

The majority of biomarker studies in therapeutic clinical studies are nested within the trial design structure. This makes sense in many cases, as that will be the first opportunity the drug developer has to collect human samples from properly matched healthy-control and relevant-diseased patient populations. The biomarker validation work will often have been done either *in vitro* or in animal models.

However, there are multiple examples of such nested studies that simply did not work – and there are major pitfalls to this kind of approach which might explain why this is the case.

The most glaring of these issues is the degree to which the relationship between the biomarker(s) and the clinical outcome is understood (correlative or causative?). If things go well, and the biomarker changes do correlate with outcomes – for example, rise relative to normal with worsening pathology, then fall with successful treatment – the drug developer may well be able to claim there is some mechanistic, causative relationship between them.

But what happens when changes in the selected biomarkers do not correlate with outcomes? And what can be done when a clinical trial has already progressed into later stages, where it is difficult or costly to then retrospectively examine other potential surrogate markers?

“Many drug developers will seek to set surrogate markers as clinical trial end-points. This is a reasonable approach, since most trials will not continue long enough to fully demonstrate treatment outcomes, such as mortality”

Table 1: Major European biobanks

Biobank	Sample types	Size	Features
Bavarian Red Cross Blood Donor Bank	Plasma only	400,000 male and female donors in Bavaria	Longitudinal samples available
Hunt Biobank	Blood, plasma, serum, urine	100,000 male and female donors in Norway	Single sample provided by each participant
International Agency for Research on Cancer	Plasma, serum, erythrocytes	520,000 male and female donors across Europe	Single sample collected on entry to the European Prospective Investigation into Cancer and Nutrition (EPIC) trial
Janus Serum Bank	Serum	317,000 male and female donors in Norway	Samples available at roughly four- to five-year intervals
UK Biobank	Plasma, serum, urine, saliva	500,000 male and female donors in the UK	Samples available at five-year intervals; only 4% donated >1 sample
United Kingdom Collaborative Trial of Ovarian Cancer (UKCTOCS)*	Serum only	200,000 female donors in the UK	Longitudinal samples available annually for 10 years

* Exclusive commercial access available via Abcodia

Coming Up Short

These problems often arise because many biomarkers do not sufficiently meet sensitivity and specificity criteria that would enable their effective use in a trial. There are a number of reasons for this. Those developed in animal models may not translate particularly well to human populations. Where samples are accessed from hospitals or other commodity human sample providers, only a small number of diseased cases may be available, and there might be variable standard operating procedures for collection and a lack of substantial information on sample history. It can also be difficult to then properly match healthy controls to diseased cases, even if this work is carried out during the early clinical phases.

Furthermore, disease progression may be slow – requiring recruitment of large numbers of patients – and many drug developers are constrained by either financial or corporate realities. Finally, the robustness of analytical techniques for samples collected as part of a randomised clinical trial could be an issue.

Simply assessing what the variation of a biomarker is within a healthy population can be extremely difficult. All of these problems argue for engaging in systematic biomarker validation in well-characterised human sample cohorts before the commencement of clinical testing.

Biobank Resource

To avoid many of these complications, it is important to validate changes in biomarkers against evidenced disease phenotypes and clinical outcomes in well-curated sample sets before clinical trial initiation. Understanding the disease pathway enables selection of potentially multiple relevant biomarkers that can be assessed throughout clinical development, as well as enabling comparison of several therapeutic candidates or dosages relevant to a given trial.

In this regard, many of the European human biological sample banks have matured to the point of enabling substantially expedited biomarker and diagnostic validation for therapeutic clinical trials. They therefore represent an increasingly important resource for the pharmaceutical industry – not only as both regulatory authorities and payors move to incorporate companion diagnosis into their review processes, but also out of sheer business necessity. The cost of getting a drug to market may be debatable, but it remains indisputably enormous, so the advantage provided by high-quality biobanks is as critical as it is obvious.

About the authors

Simon Goldman's work with Abcodia focuses on developing collaborations with a range of industrial and academic partners for biomarker and diagnostic validation across a range of chronic diseases. He is also managing the rollout of a groundbreaking new test for ovarian cancer. Simon spent seven years at Goldman Sachs JBWere in Australia, before moving to the UK and completing his PhD and postdoctorate in Auditory Neuroscience at the University of Cambridge. He continues to teach Cambridge undergraduates in Macroeconomics, Finance, Neurophysiology and Neuropsychology.

Email: simon.goldman@abcodia.com

Mike Fisher is Abcodia's Director of Strategic Alliances, responsible for developing collaborations that access the company's longitudinal biobank. He is a medicinal chemist with over 15 years of postdoctoral experience in research, project management, business development and consulting. Mike helped develop the Bionow biocluster in northwest England and was a founder of the Northwest Genetics Knowledge Park. Previous roles include three years with UKTI as the British Government's North American advisor on the life sciences industries, and Business Development Director of Bio Nano Consulting.

Email: mike.fisher@abcodia.com