Why are biomarkers important?
I think it is because it is a win-win situation for all parties involved. It is good for the patient because biomarkers help to identify specific patient populations that will respond to drug therapies and just as importantly, those patients that will not respond to some drug therapies. It is good for the drug companies because it helps to get drugs approved as they are targeted to a specific patient population. Biomarkers can also play a significant role in identifying and preventing those patients that might suffer severe side-effects and which may also derail the approval of a drug in specific sub-populations. And it’s a win for the healthcare system in general because we do not have drugs prescribed that are not efficacious and we can prescribe more targeted drugs that help patients recover and respond faster, so the overall cost of drugs would go down.

What biomarker services do you offer at Quest?
We offer the complete spectrum in biomarker services. We can get involved with drug companies in the discovery of which biomarkers help to identify those patients who will benefit from their drugs. For those biomarkers identified in the discovery phase, we can develop them into specific diagnostic assays and can perform those assays during clinical trials to obtain what we call clinical validation.

Once the clinical validation is done, since Quest has the largest reference laboratory in the world, we can make those assays available to physicians so they can request this biomarker diagnostic assay for their patients to determine if this new drug is good match for each patient.

We can also work with in-vitro diagnostics (IVD) companies to develop these assays into kits, which then get regulatory approval as diagnostic assays which are either FDA or “CE” marked, in Europe.

How and why do you validate biomarkers?
There are two aspects to validating assays. The technical validation is when we demonstrate that the assay measures what we think it measures. For example, with an assay that measures c-reactive protein, the technical validation determines how sensitive and specific the assay is at measuring the amount of c-reactive protein, or whether the assay might be cross-reactive with any other proteins?

A clinical validation is related to demonstrating the correlation of the biomarker assay to clinical outcomes. For example, it might demonstrate that patients that have a certain level of protein or a specific genetic marker will respond to a drug, and those that do not have that level of protein or do not have this specific genetic marker will not respond to the drug. Similarly, it can be used in patient analysis. Patients whose cancers have these specific mutations might respond to a drug, and those that have an entirely different set of mutations will not respond. A clinical validation relates to outcomes and choice of therapies.

How are biomarkers integrated into clinical trials, how has this resulted in the growth of companion diagnostic assays?
This is the best part! Clinical validation comes from a clinical trial and we can do this in a proactive way or a reactive way. Let’s say we have a drug in a Phase II trial that was given to 20 patients with high cholesterol, 10 of the patients responded to the drug and their cholesterol level went down. Ten patients were treated with the same drug and their cholesterol level did not change. These are what we call responders and non-responders. Our job is to determine what genetic factors, what biomarkers, are associated with the patients that respond to the drug and are different from those patients that did not respond. That is the clinical validation, and that is how they are incorporated into clinical trials.

In a translational way we can sometimes find specific biomarkers early in the drug discovery process, proactively before we get into the trial, and we have an idea of which biomarkers to look for. Then we can incorporate those assays into the clinical trial. Sometimes, after a clinical trial shows that some patients responded well, but some didn’t, we can identify biomarkers which are correlated with response and non-response. This is the reactive approach.

The advantage of both approaches is that we can target the specific patients that will benefit from the drug, once we know which genetic factors and protein biomarkers are associated with response. Once the correlation between biomarker and drug response is established, the pharma company can set up another trial and in this trial they would only give the drug to those patients that have the characteristics associated with response and in that case instead of it only being 50% responsive, we can now move it up to a 90% or ideally 100% response rate.

As this is in clinical trials, the drug has not been approved and the diagnostic assay has not been approved. It only becomes a true companion diagnostic when the regulatory
agency approves the drug and deems that the drug is only to be prescribed to those patients that have certain biomarker characteristics. The doctor then looks at the package insert and sees that he can only prescribe the drug for certain patients. The doctor needs to have a laboratory to run this companion diagnostic assay on these patients to determine if these people fall into the responder or the non-responder category. So, the doctor gets the result from the diagnostic test, the result indicates that the patient is a good candidate for the drug, and the doctor prescribes the drug. It’s a win-win as the drug has been shown to be effective in this specific patient population.

**How does this fit into personalised medicine?**

The goal of personalised medicine is that the patient gets the right drug for their specific disease. So, for example, we know that all breast cancers are not the same. We know that they have different mutations in different pathways. With a specific companion diagnostic assay, we can characterise which type of breast cancer a specific patient has and then determine from the various anti-cancer drugs which drugs the patient is likely to respond to, and importantly, the drugs that won’t be effective.

There are two sides to the benefits of personalised medicine. One side of personalised medicine determines which drug is best suited to treat their specific form of disease. However, the other side is that we don’t waste money on drugs and time using drugs that we now know would not be effective because of these companion diagnostic tests.

**What are the key challenges to developing a clinically validated companion diagnostic?**

There are some challenges, but its really just a case of risk:benefit ratios. The risk that you get the wrong diagnostic test is far outweighed by the benefit of getting the right one. There have been examples where the industry has promoted a specific biomarker and it turns out with much larger studies that the difference between responders and non-responders really didn’t pan out. Those examples are few and far between.

In the vast majority of cases, most drug companies now work on biomarkers because they know that they will be able to help target drugs more effectively.

**What considerations are there for development of biomarkers throughout the clinical trial process?**

The first thing you have to think about is the cost:benefit ratio. Let’s take anti-depressants as an example. A lot of people are working on biomarkers for depression because it is very difficult to predict the efficacy of anti-depressants. Oftentimes physicians simply put a patient on an anti-depressant to see if it works and if it doesn’t, they will switch them to a different class of anti-depressant drug, and if that one doesn’t work, they will move them onto a different class until they find one that works. The problem with the biomarker strategy attached to anti-depressants is that a lot of anti-depressants are generic drugs, so the cost of prescribing a generic drug compared to the cost of prescribing a companion diagnostic assay becomes more equivocal at that point. To the physician, it is relatively inexpensive to prescribe a generic drug therefore the cost of a good companion diagnostic assay for anti-depressants also has to be very inexpensive. Unfortunately, what is not taken into consideration is that the patient suffers for several months because they are taking ineffective anti-depressants.

If a therapy is new and very expensive, and some anti-cancer drugs can be $10,000 to $20,000 per year, and an inexpensive diagnostic test is used, that ratio is very beneficial. I think you can see that a $100 test to show you that a $10,000 drug is ineffective is a good use of money. A $2,000 diagnostic test to determine a drug that costs much less than that or is equivalent in cost becomes much less economically favourable. One of the challenges is to make sure that the cost of the diagnostic is in line with the cost of the therapy.

**How do you use biomarkers to determine drugs suitable in different genetic populations?**

We all have genetic differences. There are a few examples of biomarkers in Asian populations which are not present in western European populations because of genetic differences. It is very possible that a biomarker that is identified in a western European population may not be associated with response and non-response in other cultural populations. It is possible that when you target certain genetic populations you may need a different biomarker for a different genetic background.

The idea is that biomarkers could be effective in one genetic population but not effective in another population, but that only comes from clinical studies. For example, Quest has a lab in China because a lot of drug companies want to do clinical trial testing of their drugs in Chinese populations to ensure that their drugs will be effective in that genetic population.

**How will biomarkers work in future clinical trials?**

I think it is an evolving field, and I can easily see how it will affect the design of clinical trials. Currently, clinical trials are designed to prove the efficacy of the drug in the entire disease population, so, for example, all people that have high cholesterol, or all women that have breast cancer.

In the future I can see two changes; one is that clinical trials will be much more targeted based on a biomarker, and that drugs will only be tested on patient populations that has a specific biomarker.

Secondly, I see that pharma companies will use clinical trials to discover biomarkers in the disease population. For example, pharma companies will design a clinical trial to treat the entire disease population. Let’s take for example the trial of 40 patients in which 20 subjects respond, and 20 subjects don’t respond. They can then determine which genetic factors are associated with response or non-response by using a technique such as whole genome sequence analysis, which is where we can understand your entire genetic sequence in a relatively short period of time. If we can determine the entire human genome sequence of those responders and compare those to the non-responders, we can determine which genetic factors are associated with response and non-response. On the basis of this information, pharma companies can design the next clinical trial using those genetic differences in the human genome to select and target those patients that will respond to the drug.

In the future, I envision that this science will eventually allow you to go to your doctor, you give him a drop of blood, and once he has your entire genetic sequence and he can determine how best to treat you. That’s the goal of personalised medicine and that’s how clinical trials will be designed in the future.

**For more information on the use of biomarkers in clinical trials visit: www.questdiagnostics.com/clinicaltrials.**