Two Covance executives discuss a CRO’s role in supporting Companion Diagnostics and the benefits of a Central Laboratory/Pharma Companion Diagnostics Partnership

Companion diagnostics, as a field, is rapidly advancing as the biopharmaceutical industry increasingly turns its focus to discovering and delivering targeted, personalized medications. By 2015, the worldwide companion diagnostics market is estimated to be worth $3.45 billion, according to London-based market research firm Visiongain. Companion diagnostics is essentially a test that is administered to a patient to determine whether a drug will be efficacious, or could result in an adverse event. Central laboratory involvement is also growing. With their intimate understanding of the drug development process and practical experience developing and deploying biomarkers, they are increasingly acting as partners with, and facilitators between, biopharma and diagnostic companies. Following is an interview with Covance’s Central Laboratory Services, Thomas Turi, Ph.D., Vice President Science and Technology, and Mark Roberts, Ph.D., Director, Diagnostics Development.
Pharma companies see the significant benefit that companion diagnostics bring to the drug development process. As Covance partners to develop the correct tests, and then apply those tests to the clinical trials, the results are faster development times, reduced cost and optimal patient treatment.

Q: With the emergence of personalized medicine, we are hearing a lot about companion diagnostics: What exactly is a companion diagnostic?

TURI: A simple definition is that companion diagnostics are assays, or tests, that are designed to help physicians in making the best treatment decision for their patients. Companion diagnostics help them by providing data that help identify a specific drug or class of drugs that is best for the treatment of the disease in that specific patient.

Q: Why the growing interest in companion diagnostics?

TURI: The answer is really two-fold. First, the cost and timelines for developing safe and efficacious drugs have reached unacceptable levels. Second, there have been remarkable advances in our understanding of disease mechanisms, our ability to accurately map the genetic basis for many diseases and new technologies that enable us to precisely image or measure specific biomarkers for disease stratification and drug efficacy. Combined, these drivers enable the design of better, more efficacious clinical trials that facilitate clearer and earlier go or no go decisions.

Q: What makes an effective companion diagnostic?

ROBERTS: It’s quite simple, one is that it has to work, and two is it has to be available. Obviously, the data that comes out of the assay has to be good, it needs to be very specific, and it needs to give unequivocal data. In terms of availability, you have to produce the results in a clinically relevant time frame, so if a patient is located in Europe then sending the sample to America isn’t going to be the right way to do it. You have to tailor your commercialization strategy to the needs of the assay and the patient, so collaborating with the global diagnostic partners that have a large installed base of high quality technology is essential. If the assay isn’t available, then it won’t be used, and it will dramatically impact the uptake of the drug. There has been a shift in thinking by pharma. Ten years ago, all they wanted were blockbuster drugs, now some of the products are being targeted to less than 50% of the patient population, and they are starting to see greater clinical efficacy and earlier adoption by physicians and patients. This is starting to change their opinion on how to approach the market. It all comes down to efficacy, because drugs that are efficacious will have a place in the market and command premium pricing.

Q: Why is it important?

TURI: The increasing demands by patients, physicians and healthcare organizations for better, more efficacious and cost effective therapies require new ways of approaching drug discovery and development. Even with all the advances in the drug development process, many times, it is still hit or miss. With the added information gained from the companion diagnostics test(s), the likelihood that the drug being tested will be success-
Dedicated Dialogue

TURI: To accelerate the drug development process pharma companies are adopting companion diagnostics strategies earlier in the drug development process and running the clinical trial for the diagnostic within the drug trial. Covance, with its primary focus on running clinical trials is in a unique position to partner with the drug developers to execute their drug / companion diagnostics co-development strategies.

ROBERTS: Clearly, both the pharmaceutical companies and the diagnostic companies are aware of the needs of their partners, but neither partner appreciates all the complexities required to deliver an effective diagnostic. Covance has a unique perspective, as we partner very effectively with both biopharmaceutical companies, diagnostic companies and regulatory agencies, we have a better view of what is required to implement an effective companion diagnostic and an effective clinical trial design. We can tailor our approach to ensure we deliver on all the disparate needs. Beyond that, you’re looking at things like patients, and patient advocacy groups, health insurers, different agencies, regulators, it’s bigger and getting bigger, and is much more complex. Because of Covance’s broad set of capabilities to not only focus on the scientific and the clinical aspects, but also the commercial and economic positioning of these products through our market access group, really makes us very attractive to these organizations.

Q: With the advent of an informed patient-base, personalized medicine and the need for companion diagnostics along with associated domain expertise, the landscape has obviously changed. How then do pharmaceutical companies (and their CRO partners such as Covance) recognize and address the other stakeholders and their often different needs and goals? What are the needs and goals? And who are the stakeholders?

TURI: As with any aspect of the drug development process, co-development of a companion diagnostics is not without its challenges. There has been a limited number of drug – companion diagnostics co-development examples to guide the industry so the industry is essentially building the plane while it’s in flight. Moreover, the regulatory environment is still evolving. While the drug and diagnostic development process on their own are well understood, neither the FDA nor the CMS have developed standards...
or guidelines for co-development of companion diagnostics tests where testing takes place within a CLIA-compliant laboratory. While work is underway to refine these regulatory standards, there is still much to do.

Also, the timelines for implementing a companion diagnostic assay have historically been very constrained requiring flexible resources and strong scientific and project management skills in order to implement a development stage assay in support of a global clinical trial. Delays in implementing the assay result in delays to the start of the trial.

Q: Could we talk about companion diagnostics and its importance in clinical trial design and how drug/companion diagnostic co-development is rapidly changing the drug development process.

ROBERTS: If you look at the early examples of companion diagnostics, they were often introduced later in the drug development process, when differences in the response were more visible. This often necessitated additional trials with associated cost and timeline delays.

As the market and knowledge base evolves, the pharma clients are starting to introduce their companion diagnostic strategy much earlier in the process. This allows clinical validation of the assay to show that it is actually predictive of outcome. You can then use that assay to drive the late stage trial design, allowing you to concentrate on your target population and enriching your data. Early involvement is driving great advances in the trial design process. We have seen the timelines shortened, where data integration has been easier and the drug has been able to progress through to the pipeline at a faster rate. Whether you use it to drive the proof of concept or ultimately registration trials, the involvement of this tool within the trial design has made a significant impact.

The impact of companion diagnostics on a clinical trial really focuses on not just the number of patients, but what kind of patients are enrolled in the clinical trial. Moreover, it’s also about patient stratification at very early stages, who is in the trial, what are the requirements, and inclusion/exclusion criteria which are becoming much more specific. No longer is it just based on demographics and geography, but an actual biomarker or genetic marker positive patient. That begins to make these trials much more specific and places increasing demands on availability of appropriate investigators that will be interested in these types of studies. In order to identify the right investigator, who can rapidly enroll patients, you need an extensive investigator database. Covance brings that extensive database to the table as part of our product offering.

Q: How does the current in-process regulatory environment impede mapping out of a successful strategy?

ROBERTS: The guidelines and processes around drug development are very clear, as are the guidelines and process around development of clinical diagnostics. However, when you put them together, the water becomes muddy because now what you’re doing is co-developing a drug and a companion diagnostic. You’re developing the combination product, and you have a pharma company that is working with one division of the FDA, and a diagnostic company working with another, different division. On top of that, CMS regulations govern the lab environment, further complicating how the co-development process is actually implemented. We here at Covance are spending a lot of time working with CMS and the FDA to try to craft some guidance around rules of engagement and roles and responsibilities. Currently, there is an inherent risk across the whole trial. If the data isn’t captured correctly, the drug trial is at risk, the diagnostic trial is at risk, and ultimately any potential noncompliance at the labs place an additional risk. The industry needs to focus on clearly defining these roles and responsibilities so they can move forward with a robust assay in support of the regulatory finding.

Q: How are pharmaceutical companies focused on companion diagnostics?

TURI: Pharmaceutical companies see the significant benefit that companion diagnostics bring to the drug development process. As Covance partners to develop the correct tests, and then applies those tests to the clinical trials, the results are clear: faster development times, reduced cost and optimal patient treatment.

Q: Given companion diagnostics is the future of personalized medicine, why so few companion diagnostics and why the difficulty of translating biological data into predictive biomarkers?

ROBERTS: The challenge has been trying to actually validate a biomarker
and develop that into a diagnostic. That is as complex in terms of establishing proof of concept that the marker is truly predictive, as it is for developing compounds. There is a parallel science that goes on in discovering an informative biomarker, validating that it actually differentiates a patient population or that it predicts a response or a safety signal. That science requires a lot of investigation and confirmation, especially in oncology because so much of it relies on looking for genetic markers. It really comes down to understanding the biology and how those markers tie into making predictions. There is also a commercial side to this. If you consider the cost of creating and validating a predictive marker, few if any of the diagnostic companies can afford to do that on their own. When the industries come together under a co-development model the diagnostic company can in essence piggyback the drug trials. This makes it a lot more cost effective for the diagnostic company to bring forward the companion diagnostic. While there are less than 20 companion diagnostics currently approved by the FDA, there are hundreds of drugs out there that have some kind of biomarker component mentioned in the labeling. Currently, there is an explosion of early stage companion diagnostic development activity which if successful, will result in an exponential increase in approvals over the next five years.

**Q:** If personalized medicine is going to start anywhere, it must first start in oncology, and then there’s the question how can you build an effective responsive price and reimbursement standard to establish that there is sufficient incentive for the industry to develop diagnostic tests that insure the right patients will benefit from the best drug for their condition. And while this has been working for oncology will it work with other medicines for other therapeutic areas?

**ROBERTS:** Oncology has led the way, and there have been tremendous advancement in the knowledge of molecular pathways as well as advancement in technologies that aid in understanding specific genetic alterations. Clearly, oncology was an area lacking an effective solution and one everyone was looking for a breakthrough in. But now we are seeing such advances across all treatment areas, that it really is becoming the norm in a wide number of studies. In every indication, there are always subsets of patients that will not respond to treatment. The better we can identify patients who respond to specific treatments, the better off we all will be, so there is an increase in the use of companion diagnostic for any given disease or specific mechanism that is being evaluated.

**Q:** What does the future of companion diagnostics look like and what does it mean to the patient?

**TURI:** Companion diagnostics will change the way we develop drugs. They will provide a greater understanding of the disease while pinpointing the right type of treatment. As more drugs are developed with companion diagnostics, patients will receive what some call “tailored-therapeutics.” Simply put, they will receive the drug that gives them the best chance for a cure, in the shortest amount of time. Right now we are seeing these advances bear fruit in the oncology field. A person’s genetic makeup has a direct impact on how they will respond to a specific treatment - if we are able to characterize that during the clinical trial process, we can design a more effective clinical trial. We’re now seeing the same approach applied to other therapeutic areas with very exciting results.

**About Covance,**

Covance, the world’s most comprehensive drug development company, is dedicated to advancing healthcare and delivering Solutions Made Real™. The company, headquartered in Princeton, New Jersey, has more than 12,000 employees located in over 60 countries. Information on Covance’s solutions, press releases, and SEC filings can be obtained through its website at www.covance.com.

**Forward-Looking Statements**

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