Successful Companion Diagnostic Development: Current trends and recommendations

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Examining the trends in personalized medicine sheds light on ways to create successful partnerships between sponsors, laboratories, and manufacturers of in-vitro diagnostic products (IVDs) to develop more efficiently stand-alone diagnostics, companion diagnostics (CDx), and complementary diagnostics. This is particularly relevant in light of the paradigm shift on the horizon for developing and ensuring reimbursement of such personalized medicine solutions with new technologies.

Key trends for personalized medicine

In today’s market, there is tremendous downward pressure for reimbursement. We’ve seen a long-term shift in the laboratory business model from using complex regional laboratories to physician office labs and point of care testing. Soon, patients will be using wearable or embeddable nanotechnologies with real-time data transfer to a data hub.

We have also seen a focus in the market toward smaller populations to be treated with specific drugs, not only for orphan indications or rare diseases, but also in major indications like cancer, where targeted drugs are being used to only address patients whose tumor is harboring specific mutation(s). The need to prove the clinical utility of a diagnostic or a CDx in order to be reimbursed is increasingly important, and several academic studies, or yet, from Health Management Organization/Insurers aim to demonstrate such clinical utility for evidence-based reimbursement.

Earlier launch of drugs and breakthrough designation approvals increase expectations for real-world evidence – and the threat of re-evaluation of drug efficacy and safety after drug approval and commercial launch. Local jurisdictions and authoritative bodies (e.g. the Food and Drug Administration [FDA]) are allowing a drug to be approved and launched, but are often requesting Phase IV data post-launch to ensure safety. Payers are also expressing interest in post-marketing outcomes and analytics to establish value, and sometimes integrating testing programs as a prerequisite for expensive therapies.

We’ve also witnessed technical shifts in the laboratory services offered, from routine or safety testing (e.g. chemistry, coagulation, urinalysis, hematology, serology, hormone testing) to highly complex testing, such as 10+ color flow cytometry, molecular pathology and genomics (e.g. Next Generation Sequencing [NGS]). Similarly, we have seen a shift toward high complexity test interpretation, including polymerase chain reaction (PCR) variance calling and whole genome/exome sequencing and algorithm-based panels. The FDA has been open to considering NGS custom and backbone panels for CDx purposes. In NGS backbone panels, a subset of variants and callings are chosen in order to generate a
CDx product for a given drug, always using the same multiplex NGS assay. Though the cost is a limiting factor, NGS backbone panels could be truly revolutionary to assist drug development in the future.

There are regulatory trends in personalized medicine that call for increased oversight, including the new draft FDA Guidance on Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product. This guidance provides direction for co-development, including investigational device exemptions (IDEs) and clinical trial assays (CTAs) to support patient selection. Validation standards require that laboratories ensure that the validation matches the intended use of the biomarker. The Research Use Only (RUO) designation can be made into a potential clinical trial assay under appropriate development and labeling as an Investigational Use Only (IUO), or if the test developer ensures adequate controls and labeling are in place. For enrollment studies, the CTA should use a single testing protocol, and local testing should be avoided to ensure data are comparable across sites and time periods.

The FDA also approved a drug for a new indication on the basis of using a genetic test without a pre-market approval or notification, but with a promise that a CDx would be developed in the future. We have also seen the emergence of a subclass of CDx called complementary diagnostics (see below).

**Complementary diagnostics**

Historically, the industry has been using a very loose definition of CDx tests. Regulatory bodies are working to define the true CDx tests which are absolutely required to identify patients who are likely to benefit from a treatment, and to differentiate them from those tests that are helpful, but not absolutely required to prescribe a given drug. As stated above, the second category referred to as complementary diagnostics are “diagnostics that are not required, but provide significant information about the use of a drug.” There are still many unknowns about this later class of diagnostics and the value propositions for the pharmaceutical industry, IVD manufacturers and testing laboratories. Reimbursement for laboratories for complementary diagnostic testing also remains to be clearly defined.

**The power of personalized medicine**

Personalized medicine plays an important role in drug development today, and its impact is deemed to increase for many years to come.

Personalized medicine is important in various indications. In fact, in 2014/2015 personalized medicines accounted for 25% of the FDA novel drug approvals and oncology was a particularly active area comprising almost half of those approvals. Oncology biomarkers for personalized medicine solutions tend to target mechanism of action (MOA), pathway, or related to the drug target itself. Other disease areas also employ metabolism, exposure-related, and germline genetic disorder-related biomarkers.

*Figure 1* shows the value chain for personalized medicine lab testing solutions. There is a true continuum wherein biomarkers (putative CDx) can be used early for pre-clinical, translational science, through clinical development, then to support drug FDA-filling, and product (both drug and CDx) launch. The value of a biomarker assay increases as the development of a drug that
is reliant on such biomarker progresses and during which period a putative CDx biomarker is shown to have a clinical utility as a CDx. Throughout the discovery and clinical development phases, a preferred central laboratory partner is able to offer support from the very onset of the candidate CDx discovery through its commercial launch. There are service providers, such as Q2 Solutions and its parent companies, QuintilesIMS and Quest Diagnostics, which offer services across this full continuum. The spectrum of testing services differs for LDTs and various manufactured in-vitro diagnostic devices, with LDTs covering the full continuum of care.

**Figure 2: Spectrum of testing services**

Shows the range of uses from determining responders to predisposition

*Some LDTs have received Premarket notification*
Is LDT still the best option?
When trying to develop a biomarker, develop an assay, and go to market with a drug there are multiple approaches to take. Here we outline important considerations for each approach, including scientific and business factors that may present obstacles to success.

Early IVD partnering case
Investigators who want to develop a true IVD are strongly encouraged to meet with the regulatory bodies as early as Phase I to receive guidance about co-development and potentially an IDE for the biomarker assay. The MOA, IVD performance, platform, and intellectual property (IP) need to be defined, with a clear understanding of the drug development risk that is acceptable to commit to the IVD or CDx in the future. This approach can be very costly, and there is an up-front commitment required despite a lack of surety about whether the drug and IVD are going to be effective.

Typical LDT/IVD partnering development
Early engagement is also required in the use of typical LDTs, which can be bridged during Phase II/III to an IVD with the potential to become a true CDx. Typically, the elevated early phase drug development risk suggests some IVD investment delay. The LDT serves as a tool to risk mitigate the IVD investment, and to refine the IVD specifications. The relationship between the biomarker and the drug MOA, the IVD performance, Intellectual Property, sample type and the platform to be used need to be clearly defined. If the early phase I/II LDT is using RUO kits/reagents or Analyte Specific Reagents (ASR) or instruments with an intended bridge to the final IVD, then a strong relationship with an IVD manufacturer becomes more important. In other instances, it may be premature to commit to a specific IVD platform, and better to develop an LDT and engage in comparative platform and orthogonal studies to better inform an IVD decision. Lastly, one needs to consider that the bridging phase from an LDT to an IVD can delay trials or necessitate retesting of samples.

FDA regulated LDT development & commercial
Though the draft LTD framework guidance is available, the future regulatory environment around LDTs is uncertain. In fact, recently the FDA announced that it will revisit its position towards the Laboratory Developed Test (LDT) Framework. There are a small but growing number of lab services (LDTs) that have been filed as IVDs and cleared or approved by the FDA. This is a suitable solution when test content is still not clear, and we lack understanding about the timing and scientific requirements around assays. Certain lab methodologies may not lend themselves to a manufactured IVD kit and require a lab partner. Or there may be a rationale to minimize inter-laboratory variance. Orphan indications that are too small for an IVD due to significant costs may also be candidates for FDA LDTs. Additionally, new tests to reposition approved drugs or CDx drug salvage programs may have extreme commercial timing considerations that lend themselves to an FDA LDT path.

First-year average therapy drug revenues are estimated at approximately $5M per day for the top 200 pharma products (Evaluate Pharma 2015). If first-year revenues are in the $1M - $2M range, a 6-12 month LDT FDA path can have a substantial revenue impact to pharma.

Top laboratory partnership models for optimizing CDx clinical trials
CDx development also relies on effective partnerships between groups with the required expertise to optimize probability of success. Q2 Solutions has successfully used a number of partnership models, each with embedded roles and responsibilities for the specific partners involved.

Two-way partnerships (Figure 3) between the lab and IVD manufacturers place study execution responsibilities with the

Figure 3: Conventional CDx pharma-lab relationship
Roles and responsibilities for 2-party CDx development

Pharma
- Drug Development
- Early Biomarker/R&D/ IP license/Tech transfer
- Protocol Development
- Testing/reporting specification
- Regulatory (IND)

Laboratory
- Receive and process samples
- Test, report and collect data
- Monitor laboratory & sample QC

Pre-study
- Assess feasibility of clinical assay*
- Select methodology and platform*
- Provide CDx strategy/regulatory support

In-study
- Provide technical, medical and regulatory support
- Adhere to CDx assay protocol
- Monitor sites, logistics, pre-analytics

*Bridging study
- Validate and deploy the assay
- Develop study specific SOPs
- Distribute collection device and sample handling instructions

*LDT/RUO/IUO prototype to lockdown assay

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lab and assay/platform definition, reagents and ownership with the IVD vendor. Another model partners the laboratory with a pharmaceutical company. Q2 Solutions successfully partnered in this way in the STRATIFY JCV® clinical trials where we supported development of the first FDA-authorized blood test for the detection of antibodies to the polyomavirus JC virus (JCV) which can lead to progressive multifocal leukoencephalopathy (PML). We used an LDT framework to develop the assay and stratify the patients who are likely to benefit from the assay. The assay was used not only in clinical trials, but also cleared as a de novo 510k lab service, a CE-mark (kit) and later an FDA 510(k) cleared device (kit) by Focus Diagnostics (formerly a division of Quest Diagnostics, now a DiaSorin subsidiary). A special patient assistance and physician program was developed servicing the U.S., and some international markets through the single Quest Diagnostics Focus Diagnostics Lab with unique branding and test codes provided by our parent company Quest Diagnostics.

A more complex model (Figure 4) partners the pharmaceutical company with the IVD manufacturer and the laboratory together under a single Master Services Agreement (MSA). Together, the partners define exactly what is needed to bring the assay into a laboratory, perform a clinical trial, review all the data that are generated, and submit for approval. In this model, it is important that the laboratory strictly complies with the IVD vendor’s instruction for validating and deploying the assay to test the patient samples. For instance, in one case Q2 Solutions has partnered with a sponsor and an IVD manufacturer to design and score an immunohistochemistry test for a major cancer indication. Our team of pathologists were very familiar with the MOA and derived a scoring scheme to report back to the manufacturer to help identify responders. The assay was then launched across the Q2 Solutions global network of laboratories, all led by a Q2 Solutions chief pathologist under agreement with the IVD company and the sponsor.

**The future of partnering for CDx development**

Partnerships with labs today tend to be limited in scope, including Service Central Lab Agreements with a phase gate approach where a single phase of development is contracted, after which the sponsor can move to a new lab partner for work in future phases. This model is not optimal, as it leads to a loss in efficiency and lessons learned. Other models used currently involve single, narrow scope commercial phase agreements or end-to-end, single project scope sequential deals.

The future of lab partnerships, however, includes broader scope relationships between preferred vendors and sponsors, and could also include commercial services and informatics/analytics. Together, the three entities will determine the types of assays and the specific biomarkers that are needed to drive the pipeline forward. These agreements alleviate timeline pressure and have a focus on individual statements of work through the full value chain.

When choosing a laboratory partner, sponsors should require a deep understanding of biomarkers and a broad spectrum of available assays. For example, the number of PD-1/PD-L1 trials has increased dramatically over the past three years (Figure 5). Many patients have been found to be PD-L1 negative by IHC, but have received benefit from anti-PD-1 drug treatment. To better define patients who can benefit from anti-PD-1 or anti-PD-L1 drugs going beyond conventional IHC, Q2 Solutions developed a strategy for a sponsor and has put a holistic approach to biomarker identification in place, using a varied set of new platforms and approaches that have been shown to be linked to response to anti-PD-1. This holistic model requires a lab partner with knowledge in multiple laboratory science and clinical disciplines as well as experience collaborating with multiple IVD partners as shown in Figure 6.

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**Figure 4: Tripartite CDx relationship model**

Integrated partnering to support optimized CDx development and commercial success

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<thead>
<tr>
<th>Pharma</th>
<th>IVD Vendor</th>
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<tbody>
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<td>– Protocol Research Assay (PRA)</td>
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<td>• Install, validate &amp; operate Dx platform</td>
<td>• Develop study specific SOPs</td>
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<td>• Perform Dx assay transfer, proficiency training &amp; testing</td>
<td>• Adhere to CDx assay protocol</td>
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<td>• Test, report and collect data</td>
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<td>• Distribute collection device and sample handling instructions</td>
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<th>Study execution</th>
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Lessons learned

Successful partnerships for CDx strategies require a laboratory with a strong foundation in biomarkers, including discovery of candidate biomarkers and the ability to confirm and validate biomarker leads using orthogonal methods, engaging external expertise as needed.

All partners should be engaged as early as possible. It is never too early to involve a laboratory partner. Constant communication between all partners, including regulatory authorities where feasible, is critical. Risks associated with cost, feasibility and timelines should be identified and mitigated as early as possible.

It is important to identify clear roles and responsibilities for all parties during the execution of the clinical trials, emphasizing deliverables, timelines and the escalation process. All parties should identify critical tasks, discuss potential risks, and ensure collective signing off on agreements and on any ulterior modifications under change control. Initial results generated with clinical trial samples must be reviewed jointly by subject matter experts from all parties to be clear on the performance of the assay, so that course corrections can be made early.
To develop a clinically and commercially viable CDx strategy, partners need to ensure that the assay is reduced to practice. Real-world feasibility; platform; sample type and collection; pre-analytics (including shipment and stability); throughput; and the percentage of test repeats and generation of unambiguous results all need to be considered in the context of multiple jurisdictions. Assay robustness and clinical utility should be ensured using clear, actionable medical value cutoffs. Lab commercialization implications should be considered with respect to reimbursement, education, and asymmetry in revenue between the IVD manufacturer and the drug developers.

Personalized medicine is already transformative, and development of a CDx strategy is pivotal to improve drug clinical development and meet the promise to improve patient care. Market trends, real-world evidence and regulatory imperatives are driving the need to develop viable CDx strategies. And most importantly, patients want and deserve the most precise therapies that science can offer. Strong partnerships between drug developers, IVD manufacturers and highly experienced laboratories can ensure the greatest probability of success if all parties collaborate to thoughtfully and diligently invest their efforts into identifying the best approach to meet their needs.

Recipe for success

The elements required for successful development of a CDx can be summarized in six key points:

1. Develop a scientifically, clinically, and commercially viable CDx strategy.
2. Identify the right partners with the right expertise and track record.
3. Engage all partners early in the development process.
4. Treat your partners as your colleagues, not as vendors. Their success is your success. Their failure is your failure.
5. Change is inevitable. Accept and manage change to your advantage.
6. Communicate constantly with all partners.

About the authors

Patrice Hugo, Ph.D.
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Dr. Patrice Hugo has more than 25 years of experience in senior scientific leadership positions. Prior to coming to Q2 Solutions, he served as Associate Vice President & Chief Scientist of LabCorp/Covance Central Laboratory Services, Chief Scientific Officer at Clearstone Central Laboratories, Executive Vice President R&D at Caprion, and Chief Scientific Officer and Vice President R&D at PROCREA BioSciences.

As Chief Scientific Officer at Q2 Solutions, Dr. Hugo leads scientific strategy to enhance its laboratory service offering, ensures global scientific instrument/methodology/test harmonization and delivery of high-quality test results in certified laboratories worldwide, and manages scientific activities across central laboratories and Centers of Excellence such as Genomics, BioAnalytical, ADME, Immunogenicity/Ligand Binding and Vaccine facilities worldwide.

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Richard Heichemer is scientific advisor for companion diagnostics at Q2 Solutions. In this role he leads business development and scientific strategy for CDx to enhance our laboratory service offering and provides a solution-driven approach to our pharmaceutical and biotech partners for their CDx projects.

Richard brings more than 30 years of experience within the pharmaceutical, medical device, and clinical laboratory sectors. Most recently Richard was Director, Companion Diagnostics at Quest Diagnostics. His areas of therapeutic experience are Oncology, Infectious Diseases, Genetics/ Rare Disease, and Immunology and his areas of technology and licensing experience are Biomarker discovery, IHC, FISH, genomics, signatures (RNA, SNP, and biomarkers), ELISAs, and protein detection methods.

Following a Master’s degree in Microbiology from the University of Rochester, he earned his MBA in Finance from New York University.
References