A New Paradigm for Personalized Medicine and Companion Diagnostics: The Contract Diagnostics Organization

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Abstract: In the era of personalized medicine, pharmaceutical companies are actively seeking partners to develop Companion diagnostics. Common choices of partners include large diagnostic manufacturers and traditional Contract Research Organizations (CROs), neither of which provides an entire solution. Diagnostics companies have an intrinsic bias toward internal product lines, and are therefore incentivized to direct diagnostics development toward an existing technology platform. The expertise of a CRO lies in the monitoring of pharmaceutical programs, not in diagnostics. In addition, few traditional partners have significant clinical laboratory experience or offer accredited clinical laboratories to ensure that the diagnostic clinical trials are designed for, and conducted in, laboratories that meet regulatory standards. Lastly, these organizations are inexperienced in managing and coordinating the multiple partners required in the development process.

The Contract Diagnostics Organization (CDO) is a new concept designed to aid pharmaceutical companies in addressing challenges in companion diagnostics development. This business model provides pharmaceutical companies a complete outsourcing partner to initiate and manage the parallel development of companion diagnostic tests in synergy with drug development. The CDO combines all of the necessary services, including diagnostics research, an accredited clinical laboratory, project management and regulatory, manufacturing, and consulting in an integrated, technology-independent manner. Thus, the CDO focuses on its pharmaceutical partner's business objectives and ensures the speediest path to market a valuable, personalized drug for patients.

Keywords: Personalized Medicine, Companion diagnostic, Contract Research Organization (Cro), Contract Diagnostic Organization (Cdo).

INTRODUCTION

For many years now, the public, scientific, and business communities have been anticipating the era of personalized medicine. As the concept has progressed and regulatory input has increased with it, the need for high-quality and highly efficient companion diagnostic development has also grown. In response, pharmaceutical companies have actively sought appropriate partners to develop companion diagnostics.

Common choices for partners to date have been large diagnostics companies and traditional contract diagnostics organizations (CROs). Traditional contract diagnostics companies have their own product lines and may therefore not choose approaches that best target the pharmaceutical companies' objectives. CROs also may not have the specific expertise necessary to develop diagnostics, as they have the most experience with pharmaceuticals. In addition, few traditional partners can ensure that clinical trials for diagnostics are conducted in accredited clinical laboratories that meet the clinical regulatory standards, as opposed to the self-regulated good clinical practice and good laboratory practice standards that are applied to clinical research studies. Lastly, there are numerous overall logistical complexities that arise when managing and coordinating multiple partners in the drug development process.

Here, we discuss the Contract Diagnostics Organization (CDO), a new concept designed to assist pharmaceutical companies and address challenges in companion diagnostics development. This business model allows pharmaceutical companies a start-to-finish partner to initiate the parallel development of companion diagnostic tests in synergy with drug development.

THE PROMISE OF PERSONALIZED MEDICINE

"Personalized medicine" refers to the customization of medical treatment to the individual characteristics of each patient [1]. The term "personalized medicine" was coined in the 1990s, although the premise predated this [2].The advantages to a personalized medicine approach are theoretically clear; personalized medicine has the power to more efficiently, effectively, and safely direct health care than traditional non-targeted approaches.

Recently, the interest in personalized medicine has increased substantially; based on PubMed searches on the term 'personalized medicine' a 2011 publication found that the number of scientific publications on the subject has shown an exponential growth in the period from 1999 to 2010 [3]. From the financial perspective, the U.S. personalized medi-

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cine market was estimated to be $232 billion in 2009 [4]. It is projected to grow eleven percent annually and nearly double in size to over $450 billion by 2015. The core diagnostic and therapeutic segment of the market – comprised primarily of pharmaceutical, medical device and diagnostics companies – was estimated at $24 billion and expected to grow by 10 percent annually, reaching $42 billion by 2015 [4].

On average, a traditional therapeutic works effectively for about 50% of individuals [5], with hypersensitivity, lack of response, inability to metabolize, and adverse reactions being observed in the remainder of patients. In a recent report, it was estimated that more than 5% of hospital admissions were associated with adverse reactions to prescribed drugs [6]. Many of these are due to individual genetic differences that render one hypersensitive to the drug, or unable to metabolize it properly [7]. One intent of a personalized medicine approach is to reduce these adverse events substantially and increase the effectiveness of treatment; the right drug at the right dose, for the right individual at the right time.

COMPANION DIAGNOSTICS IN PERSONALIZED MEDICINE

The commonly applied therapeutic model of "one drug for one disease" does not fit heterogeneous disease mechanisms at the molecular level [3]. A stratified approach, identifying groups of patients based on certain biologic characteristics or biomarkers has the potential to be more efficient and effective while reducing undesirable drug interactions and side-effects [3]. Even today, stratification is a key component of both diagnosis and therapy selection. Drug and dosages are modified according to key markers including patient weight, ethnicity, sex, age, and traditional diagnostics such as blood and urine analyses.

Companion diagnostics extendthis concept to include diagnostic biomarker assays and genetic testing, the results of which can be used in several modalities. A companion diagnostic result may be used to stratify patients to identify those that will respond to a particular therapeutic. Similarly, it can identify those patients that will not respond, allowing health care providers to more rapidly move onto a treatment that may be effective. For example, detection of*HER2*amplification by molecular cytogenetics analysis is used to identify patients more likely to respond totrastuzumab (Herceptin®) in breast and gastric cancers [8].

A second important use of companion diagnostics is in customizing drug dosage based on metabolism biomarker status. For example, warfarin dosage can be calculated using an algorithm (www.warfarindosing.org) that incorporates a patient's *CYP2C9* and *VKORC1* genotypes [9]. Individuals with *CYP2C9**2 and *CYP2C9*3* genotypes produce an enzyme with reduced capacity (by 30% and 80%, respecttively) to metabolize warfarin.Those with the 1639G>A *VKORC1* genotype produce an enzyme with about 50% reduced capacity. Traditional dosing leads to delayed and elevated warfarin steady-state levels, and potentially to an increased bleeding risk [10]. As such, reduced warfarin dosages are needed for those with these genotypes [10].

Lastly, a companion diagnostic may be used to monitor treatment. Quantitative analysis of the *BCR-ABL* fusion transcriptsis used to monitor imatinibmesylate (Gleevec®) treatment in patients with chronic myeloid leukemia [11], and the *PML/RARA* translocation is diagnostic and used to monitor retinoic acid therapy in acute promyelocytic leukemia [11, 12].

Companion diagnostics are required to ensure the effective, safe development and use of many personalized therapeutics. The use of genetic, molecular or other companion diagnostics stratifies patient populations by allowing healthcare providers to select a targeted therapeutic based on their patient's particular profile.

The use of composite biomarker signatures, the first step in companion diagnostic development, has become more common in the clinical development of therapeutics. Biomarker research has been of considerable interest to the clinical and basic science communities. For example, between 1986 and 2009, the National Institutes of Health (NIH) awarded over 28,000 grants containing the term "biomarker," [13] a large increase from previous years. The total funding for these awards in 2008 and 2009 alone was over $2.5 billion. This demonstrates a notable upward trend in the desire to use biomarkers and personalized medicine to develop clinical therapeutics. As evidence of growth in the industry, 10% of currently marketed pharmaceuticals include biomarkers on their labels [14].

As an example, patients with metastatic colorectal cancer and somatic mutations in the *KRAS* gene are unlikely to respond to chemotherapeutic treatment with Erbitux® (cetuximab) and/or Vectibix® (panitumumab) [15].While the results of these studies are well known, and this knowledge is being applied on an *ad hoc* basis by various clinical institutions, there are currently no approved clinical guidelines or mandated testing for *KRAS* mutations prior to therapy. Various challenges in the process may contribute to the lack of these guidelines in the U.S. as clearly, an available companion diagnostic (in this case, genetic testing for somatic *KRAS* mutations in the colorectal tumor) would help physicians guide and refine their treatment options. Not only do companion diagnostics increase drug effectiveness, they can also reduce the likelihood of adverse events, save time, and decrease the financial burden on the healthcare system.

Companion diagnostics are critical to the success of personalized medicine and yet despite this, only a minority (about 1%) of marketed therapeutics have a companion diagnostic [14]. Responses from the larger pharmaceutical and biotechnology companies to create personalized therapeutics have been lower than expected. Success rates in bringing these drugs to market have also been low. A number of scientific, strategic, commercial, and regulatory factors have been attributed to this [16]. For example, retrospective identification of a useful biomarker presents many technical and regulatory challenges.

REGULATORY AGENCIES WEIGH IN ON COMPANION DIAGNOSTICS

The emergence of personalized medicine and companion diagnostics to inform clinical decision-making, along with assays to guide drug selection and dose, has led regulatory agencies to respond. The U.S. Food and Drug Administration (FDA), Health Canada and the European Medicines Agency

As reported in *The Wall Street Journal*, the co-development of a therapeutic and companion diagnostic was problematic from a business perspective [25]. Pfizer developed and manufactures Xalkori. ®They partnered with a large diagnostics company, Abbott Molecular, to develop a molecular cytogenetics companion diagnostic test kit for analyzing *ALK*. Early on, Pfizer researchers were reportedly hesitant to supply Abbott with some of its tumor tissue containing *ALK* gene rearrangements, while expressing concerns that Abbott did not appear to be apprising them on progress developing the test [25]. Abbott also appeared to resist Pfizer's desire to train commercial laboratories on using the test well ahead of FDA approval, because Abbott was concerned that the laboratories could forget how to conduct the assay while waiting for the drug and test to go on sale [25]. Resisting expenditure of resources prior to an FDA approval was potentially another motivation in delaying training. The FDA ultimately approved Xalkori® and its companion diagnostic test kit simultaneously, but not before several delays and difficulties were experienced. The fluorescent *in situ* hybridization-based assay for *ALK* rearrangements has the advantage in that it can be performed in many laboratories.

Another partnership choice is the traditional Contract Research Organization (CRO). As described earlier, CROs' expertise is on operational efficiency of clinical trials for pharmaceuticals. This clinical trial experience may be attractive and familiar to pharmaceutical companies looking to outsource this function. However few CROs have experience in IVD development, manufacture, and medical device (companion diagnostic) validation trials. In addition, pharmaceutical companies want to ensure that clinical trials conducted for development of a companion diagnostic are run in an environment that can ensure translation to the clinical setting after marketing launch. Therefore, many are turning to appropriately licensed and accredited clinical laboratories. This necessitates partnering with a laboratory possessing and maintaining those credentials, a service many traditional diagnostics companies and CROs do not offer.

From a diagnostic perspective, co-development of a therapeutic and companion diagnostic is associated with a level of uncertainty. Unlike the pharmaceutical development industry, where there is an understanding that a large number of potential drugs will fail clinical studies (and that the associated revenues will be derived from a very small cohort of successful drugs), no such expectation currently exists in the diagnostic development space. Therefore, while the co-development of a diagnostic and therapeutic is advantageous from a cost and efficiency perspective, the high number of late stage compound failures makes a co-development agreement less financially desirable from a diagnostic perspective, due to the significant risk and high cost involved in developing diagnostics for drugs that never receive regulatory approval. Thus, diagnostic companies may be hesitant to share the financial burden for companion diagnostic development.

Lastly, drug developers must overcome several logistical complexities when managing and coordinating multiple partners in the process: Research and Development (initial research and biomarker development), a Diagnostics Company (to develop and possibly manufacture an assay kit), a CRO (to conduct validation trials), regulatory personnel, and Clinical Laboratories (to perform assay validation and trial testing). All of these steps can cause product delay and introduce points of inefficiency (Fig. **3**).

Fig. (3). Biopharmaceutical companies' traditional role in personalized medicine.

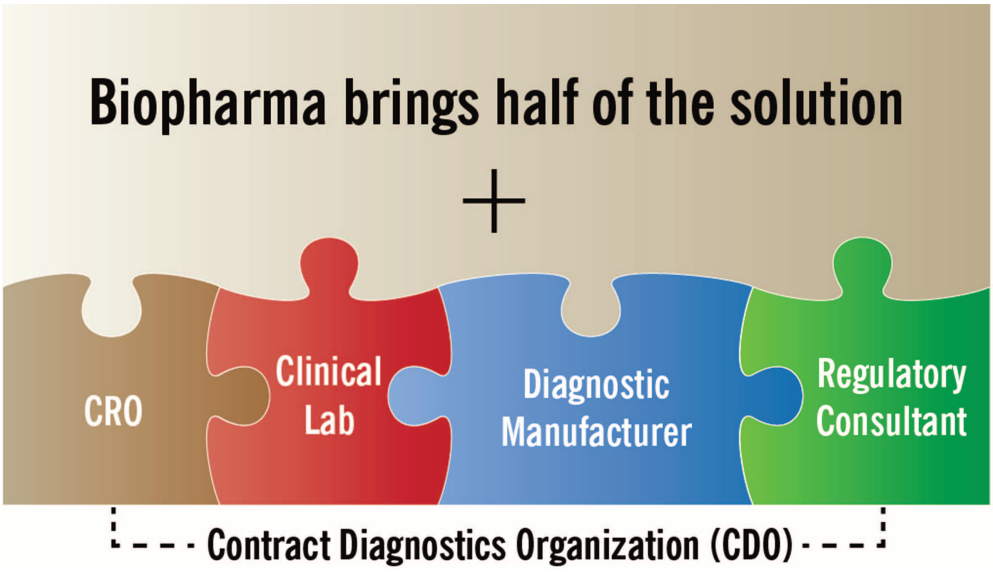

Fig. (4). Various services offered by a CDO, all housed within one organization.

AN INTEGRATED SOLUTION – THE CONTRACT DIAGNOSTICS ORGANIZATION

The Contract Diagnostics Organization (CDO) is a new business model, which allows pharmaceutical companies to outsource to a single partner offering integrated services within one organization, to initiate the parallel development of companion diagnostic tests in synergy with drug development. The CDO combines diagnostics research, a licensed and accredited clinical laboratory, manufacturing, and consulting, in an integrated, technology-independent manner (Fig. **4**).

A CDO can design, manage, and coordinate all aspects of clinical trials for the development of a diagnostic product – from assay concept to regulatory submission and commercialization. This can include (but is not limited to) 1) Developing novel assays or validating established assays; 2) Developing, managing, and conducting a clinical research project; 3) Developing a Case Report Form (CRF)/Study document; 4) Submitting and managing Institutional Review Board (IRB) documents; 5) Laboratory services; 6) Managing FDA submissions for 510(k) or Premarket Approval (PMA) clearances; and 7) Writing papers for publication.

A CDO partners with clinical laboratories (ideally CLIA certified and CAP accredited), which can offer access to a full complement of specialty testing services.

Additionally, some CDOs have manufacturing capabilities for a specific diagnostic product, which allows them to custom develop IVD kits, reagents, or products for a research project, clinical trial, or product commercialization. Examples include manufacturing reagents, sample collection kits, or entire diagnostic assays.

In addition, a CDO can offer biopharmaceutical and diagnostics consulting services. For example, this can include consulting for: 1) Assay development, platform evaluation, and validation; 2) Management of all levels of regulatory compliance, processes, applications, and approvals; 3) FDA interface (product life-cycle support/management); 4) Technology utility, application, fit-for-purpose, and patentability; 5) Market and competitor analyses; 6) Mergers and acquisitions.

In conclusion a CDO eliminates the need for outsourcing to, and coordinating across, multiple partners. It also builds in flexibility and the ability to implement an efficient, nimble strategy that may naturally shift as development continues.

CONCLUSION

The basic science behind personalized medicine will continue to offer a myriad of choices for pharmaceutical companies to create companion diagnostics in healthcare. The downstream market for patient-customized therapeutics has significant untapped potential. However, the traditional bench-to-bedside development of a pharmaceutical product needs to be coordinated with that of a companion diagnostic. The CDO combines all of the necessary services, including biomarker research, a licensed and accredited clinical laboratory, manufacturing and consulting, in an integrated, technology-independent manner. As a CRO is the standard outsourcing partner for pharmaceutical clinical trials, a Contract Diagnostics Organization is specifically suited for outsourcing of companion diagnostics co-development.

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CONFLICT OF INTEREST

Drs Cotter and Moore are Principals at ResearchDx, LLC

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